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March 28 - April 1, 2023 | Gothenburg, Sweden

P0001 / #1038

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

THE BIOLOGICAL MECHANISMS, INDICTED IN NEURONAL CELL DEATH, ARE PERTINENT IN THE MANAGEMENTS OF NEURODEGENERATIVE DISEASES.

Benjamin Adebisi
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Aims: The mechanisms involved in neuronal cell death, especially apoptosis, necrosis, excitotoxicity and autophagic cell death, play important roles in understanding the approaches towards several neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. However, most of these diseases have been linked with protein mishandling, such as, misfolded protein, impairment of protein degradation and protein aggregation; therefore, the Research aims to establish the many connections between the impaired protein metabolism and neurodegeneration, and how interception of these mechanisms could modify neurodegenerative diseases.
Methods: Several literatures by researchers in leading institutions and research firms were consulted in arriving at the different positions in the roles the biological mechanisms play in neuronal cell death.
Results: showed misfolding and accumulation of proteins, in cells, of specific areas in the affected brain have several interconnections with series of biopathological mechanisms and pathways, which include impaired DNA repair, defective intracellular transportation, oligodendrocytes dysfunction, neuroinflammation, astrogliosis, excitotoxicity, impaired homeostasis, disturbed RNA metabolisms and mitochondria dysfunction. The associations of the various biological process, initiating protein aggregation, and neuron loss, in fact, are the major reasons for the complexities and heterogeneity in diseases' severities, symptoms and prognosis.
Conclusions: Therefore, understanding the various mechanistic pathways, plus, strategies to intercept their progressive neurodegenerative processes will be very important in managements of the neurodegenerative diseases.

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P0002 / #2540

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

SEX-SPECIFIC REGULATION OF B-SECRETASE: A NOVEL ESTROGEN RESPONSE ELEMENT (ERE)-DEPENDENT MECHANISM IN ALZHEIMER'S DISEASE

Rena Li[1], Jie Cui[2], Ghania Ait-Ghezala[2], Kumar Sambamurti[3], Yong Shen[4]
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Aims: Women have a higher prevalence and incidence of Alzheimer's disease (AD) than age-matched men, and loss of estrogen might be partially responsible for the higher risk of AD in aged women. While β-Secretase (BACE1) plays an important role in AD pathogenesis, whether BACE1 involved the sex difference in AD pathology remains unclear. This study investigated the hypothesis that estrogen regulates BACE1 transcription via the estrogen response element (ERE) and designated pathways.
Methods: Using estrogen receptor (ER) knockout mice and mutagenesis of EREs in HEK293 cells, we demonstrated sex-specific inhibition of BACE1 transcription by estrogen via direct binding to ERE sites and ERa.
Results: We also used a repressor of estrogen receptor activity (REA) and showed that a REA-ERE complex downregulated BACE1. A ChIP assay analysis determined that all three EREs at the BACE1 promoter were required for estradiol-mediated downregulation of BACE1 transcription in mice. Lastly, we confirmed the impairment of the REA pathway in the cortex of female AD patients.
Conclusions: Our study identified an estrogen-specific BACE1 transcriptional regulation pathway from cell and animal models to AD patients.

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P0003 / #2265

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

GENE EXPRESSION IN SLEEP FRAGMENTED VERSUS UNDISTURBED SLEEP IN MOUSE MODELS: RELATION TO AMYLOID BETA PATHOLOGY IN ALZHEIMER'S DISEASE

Sarah Barth[1], Leanna Mccarty[1], Valeria Buzinova[1], Savannah Turton[1], Samantha Padgett[1], Tyler Jessup[1], Haleigh Whitlock[1], Katharina Kohler[1], Marilyn Duncan[2], Carrie Johnson[1], Michael Murphy[1]
[1]University of Kentucky, Biochemistry, Lexington, United States of America, [2]University of Kentucky, Neuroscience, Lexington, United States of America

Aims: Recent publications show deleterious effects of either sleep fragmentation (SF) or sleep deprivation on amyloid-beta pathology in both humans and in various genetically modified mouse lines. For example, chronic SF increases amyloid-beta 42 and neuroinflammation in the hippocampus but not the cortex in female 3xTgAD mice (Duncan et al, *Neuroscience*, 481:111-122, 2022). In this study, we examined whether chronic SF and amyloid-beta affected the expression of other AD-related markers (*ADAM10, BCAR3, SRY, BDNF, FNDC5*, and others). Because sleep deprivation alters clock gene expression in the cortex, we investigated whether SF affects clock gene expression (*Per1, Bmal1,* and others) as they relate to SF and amyloid-beta accumulation in two AD-relevant mouse lines (3xTgAD and an APPxPS1 knock-in mutant).
Methods: We first performed SF in 1-hour shifts four times daily evenly interspersed throughout the light phase, Monday-Friday, for 3-4 weeks. During SF shifts, mice were kept awake with novel objects and gentle stimulation with a paintbrush; control mice (US) were undisturbed. Sleep was recorded using PiezoSleep cages, and amyloid-beta was extracted and analyzed (via ELISA); RNA was extracted, converted to cDNA, and gene expression assessed via RT-PCR using QuantStudio 7.
Results: Unlike in the 3xTgAD mice, SF did not lead to increased amyloid-beta accumulation in the APPxPS1 knock-in mice. Interestingly, expression of clock genes (e.g., *Per1* and *Bmal1*) did not show a significant change in expression in the 3xTgAD mice in spite of notable shifts in the amount of sleep between light and dark phases.
Conclusions: Sleep disruption across different AD-related mouse models does not necessarily lead to uniform effects on AD-related outcomes. Funding provided by NIH (AG068215).

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P0004 / #2586

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

NONAGGREGATING PEPTIDES DERIVED FROM ALTERNATIVELY SPLICED ISOFORMS OF HUMAN IAPP AND GDNF INHIBIT AMYLOID FORMATION

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Aims: Amyloidosis due to brain amyloidosis induced by amyloid-β (Aβ) is the key pathogenic event in Alzheimer's Disease (AD), whereas islet amyloid polypeptide (IAPP) in human islets leads to β-cell dysfunction, There are no drugs currently available that inhibit these two amyloidosis diseases. We are investigating endogenous amyloid inhibitors derived from alternatively spliced isoforms of human IAPP and GDNF genes.
Methods: 1. Participants: A cohort of 10 individuals with high-probability early AD according to the NIA-AA and IWG-2 criteria and 19 cognitively normal healthy controls. Individuals.
2. Selected Reaction Monitoring (SRM)-MS assay: SRM data were collected using Analyst software and processed using MultiQuant software (Sciex, version 3.02 with Scheduled-MRM-Algorithm). The relative quantitation value of each given peptide was obtained by summing transition peak area ratios of the light (unlabeled form) per heavy (stable-isotope-labeled standard peptide analogs) from targeted peptides. 3. Thioflavin T amyloid reporter assay: Equal molar concentrations of IAPP37 and Aβ42 with the inhibitory IAPP25 and DNSP11 peptides were measured in the fibrillation kinetic assays.
Results: We uncovered two novel hominid-specific IAPP isoforms encoded by 4 exons instead of the conventional 3 exons: hIAPPβ, which encodes an elongated propeptide, and hIAPPγ, which is processed to mature IAPP25 instead of IAPP37. We found that IAPP25 inhibited the aggregation of IAPP37 and Aβ42. Furthermore, DNSP11, a peptide derived from GDNF in α-cells, also inhibited the aggregation of IAPP37 and Aβ42. Using a quantitative selective reaction monitoring (SRM) proteomic assay, we found that IAPP25 was reduced in postmortem islets from T2DM cadavers, whereas hIAPPβ was increased in the postmortem cerebrum and reduced in the plasma of AD patients.
Conclusions: Our study provides potential IAPP25 and DNSP11 targets for diagnostic and therapeutic applications in Alzheimer's Disease.

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P0005 / #2279

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

AMYLOID BETA PEPTIDE FOLLOWS A DAILY RHYTHM IN THE OLFACTORY BULB AND CEREBELLUM IN WILD-TYPE AND APP X PS1 MICE

Valeria Buzinova[1], Carrie Johnson[1], Savannah Turton[1], Sarah Barth[1], Samantha Padgett[1], Tyler Jessup[1], Katharina Kohler[1], Haleigh Whitlock[1], Marilyn Duncan[2], Michael Murphy[1]
[1]University of Kentucky, Biochemistry, Lexington, United States of America, [2]University of Kentucky, Neuroscience, Lexington, United States of America

Aims: Amyloid beta plaques are one of the more prevalent biomarkers of Alzheimer's Disease (AD). Other publications have researched the various mechanisms regarding the clearance of amyloid beta. Recent studies have also investigated the relationship between circadian rhythms and AD. However, these studies have not examined many regions beyond the hippocampus, and investigation of this phenomenon in wild type (WT) mice has been extremely limited.
Methods: We chose to utilize an APPxPS1 mutant knock-in (KI) line because they express the amyloid precursor protein (APP) at normal levels under the normal pattern of expression. Mice were acclimated to a 12:12 light:dark cycle for two weeks. Mice were then switched to housing in continuous darkness (D:D) for 24-48 hours. Animals were euthanized in groups of 16 at 3 hour intervals starting after the first 24 hours in D:D (N = 128). Each group contained equal numbers of WT males and females, KI males and females. Time at euthanasia is expressed as Zeitgeber Time (ZT) and correlates to the 24-hour clock, with 7 am = ZT0. Immunoassays were done with the olfactory bulb and cerebellum tissues to determine whether amyloid beta levels oscillated at different ZT points throughout the day.
Results: There was similar time-dependent change in amyloid beta in both regions examined. Amyloid beta declined to a minimum at ZT4 (early in the light phase) and peaked in the dark phase between ZT13 and ZT16. Despite less amyloid beta in the cerebellum, the time-dependent pattern of amyloid beta levels was essentially the same.
Conclusions: Amyloid beta levels display a circadian rhythm in multiple areas of the brain. Further, these data indicate that this biological process also occurs in WT mice. Funding provided by NIH (AG068215).

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P0006 / #2709

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

INHIBITION OF AMYLOID-BETA (1-42) AGGREGATION KINETICS BY CELL-DERIVED EXTRACELLULAR VESICLES

Vesa Halipi, Nima Sasanian, Julia Feng, David Bernson, Quentin Lubart, Daniel Van Leeuwen, Doryaneh Ahmadpour, Elin Esbjörner
Chalmers University of Technology, Biology And Biotechnology, Gothenburg, Sweden

Aims: Aggregation of the amyloid-beta peptide into amyloid fibrils is a central pathogenic feature in Alzheimer's disease (AD). Although the exact mechanisms behind this neurodegenerative disorder are not yet clear, extracellular vesicles (EVs), which are secreted by all cells to mediate non-synaptic intercellular communication, have been identified as potential disease modulators. This paper aimed to examine the role of extracellular vesicles on amyloid-beta aggregation kinetics. Understanding how EVs interact with amyloid-beta may provide key knowledge of the underlaying mechanisms behind AD and of future possible treatment strategies.
Methods: We have compared the effect of EVs from the two human cell types; SH-SY5Y, representing neurons, and HEK293-T which are kidney-derived. The EVs were characterized with Western blot analysis, nanoparticle tracking analysis, and cryo-electron microscopy. Aggregation kinetics of amyloid-beta in the absence and presence of EVs were monitored using thioflavin-T fluorescence. Morphology of the formed fibrils was studied using atomic force microscopy and cryo-electron microscopy.
Results: Our results show that EVs from both cell types significantly slow down amyloid-beta aggregation in a concentration-dependent manner. Additional experiments with fibril seeds revealed that EVs reduce the rate constant for amyloid fibril elongation (k_+), and fitted models to the experimental data using the web-based software AmyloFit further corroborated these findings. This effect on amyloid fibril elongation resulted in the formation of significantly shorter amyloid-beta fibril
fragments.

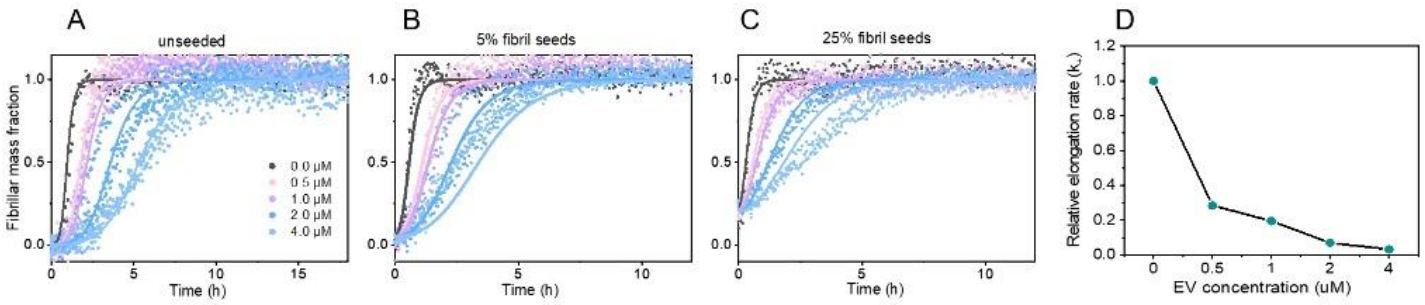

Figure 1. (A-C) Effect of SH-SY5Y EVs on unseeded and seeded aggregation of Aβ (1-42) monitored by changes in fibrillar mass fraction as function of time; (A) Unseeded, (B) 5% pre-formed fibril seeds, and (C) 25% pre-formed fibril seeds. (D) Decrease in elongation rate constant, k_+, with increasing EV concentration.

Conclusions: Our findings show that EVs reduce the rate of amyloid-beta fibril elongation, suggesting they may be neuroprotective. However, the formation of short amyloid fibrils have been associated with enhanced neurotoxicity, and cell viability studies are therefore underway to better pinpoint the pivotal balance between neuroprotective (aggregation inhibitory) and neurotoxic effects of EVs. Our data thus contributes to understanding the role and impact of EVs on amyloid-beta-mediated neurodegeneration.

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P0007 / #1726

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

BINDING OF SOLUBLE AMYLOID BETA OLIGOMER SPECIES TO HUMAN IPSC-DERIVED EXCITATORY NEURONS ASSESSED USING A PANEL OF AB ANTIBODIES

Erika Cline[1], Wei-Li Kuan[2], Sanofar Jainul Abdeen[3], James Cruse[3], Adam Kinne[3], Mahsan Rafizadeh[1], Martin Crossley[2], James Smith[2], Clare Jones[2], Jasna Jerecic[1]
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Aims: Soluble amyloid beta oligomers (sABOs) accumulate in Alzheimer's disease (AD) and contribute to neuronal impairment through targeting of synapses. Myriad sABO species have been identified in cultured cells, cerebrospinal fluid, and brain tissues from AD patients and animal models and their functionality assessed, with results varying by analytical method and antibody. However, it remains unclear which sABO species are most relevant to AD pathogenesis. The objective of this study was to determine how sABO size affects synaptic binding and immunoreactivity to a panel of anti-Abeta antibodies.
Methods: Different sABO species, a mixture of sABOs with a large size distribution (i.e., synthetic ADDL preparation) and three size fractions of sABOs, as well as Abeta monomers were applied to human iPSC-derived cortical excitatory neurons. Neuronal binding was visualized with a panel of anti-Abeta antibodies via high content immunofluorescent imaging. Co-localization with the postsynaptic protein drebrin and baseline tau phosphorylation levels were also measured.
Results: Differential levels of binding to iPSC neurons were observed for each Abeta population by each antibody. The commercial antibody 82E1 was the least selective, recognizing all sABO species and monomers. A panel of anti-ABO antibodies lacked monomeric binding and demonstrated differential selectivity for high, mid, and low molecular weight sABO fractions. Most of the binding for all sABO populations showed co-localization with drebrin, giving evidence for synaptic targeting.
Conclusions: Human iPSC-derived excitatory neurons are a suitable model for assessing binding of sABO species. Results provide evidence that sABO size may influence neuronal binding and substantiate the importance of antibody selection in assay results. Future studies will incorporate downstream readouts such as a time-course of tau hyperphosphorylation to assess structure-function relationships of sABO species more thoroughly.

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P0008 / #2719

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

INTRACELLULAR TRAFFICKING OF AMYLOID-B IN CULTURED NEURONAL CELLS.

Andrea Ramnath, Elin Esbjörner
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Aims: We use a new palette of amyloid-β (Aβ) peptides, which are labelled at different surface exposed residues, to explore how the labelling site affects aggregation propensity. This new set of labelled peptides provides a new approach to study intraneuronal aggregation (with confocal microscopy and flow cytometry using FRET), and we can combine this with enlarged endosomal models to visualise intraneuronal aggregation events, as well as to mimic pathological alterations relevant to Alzheimer's disease (AD). Studying the intraneuronal aggregation of Aβ in this way provides a deeper understanding of the underlying causes of neurodegenerative diseases such as AD, which may subsequently provide insight into potential targets for therapeutics.
Methods: We use confocal microscopy and flow cytometry (and FRET) to study the intracellular trafficking of the new palette of fluorescently labelled Aβ peptides in enlarged early endosome model cells.
Results: Thus far, in this ongoing project, we have been able to visualise the accumulation of Aβ in the enlarged early endosomes of an existing cell line model, using confocal microscopy. We have also seen that the labelling site of the Aβ peptide affects the uptake efficiency of Aβ in cultured neuronal cells, using flow cytometry.
Conclusions: It has been shown that early endosomes, which are a major site of Aβ peptide generation, are distinctly enlarged within neurons in the AD brain.. We have so far seen preliminary indications that enlarged early endosomes could play a role in the accumulation of Aβ. We have also seen that the different labelling sites of Aβ can provide insight into the potentially important surface exposed residues of the Aβ peptide that are necessary for cellular uptake, either by affecting extracellular oligomer formation or by affecting the cell surface interactions.

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P0009 / #1124

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

EFFECT OF SEX HORMONES ON THE KINETICS OF AMYLOID BETA IN AN AWAKE AND BEHAVING MOUSE

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Aims: Alzheimer's disease (AD) is a neurodegenerative disease that is hallmarked by the accumulation of amyloid-beta (Aβ) and tau, followed by a progressive decline in cognitive acuity. Interestingly, AD affects women at a higher rate than men, even when controlling for differences in lifespan. Clinical trials utilizing hormone replacement therapy in older women have yielded conflicting results. To explain this difference, we looked at the direct effect of sex hormones on the temporal kinetics of brain interstitial fluid (ISF) Aβ using in vivo microdialysis.
Methods: Animals were implanted with microdiaylsis probes targeting the hippocampus and microdialysis was performed and samples were collected every 90 minutes over three days. In the first set of experiments, female animals were injected intraperitoneally with beta-estradiol or progesterone. In the second set of experiments, northindrone, a progesterone receptor agonist, was infused through the probe directly targeting the hippocampus. Vaginally gavage was performed daily to monitor the estrus cycle of the animals, and samples were processed at the end of microdiaylsis using an in house amyloid beta sandwich ELISA.
Results: Female animals dosed with beta-estradiol saw an increase in amyloid beta within 12 hours of dosing. Animals dosed with progesterone saw a decrease in amyloid beta in a similar time frame. Animals dosed via reverse microdiaylsis with northindrone saw an immediate decrease in amyloid beta. Estrus status had no effect on the results of these experiments.
Conclusions: These novel results suggest a differential effect of the two most prevalent sex steroids in females, and work is ongoing to uncover the underlying mechanism of this effect.

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P0010 / #2759

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

THE IN-TISSUE MOLECULAR ARCHITECTURE OF B-AMYLOID PATHOLOGY IN THE MAMMALIAN BRAIN

Conny Leistner[1], Martin Wilkinson[1], Ailidh Burgess[2], Stanley Goodbody[1], Yong Xu[3], Susan Deuchars[1], Sheena Radford[1], Neil Ranson[1], Rene Frank[1]
[1]University of Leeds, Faculty Of Biological Sciences, Leeds, United Kingdom, [2]Francis Crick Institute, Francis Crick Institute, London, United Kingdom, [3]AstraZeneca, Astrazeneca, Cambridge, United Kingdom

Aims: Amyloid plaques composed of focal deposits of Aβ fibrils are a hallmark of Alzheimer's disease (AD). Cryo-EM structures of individual b-amyloid fibrils purified from human brain have been determined using cryoEM. However, the molecular architecture of the amyloid plaques that are a hallmark of Alzheimer's disease within fresh mammalian brain is unknown. Here we sought to determine in the in situ molecular architecture of amyloid plaques within a knockin mouse model of familial Alzheimer's disease.
Methods: We used cryogenic correlated light and electron tomography to determine the native, in situ molecular architecture of β-amyloid in the brain of a mouse model containing the Arctic familial AD mutation (*App*$^{NL-G-F}$). We also used single-particle cryoEM to determine a near-atomic structure of Arctic Aβ fibril purified from this tissue.
Results: Cryo-electorn tomographic reconstructions showed that in-tissue Aβ fibrils were arranged in a lattice or in parallel bundles within a plaque, and are interdigitated by subcellular compartments, exosomes, extracellular droplets and extracellular multilamellar bodies. At the atomic level, the Arctic Aβ fibril differed significantly from earlier structures of Ab amyloid extracted from *App*$^{NL-F}$ mice models and human AD brain tissue, showing a striking effect of the Arctic mutation (E22G) on fibril structure. Cryo-electron tomography of *ex vivo* purified and in-tissue amyloid revealed an ensemble of additional fibrillar species, including thin protofilament-like rods and branched fibrils.
Conclusions: The structure of the Arctic Aß could explain the inability of the diagnostic reagent Pittsburgh B to detect Arctic amyloid in PET imaging of patients and animal models. The ensemble of fibrils, protofilament-like rods, and branched amyloid revealed by cryo-electron tomography provide a structural model situated within abnormal cellular and molecular constituents, that characterises amyloid plaque pathology.

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P0011 / #1495

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

SINGLE-MOLECULE METHODS CHARACTERISE PROTEIN AGGREGATES AND THEIR TOXICITY IN ALZHEIMER'S DISEASE

Elizabeth English, Shekhar Kedia, Matthew Cheetham, John Danial, Yu Zhang, Jeff Lam, Zengjie Xia, Melanie Swang, Emre Fertan, David Klenerman
University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom

Aims: Increasing evidence indicates fibrillar aggregates of amyloid-β (Aβ) and phosphorylated tau (p-tau), characteristic of Alzheimer's Disease (AD), are inert. Smaller soluble aggregates, oligomers, may be more toxic; but finding appropriate methods to study these remains challenging. This research aims to identify methods to detect and characterise AD-relevant aggregates within mixed samples from brain tissue. Aggregate number, morphology and toxicity will be measured across brain regions and disease stages to evaluate aggregate changes in relation to AD initiation, progression and maintenance.
Methods: Proteins were extracted from post-mortem brain tissue, via soaking in artificial cerebrospinal fluid to extract soluble proteins, and homogenising to extract insoluble and remaining soluble proteins. Total protein content was quantified by BCA assays. Antibodies were selected to bind Aβ, tau, α-synuclein, ASC and APOE in single-molecule pull-downs to measure aggregate quantity by diffraction-limited and super-resolution fluorescence microscopy. This is the first study to utilise aggregate-specific Simoa® to cross-validate brain aggregate quantities. Super-resolution microscopy characterised aggregate size and shape. Toxicity was evaluated using membrane permeability and inflammatory assays.
Results: Comparing end-stage AD prefrontal cortex with a healthy control identified larger protein aggregates, greater proportions of rounded Aβ structures and eccentric p-tau structures, and higher numbers of soluble Aβ and p-tau aggregates in late-stage AD than in health. Membrane permeabilisation was discovered not to be an important toxicity mechanism in late-stage AD.
Conclusions: Single-molecule methods are suitable to detect AD-relevant aggregates and increase our understanding of aggregate changes across AD, with indications that aggregate number, size and morphology may influence toxicity. There is scope to apply these methods to other samples, such as biofluids, which together with early-stage AD brain samples may uncover aggregates responsible for AD.

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P0012 / #2784

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

AMYLOID-BETA (AB) HYPOTHESIS AND ALZHEIMER'S DISEASE: A REVIEW OF SELECT META-ANALYTIC REVIEWS

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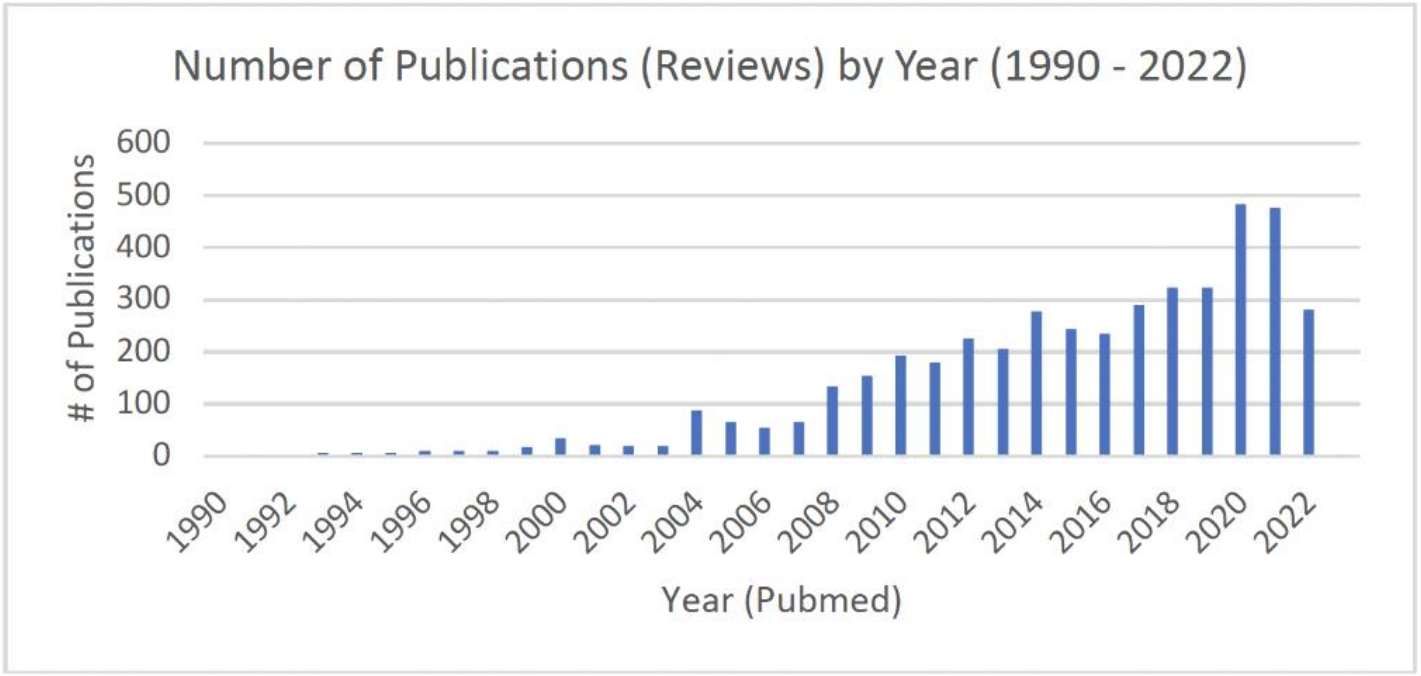
Aims: Background: Literature reviews, narrative and meta-analyses are published by experts to establish the state-of-the-art in their field. Alzheimer's disease (AD) research linking amyloid-beta (Aβ) hypothesis to AD is controversial. If scientific literature reviews are meant to enlighten the research community, then the large number of literature reviews available should serve to diminish controversy. However, confusion and controversy remain at all levels of scientific and non-scientific media. Pharmaceutical companies have invested over $45 billion in over 1,000 clinical trials over the past two decades (1). Yet no treatment has been shown to be effective, calling attention to the controversies, failed clinical trials and drugs based on the Aβ hypothesis. Objective: To examine meta-analytic reviews focusing on the relationship between Aβ hypothesis drugs and AD.
Methods: To identify literature, we created a search query focused on terms related to the Aβ hypothesis and AD. Using PubMed's API, 9,739 articles were identified. 3,905 had full text access.
We filtered on meta-analysis to identify 57 articles for review.
Results: Because meta-analyses are considered to be comprehensive and objective, we focused this review on published meta-analyses. Of the reviews located (57), 12 meta-analyses met inclusion
criteria.



There is a consensus among the 12 meta-analyses that reduction in amyloid levels alone is unlikely to substantially slow cognitive decline, and results suggest that use of anti-amyloid drugs is not a viable strategy for the prevention or treatment of Alzheimer's disease.
Conclusions: Although the volume of reviews is large, the strength and direction of the Aβ hypothesis drugs and AD remain controversial. The 12 meta-analyses reviewed point to a consensus - after many years, at great financial costs, and harm to patients, pharmaceuticals
companies should not pursue Aβ hypothesis drugs.

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P0013 / #1811

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

FSH AS A RISK FACTOR FOR ELEVATED BETA AMYLOID IN THE SERUM OF PATIENTS WITH PREMATURE OVARIAN FAILURE

Milena Erić Jovičić[1], Svetlana Jovičić[2], Natalija Pavlovic[3], Svetlana Vujovic[3]
[1]Institute of virusology, vaccine and sera Torlak, Department For Diagnostic Prodact, Belgrade, Serbia, [2]Clinical centar of Serbia, Institut Fo Nephrology, Belgrade, Serbia, [3]clinical centar of serbia, Centar Of Infertilitet, Belgrade, Serbia

Aims: Women are at greater risk than men for developing Alzheimer's disease during their lifetime. The aim of our study is to determine the relationship between FSH and beta amyloid in the serum of patients suffering from premature ovarian failure.
Methods: In the serum of affected patients, FSH and beta amyloid were determined using the Elisa technique.
Results: The results of our study conducted on 78 patients suffering from POF and 75 controls showed that there is a positive correlation between the values of FSH and beta amyloid in the serum.
Conclusions: From this, we can conclude that FSH can be a target for future therapeutic research.

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P0014 / #1911

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

CORRELATION OF BETA AMYLOID AND ESTROGEN IN THE SERUM OF PATIENTS WITH PREMATURE OVARIAN FAILURE

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Aims: Women are at greater risk than men for developing Alzheimer's disease during their lifetime. The aim of our study is to determine the relationship between beta amyloid in the serum of patients suffering from premature ovarian insufficiency.
Methods: In the serum of affected patients, beta amyloid and estrogen were determined using the Elisa technique.
Results: The results of our study conducted on 78 patients with POF and 75 controls showed that there is a negative correlation between beta amyloid and estrogen levels in the serum.
Conclusions: From this we can conclude that estrogens can be a target for testing therapy in patients and opens a new avenue.

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P0015 / #316

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

BIOPHYSICAL MARKER FOR AB GROWTH PATHWAY VIA THE AB STRUCTURE-SPECIFIC LABEL-FREE TERAHERTZ MONITORING

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Aims: A variety of different amyloid β(Aβ) aggregate forms have been linked with severity of Alzheimer's disease and its aggregation pathway can be a primary biomarker for diagnosis. However, pathophysiology associated with biophysical or structural conformation of Aβ is not clearly understood, and therefore we need a clear structure-based marker.
Methods: We recently developed the water-based near-field terahertz(THz) spectroscopy technique to measure Aβ aggregation states in solution and different optical conductance of the Aβ forms can provide a distinguishable biophysical marker(-c). By noting monotonic conductance change with frequency in monomers following Drude tail and nonlinear conductance changes in oligomers and fibrils adopting the localization parameter in Smith model, we derived a structure-specific discrete metric, which is a structurally defined a biophysical marker of Aβ aggregation states with modified Drude-Smith model ($\sigma(\omega) = \sigma/1-i\omega\tau[1 + (-c)/1-i\omega\tau]$). As a result, the biophysical marker(-c) around 1 in fibril, around 0.64 in oligomer, and nearly zero in monomer, independent of Aβ concentrations.
Results: We investigate Aβ dynamics to identify various morphological phase transitions from monomers to fibrils by the structure-specific biophysical marker($0<-c<1$) under physiological conditions, body temperature and medium(*e.g.*, buffer vs Matrigel). We clearly reveal the rate-limiting, stepwise nature of Aβ aggregation process, identifying three steady-states for monomers, oligomers, and fibrils, separated by two transition-states of mono-oligo and oligo-fibril. Furthermore, the time evolution of Aβ phase transformations is well described by the universal rate-limiting equation scaled by kinetic parameters; transition time and growth rate.
Conclusions: This biophysical marker for the Aβ structural change revealed the stepwise Aβ aggregation dynamics in real-time and can ultimately facilitate early AD diagnosis by clearly differentiating of Aβ oligomer state between monomer and fibril states in a nanomolar concentration(~nm).

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P0016 / #2177

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

A COMBINATION APPROACH OF SURFACE PLASMON RESONANCE, IMMUNOGOLD LABELING AND SCANNING ELECTRON MICROSCOPY- A MORPHOLOGICAL ANALYSIS OF APOLIPOPROTEIN E BINDING TO AB AMYLOID.

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Aims: The aim of this work is to probe the interaction between amyloid-β fibrils, associated to Alzheimer's disease, and apolipoprotein E, a well-known ligand frequently found co-deposited to the fibrillar form of Aβ in vivo.
Methods: We have applied a combinatorial strategy where surface plasmon resonance (SPR) and immunogold labeling are used followed by a direct analysis of the sensor-chip surface by scanning electron microscopy (SEM).
Results: To study the binding of ApoE to Aβ fibrils using both SPR and SEM, Aβ fibrils were immobilized and then probed with ApoE until saturation binding had been acquired. The K_D value of the interaction between fibrils and recombinant human ApoE4 was calculated 5 nM. To visualize the bound APoE to Aβ fibrils, the gold surface of the CM5-chip was imaged under scanning electron microscopy (SEM). In this setup, the non-conducting materials amyloid fibrils can be distinguished from the background by the inelastic electron scattering when the electron beam hits the sample surface at a low accelerating voltage and then introduced the low-energy secondary electrons. Therefore, the gold beads indirectly probing bound ApoE could be readily identified due to their strong electron scattering properties and easily discriminated from the background of both the gold surface of the CM5-chip and the immobilized fibrillar sample. The results display a lateral binding of ApoE along the amyloid fibrils and illustrate how the gold beads represent a good reporter of the binding.
Conclusions: This pioneering approach exposes a technique with generic features which enables both a quantitative and a morphological evaluation of a ligand-receptor based system. With further optimization the technique is in essence will apply to most setups using SPR where an ultrastructural morphology also is of interest.

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P0017 / #1990

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

DECREASED EXPRESSION OF PROTEIN O-LINKED MANNOSE B-1,2-NACETYLGLUCOSAMINYLTRANSFERASE 1 IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease. Studies have confirmed that posttranslational modifications are implicated in the pathogenesis of AD. O-mannosylation is a conserved post-translational modification. Protein O-linked mannose β1,2-N-acetylglucosaminyltransferase 1 (POMGNT1) is a glycosyltransferase crucial for the elongation of O-mannosyl glycans. Studies have shown that changes in POMGNT1 significantly affect neurological function and maybe involved in the pathogenesis of many kinds of central nervous system disorders, including neural regeneration and degeneration, even oncology. However, the role of POMGNT1 in AD has scarcely been reported. Here, we investigated whether POMGNT1 was involved in the pathology of AD.
Methods: In this study, we first used Immunohistochemical and Immunofluorescent staining to evaluate the distribution and cell-type of POMGNT1 in the central nervous system of AD mice, then assessed the expression changes of POMGNT1 in AD models and finally detected the effect of Amyloid-β on POMGNT1 expression by western bloting and RT-qPCR.
Results: In this study, we found that POMGNT1 was widely distributed in the central nervous system of AD mice, prominently in the cerebral cortex and hippocampus. Using double immunofluorescence, we detected that POMGNT1 was only expressed in the neurons but not glial cells, including astrocytes, oligodendrocytes and microglial cells. Importantly, the expression of POMGNT1 decreased not only in the AD cell models, but also in the specific subregions of AD mice brain, both cerebral cortex and hippocampus. We also found age-related decrease of POMGNT1 in normal AD mice. We further identified that Aβ1-42 downregulated the expression of POMGNT1 both in vitro and in vivo.
Conclusions: POMGNT1 and O-mannosylation might participate in the pathology of AD.

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P0018 / #2109

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

SEX DIFFERENCES IN SLEEP AND ALZHEIMER'S DISEASE PATHOLOGY IN THE APPXPS1 AND 5XFAD MOUSE MODELS

Carrie Johnson[1], Landys Guo[2], Sarah Barth[1], Valeria Buzinova[1], Samantha Padgett[1], Savannah Turton[1], Tyler Jessup[1], Leanna Mccarty[1], Lindsay Beechem[1], William Briones[1], Anjana Subramoniam[1], Isha Jogani[1], Haleigh Whitlock[1], Michael Sucharski[1], Kimberly Bosh[1], Katharina Kohler[1], Teresa Macheda[1], Adam Bachstetter[3], Sridhar Sunderam[2], Bruce O'Hara[2], Marilyn Duncan[3], Michael Murphy[1]
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Aims: Our recent studies have demonstrated correlation between sex, sleep-wake rhythm fragmentation, and risk of Alzheimer's Disease (AD). Female mice sleep less than male mice, and female APPxPS1 mice had the largest change in rebound sleep after experimentally induced sleep fragmentation (SF). We extended our study to a second model—5xFAD to investigate sex differences from SF across mouse strains.
Methods: We used APPxPS1(N= 127) and 5xFAD(N= 52) AD mouse models and wild type (WT) controls of both sexes. For 3-4 weeks, mice were exposed to SF or undisturbed sleep (US). SF consisted of 4 daily 1hr sessions of enforced wakefulness evenly interspersed throughout the light phase. Mice were kept awake with toys and stimulation with a paintbrush. PiezoSleep cages (Signal Solutions LLC) were used for sleep recordings during the first and last weeks. Amyloid pathology was measured via an ELISA.
Results: SF caused a shift in sleep from light phase (loss) to dark phase (gain) in both APPxPS1($p<0.0001$) and 5xFAD($p<0.05$) mice and WT controls. In both strains, females slept less than males($p<0.0001$), and females were the most affected by SF. The largest increase in rebound sleep was seen in APPxPS1 females($p<0.001$). Female AD mice showed greater cortex amyloid pathology than males(APPxPS1 $p<0.05$; 5xFAD $p<0.031$). SF had no effect on amyloid-beta levels in either strain.
Conclusions: The shared characteristics in females of two mouse strains –increased rebound sleep after SF and greater amyloid pathology—suggest a sex-dependent interaction between SF, AD-related mutations, and pathology. Because two-thirds of AD cases are women, understanding the driving factors for these differences is of critical importance for disease diagnosis and treatment. Funded by NIH (AG068215 and NS116824).

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P0019 / #2224

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

INVESTIGATING VARIATION IN AMYLOID BETA PATHOLOGY IN THE PRESUBICULUM OF FAMILIAL ALZHEIMER'S DISEASE CASES

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Aims: Familial Alzheimer's Disease (FAD) is caused by mutations in either the *APP* or *PSEN1* genes which affect beta-amyloid production. Beta-amyloid aggregates in Alzheimer's disease form extracellular plaques. However, in the presubiculum beta-amyloid forms a large evenly distributed deposit rather than the plaques. Our previous work has determined that the beta-amyloid present in the presubiculum has less N-terminally truncated and pyroglutamate modified species than the neighbouring entorhinal cortex. Here we characterised the beta-amyloid deposited in the presubiculum in different FAD mutations.
Methods: Immunohistochemistry was performed on hippocampal sections from post-mortem human brain from FAD cases with a collection of *PSEN1* or *APP* mutations using antibodies against: beta-amyloid [6F/3D]; beta-amyloid 1-40 and beta-amyloid 1-42 . Slides were scanned at 20x magnification on an Olympus VS120 slide scanner. The digital image was used to capture low magnification and high magnification images of the presubiculum and entorhinal cortex for each case. Images were qualitatively assessed for morphological differences.
Results: Qualitative analysis highlighted distinct differences that could be seen in beta-amyloid morphology amongst the *APP* and *PSEN1* mutations with some cases having larger diffuse deposits compared to smaller denser deposits in others. There was an absence of beta-amyloid 1-40 accumulation in the presubiculum of multiple cases.
Conclusions: We have shown that there are different pathological characteristics that can be seen in FAD cases with various *PSEN1* or *APP* mutations in the presubiculum using multiple beta-amyloid isoforms. The presence of different isoforms and differences in morphology could provide clues to whether the presubiculum has neuroprotective effects. A greater understanding of the beta-amyloid peptides present may provide a greater understanding of the disease mechanisms in FAD.

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P0020 / #944

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

SPIN90 DEFICIENCY AMELIORATES AMYLOID B ACCUMULATION BY REGULATING APP TRAFFICKING IN AD MODEL MICE

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Aims: Alzheimer's disease (AD), a common form of dementia, is caused in part by the aggregation and accumulation in the brain of amyloid β (Aβ), a product of the proteolytic cleavage of amyloid precursor protein (APP) in endosomes. Trafficking of APP, such as surface-intracellular recycling, is an early critical step required for Aβ generation. Less is known, however, about the molecular mechanism regulating APP trafficking. In this study, we investigated the correlation of APP trafficking with SPIN90, along with Rab11, Aβ accumulation, and synaptic functionality.
Methods: - Animals : 5xFAD + SPIN90 KO mice - Antibodies and Reagents : various antibodies - Plasmids and transfection : pH-APP, vG-pH, RFP-Rab11 etc - Immunohistochemistry and immunocytochemistry - Cell culture and primary neuron culture - Protein-protein interaction assays and western blotting - Live-cell imaging for synapse physiology - Image analysis : Image J, Origin program
Results: Brain Aβ deposition was lower in the progeny of 5xFAD-SPIN90KO than in 5xFAD-SPIN90WT mice. Analysis of APP distribution and trafficking showed that the surface fraction of APP was locally distinct in axons and dendrites, with these distributions differing significantly in 5xFAD-SPIN90WT and 5xFAD-SPIN90KO mice, and neural activity-driven APP trafficking to the surface and intracellular recycling were more actively mobilized in 5xFAD-SPIN90KO neurons. In addition, SPIN90 was found to be cotrafficked with APP via axons, with ablation of SPIN90 reducing the internal accumulation of APP in axons. Finally, synaptic transmission was restored over time in 5xFAD-SPIN90KO, but not in 5xFAD-SPIN90WT, neurons
Conclusions: SPIN90 is implicated in Aβ production by regulating APP trafficking.

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P0021 / #2188

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

EARLY CO-LOCALISATION OF PHOSPHO-TAU AND BETA AMYLOID PATHOLOGY IN PROGRESSION OF ALZHEIMER'S DISEASE

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Aims: Amyloid cascade hypothesis states that Aβ and its aggregates induce pathological changes in Tau, leading to formation of NFTs and cell death. A caveat with this is the temporo-spatial divide between appearance of plaques and NFTs in spatially distinct brain regions. Existence of pre-aggregate tau and Aβ forms is well reported, raising the possibility that soluble intracellular Aβ may drive tau pathology. We explored the possibility of co-localisation of soluble forms of Aβ & Tau, in frontal cortex, which may precede the occurrence of plaques and NFTs.
Methods: Standard dot-blot immunoassays were performed on white and grey matter frozen brain tissue (Brodmann-area 8/9) from 52 cases (17 AD and 35 healthy-aged-controls). Blots were stained with primary antibodies towards HPT (CP-13, AT-8 and PHF-1), total Tau (AT5), Aβ (MOAB-2) and visualised via standard chemiluminescence. Quantification of AT-8 HPT and Aβ (4G8 antibody) plaque burden was assessed via immunohistochemical (IHC) staining within the contralateral fixed brain tissue of the same cases as was the quantification of intracellular Aβ (MOAB-2) and AT-8 HPT burden.
Results: Immunoreactivity quantification of phospho-tau and Aβ showed that all markers were significantly elevated in AD cases. In controls, all markers increased with progression of Braak stages. Positive coorelation between HPT markers (AT-8 and MC1) and Aβ was revealed. Quantification of AT-8-HPT and Aβ-plaques with IHC, failed to show a significant correlation when considered in controls or AD-cases only. Preliminary data suggest that IHC based positive correlations between HPT and Aβ are only observed when measuring intracellular Aβ.
Conclusions: The data suggests that HPT and Aβ co-occur early in disease, which are not driven by Aβ-plaque deposition & are likely caused by elevation of soluble intracellular Aβ. This study supports modified amyloid-Cascade hypothesis.

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P0022 / #1131

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

CHARACTERIZATION OF AMYLOID-BETA STRAINS FROM SWEDISH AND ARCTIC ALZHEIMER'S DISEASE IN MICE

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Aims: Alzheimer's disease (AD) is characterized by the aggregation of amyloid-beta (Aβ) peptides and tau into amyloid plaques and neurofibrillary tangles, respectively. Conformational variants of Aβ with distinct biochemical properties, or strains, may contribute to the clinical heterogeneity observed in AD. Unlike the transgenic mouse models used in previous Aβ strain studies, *App*$^{NL-F}$ knock-in mice express physiological levels of APP and predominantly produce $Aβ_{42}$. The objective of this study was to determine if the Swedish and Arctic APP mutations give rise to distinct Aβ strains that produce unique phenotypes in *App*$^{NL-F}$ knock-in mice.
Methods: Aβ aggregates were purified from Swedish and Arctic AD brains, in addition to an age-matched control case, using density centrifugation and a protease digestion. 6-week old *App*$^{NL-F}$ knock-in mice were injected with the purified material and the mice were euthanized after 6 months. The induced cerebral Aβ pathology was analyzed through immunohistochemistry and biochemical experiments.
Results: The Swedish and Arctic Aβ-inoculated mice showed higher levels of $Aβ_{42}$ and protease-resistant Aβ aggregates than control-inoculated mice. Despite their similar $Aβ_{42}$ levels, the Swedish Aβ-inoculated mice had higher levels of protease-resistant Aβ than the Arctic Aβ-inoculated mice. The mice also exhibited differences in their neuropathology, including the morphology and localization of their induced Aβ deposits.
Conclusions: These results suggest that Swedish and Arctic AD template the formation of distinct Aβ strains in *App*$^{NL-F}$ knock-in mice. Characterizing the distinct Aβ aggregates involved in different types of AD could lead to more targeted and effective therapeutics.

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P0023 / #680

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

AN ASSOCIATION OF CSF APOLIPOPROTEIN E GLYCOSYLATION AND AMYLOID-BETA 42 IN INDIVIDUALS WHO CARRY THE APOE4 ALLELE

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Aims: Carrying the Apolipoprotein E (apoE) e4 allele is associated with an increased risk of cerebral amyloidosis, but the degree to which apoE glycosylation affects its development is not clear. In a previous pilot study, we identified distinct total and secondary isoform-specific cerebral spinal fluid (CSF) apoE glycosylation profiles, with the apoE4 isoform having the lowest glycosylation percentage (E2>E3>E4).
Methods: In this work, we extend the analysis to a larger cohort of individuals (n=106), utilizing matched plasma and CSF samples with clinical measures of AD biomarkers. Total glycosylation and ApoE isoform-specific glycosylation were analyzed using a new mass spectrometric immunoassay that simultaneously detects the apoE isoforms and glycoforms (O-linked GalNAc(-Sia)-Gal-Sia, and various combinations thereof).
Results: The results confirm the isoform-specific glycosylation of apoE in CSF, resulting from secondary CSF apoE glycosylation patterns. CSF apoE glycosylation percentages positively correlated with CSF $A\beta_{42}$ levels ($r = 0.53$, $p < 0.0001$). These correlations were not observed for plasma apoE glycosylation.
Conclusions: CSF glycosylation is lower in the apoE4 isoform and in patients with cerebral amyloidosis, and it correlates with markers of AD pathology. These results indicate that apoE glycosylation has a new and important role in influencing brain Aβ metabolism and can be a potential target of treatment.

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P0025 / #1618

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

CELLULAR UPTAKE OF IN VITRO FORMED BETA AMYLOID STRAINS IS DEPENDENT OF AGGREGATE SIZE

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Aims: Objectives: It has been shown that different forms of Beta Amyloid (Aβ) aggregates have different properties in biophysical experiments as well as in pathophysiology. This could explain differences in disease severity between patients. In this project we generate and characterize strains of beta amyloid and investigate the interactions with neuron like cell lines.
Methods: Methods: Generation of different strains was done by incubating beta amyloid 40 and 42 at different ratios, different incubation times (young and mature) and sonication treatments. Characterization of the aggregates are done by fluorescents emission profiling using amyloid ligands, nano tracking analysis and transmission electron microscopy. The aggregates interaction with SHSY-5Y cells differentiated to a neuron-like state is investigated by toxicity, uptake imaging analysis and the ability of the cells to degrade the aggregates.
Results: Results: Different ratios of beta amyloid 40:42 resulted in biophysically different strains. More mature aggregates were more stable and withstood sonication treatment better. Large mature aggregates appear on/close to the cell surface when added to differentiated SHSY-5Y cells, no evidence of uptake was found. However, after extensive sonication mature aggregates were taken up by cells in a strain dependent manner.
Conclusions: Conclusions: Different beta amyloid strains can be formed *in vitro*. When forming large mature aggregates they do not easily break in to smaller fragments. This makes them relatively inert as they are not taken up by the cells thereby leaving them less toxic than the smaller aggregates. However, when broken apart into small aggregates the different strains are taken up in a strain dependent manner.

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P0026 / #1395

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

UNDERSTANDING THE ROLE OF EXTRACELLULAR VESICLES IN THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

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Aims: Extracellular vesicles (EVs) are excellent cargo vehicles for cell-to-cell communication and have been related to crucial brain functions, such as myelin maintenance and neurotransmission. Whereas cellular prion protein (PrP^C) is a Glycosylphosphatidylinositol-anchored glycoprotein with highest expression in the nervous and the immune system. It is also abundantly present on surface of the extracellular vesicles (EVs). In Alzheimer's disease (AD), EV-associated PrP^C, along with other extracellularly released PrP^C fragments is suggested to sequesters Aβ oligomers (Aβo) hence reducing the Aβo neurotoxicity, however formal evidence is still lacking. Here, we aim to study further the role of Neuro 2a- and human brain-derived EVs in Aβ fibrillization and in other pathophysiological aspects of AD.
Methods: PrP^C-expressing (WT) and -deficient (KO) EVs were obtained from WT and PrP^C-KO Neuro-2a (N2a) cells, respectively. Moreover, EVs were isolated from frontal cortex of AD patients and age-matched controls by employing a novel protocol. EVs were characterized using Nanoparticle tracking analysis (NTA), immunoblotting, and electron microscopy (cryo-EM and negative stain TEM). To further the study objectives, small angle X-ray scattering (SAXS), super-resolution microscopy (SRM), Cryo-EM, proteomic and lipidomic profiling, and associative biochemical and biophysical methods were employed.
Results: SAXS studies along with SRM and aggregation assays showed potent Aβo-sequestering properties of the N2a-derived WT-EVs, compared to KO-EVs. Lipidomic and proteomic profiling of N2a-derived WT- and KO-EVs pointed towards marked compositional differences (i.e., higher abundance of certain kinases, RNA- and DNA-binding proteins in KO-EVs). EV subpopulations also showed alterations in PrP^C expression specific to AD stages. 'Omics' studies from human brain-derived EVs are underway and will help us to better understand the neuroprotective role of EV-PrP on AD.
Conclusions: The study highlights involvement of PrP^C-expressing EVs in Aβ aggregation-rescue mechanism against Aβo toxicity, and in AD-specific EV-mediated intercellular communication.

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P0028 / #776

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

AN INVESTIGATION OF AMYLOID BETA AND TAU AGGREGATES IN POST-MORTEM HUMAN BRAIN TISSUE OF ALZHEIMER'S DISEASE PATIENTS USING CORRELATIVE LIGHT AND ELECTRON MICROSCOPY

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Aims: Alzheimer's disease (AD) is a devastating neurodegenerative disease affecting tens of millions of people worldwide. Two major neuropathological hallmarks of AD are the aggregation of the proteins amyloid beta (Aβ) into plaques and hyperphosphorylated tau into neurofibrillary tangles (NFTs). However, their formation and how they interact with their environment remains elusive. Here, we use correlative light and electron microscopy (CLEM) to investigate the structural components of Aβ and tau aggregation in the human, post-mortem brain of AD patients.
Methods: Post-mortem human brain tissue from AD donors was collected for CLEM. We perform immuno-fluorescence microscopy with multi-color labelling on free-floating 60 µm brain sections to identify pathological aggregates and different cell types such as neurons, microglia and astrocytes. The sections were then stained and resin-embedded for EM. Ultrathin (80-200 nm) sections containing the regions of interest were cut and analyzed by transmission EM.
Results: We identified antibodies that allow labelling of Aβ plaques and tau tangles without using antigen retrieval methods, which are detrimental to the tissue's ultrastructure. We established a pipeline in which we can identify the pathology of interest using 3D confocal laserscanning microscopy, and correlate this directly with the ultrastructure by electron microscopy. We observed diffuse, classical and vascular Aβ plaques which are currently studied to unravel the structural components at nanoscale.
Conclusions: We will characterize the ultrastructure of different stages of Aβ plaques and tau tangles, using CLEM and also serial block face scanning electron microscopy of individual plaques. This will allow us to gain insight into the 3D ultrastructural architecture of these aggregates.

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P0029 / #2286

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

TREATMENT OF APP X PS1 MUTANT KNOCK-IN MICE WITH THE GAMMA-SECRETASE INHIBITOR SEMAGACESTAT ALTERS SEX-RELATED SLEEP DIFFERENCES

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Aims: Loss of sleep or sleep pattern fragmentation has long been associated with an elevated risk for Alzheimer's disease (AD). Our lab recently documented differences in sleep patterns in several AD-related mouse lines, along with the observation that female mice sleep less than males, and may also be more vulnerable to the consequences of sleep disruption. We observed that these differences were particularly striking in a mutant APPxPS1 knock-in line, and were present starting at an age at which the amount of amyloid pathology was barely detectable. In this study we tested the hypothesis that this effect may be related to the function of gamma-secretase by treating these mice with the gamma-secretase inhibitor Semagacestat.
Methods: We treated male and female (n = 48) APPxPS1 knock-in (KI) mice once / day with 12.5 mg/kg of Semagacestat (LY-450139), suspended in 0.5% hypromellose, by gavage, for 28 days. Semagacestat was recently explored as a possible AD therapeutic in phase III clinical trials. Control mice received vehicle only. Sleep was recorded using the PiezoSleep system for the final 10 days of treatment, which included a 5 day period of manual sleep framentation, as recently described (Duncan et al, Neuroscience, 481: 111-122, 2022). At the end of the study, brains were collected for analyses by ELISA, immunoblot, and RT-PCR.
Results: Female APPxPS1 mice are significantly more wakeful than males, an effect that is observed in both the light and dark phases of their daily activity cycle. Treatment with Semagacestat resulted in a reversal of this effect (p=0.02) where the males became significantly more wakeful throughout the day.
Conclusions: These results suggest that pharmacological inhibition of gamma-secretase may result in sex-dependent changes in daily sleep. Funding provided by NIH (AG068215).

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P0030 / #786

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

MODELING ALZHEIMER'S DISEASE-DOWN SYNDROME IN DROSOPHILA

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Aims: Down Syndrome (DS) is the most common genetic cause of early onset Alzheimer's disease (EOAD). Triplication of *APP* in DS significantly contributes to AD development in these individuals. However, how triplication of other human chromosome 21 (Hsa21) genes affects AD risk, in people with DS, is not well understood. We aim to identify which human Hsa21 genes, when expressed at higher levels in people with DS, modulate Aß accumulation and cognitive decline.
Methods: *Drosophila melanogaster* are used as a screening tool by crossing flies that conditionally express $Aß_{1-42}$ in adult neurons with those that overexpress a Hsa21 orthologue. A negative geotaxis assay is used to assess whether neuromotor function of Aß expressing flies is modulated by overexpression of a Hsa21 orthologue. Secondly, quantification of $Aß_{1-42}$ levels is determined by ELISA. Modifiers of Aß aggregation or toxicity in the fly will be examined in human post-mortem brain tissue, to determine whether and where their expression is increased in people who had ADDS compared with EOAD alone and age and sex matched healthy euploid individuals.
Results: An initial screen has identified nine Hsa21 candidate genes that either modify $Aß_{1-42}$ levels or affect neuromotor function in the presence of raised $Aß_{1-42}$. Higher levels of *Usp47* (*USP25*), *ATPsynCF6* (*ATP5J*), *SKIP* (*SAMSN1*), *mnb* (*DYRK1A*), *Sb* (*TMPRSS2*) or *Hcs* (*HLCS*) were found to modulate the climbing phenotype of Aß expressing flies with age, whereas overexpressing *Nnp-1* (*RRP1B*), *Plp* (*PCNT*) or *Sod1* (*SOD1*) modified $Aß_{1-42}$ levels.
Conclusions: Overexpression of some Hsa21 fly orthologues can modify $Aß_{1-42}$ accumulation while others can modulate associated neuromotor function decline independently of changed $Aß_{1-42}$ levels. This suggests that increased expression of Hsa21 orthologues can affect Aß toxicity in the fly downstream of Aß accumulation.

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P0031 / #1796

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

AMYLOID BETA ACCUMULATION IN CYSTATHIONINE B-SYNTHASE-DEFICIENCY IS MEDIATED BY HOMOCYSTEINE METABOLITES-INDUCED DOWNREGULATION OF PHF8 DEMETHYLASE AND INCREASED MTOR PROMOTER OCCUPANCY BY HISTONE MARK H4K20ME1

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Aims: Cystathionine β-synthase (CBS) deficiency and the loss of histone-demethylase Phf8, which maintains homeostasis of mTOR signaling by demethylating H4K20me1, cause neuropathy in humans and mice. Our aim was to examine a role of Phf8 in neuropathy of CBS deficiency.
Methods: We studied transgenic *Tg-I278T Cbs*$^{-/-}$ C57BL/6J mice harboring human *CBS I278T* (*Tg-I278T*) variant and transgenic mouse neuroblastoma N2A-APP$_{swe}$ cells harboring human APP with K670N/M671L Swedish mutations. To recapitulate the CBS-deficiency phenotype ex vivo, cells were transfected with siRNAs targeting *CBS* or *Phf8* genes, or treated with homocysteine (Hcy, CBS substrate) and its metabolites. Proteins were quantified by Western blotting. Amyloid β (Aβ) was quantified by confocal microscopy using anti-Aβ antibody. mTOR promoter occupancy by H4K20me1 was quantified using chromatin immunoprecipitation (CHIP) assay.
Results: In brains of 1-year-old *Tg-I278T CBS*$^{-/-}$ mice, Phf8 levels were significantly reduced vs. *Tg-I278T CBS*$^{+/-}$ sibling controls while H4K20me1 was significantly elevated. Autophagy markers Bcln1 and Atg7 were downregulated while p62 was upregulated in *Tg-I278T CBS*$^{-/-}$ mice, indicating impaired autophagy. Similar results were obtained in 9-week-old mice. In N2A-APP$_{swe}$ cells, *CBS* gene silencing significantly reduced Phf8 levels and increased total H4K20me1 as well as the mTOR promoter occupancy by H4K20me1. This led to mTOR upregulation, autophagy downregulation, and significantly increased Aβ levels. The *Phf8* gene silencing also increased Aβ levels. Treatments of N2A-APP$_{swe}$ cells with Hcy, Hcy-thioacetone, or *N*-Hcy-protein (metabolites that are elevated in CBS deficiency) produced similar outcomes: attenuated Phf8, increased H4K20me1 and the mTOR promoter occupancy by H4K20me1, mTOR upregulation, autophagy downregulation, and increased accumulation of Aβ.
Conclusions: Neuropathy in CBS deficiency is caused by Hcy-metabolites-induced attenuated Phf8 expression, which increases mTOR promoter occupancy by H4K20me1, ultimately leading to Aβ accumulation.

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P0032 / #1645

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

PROBING THE IMPACT OF PLAQUE MATURATION ON LOCAL GENE EXPRESSION

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Aims: Research into the impact of plaque heterogeneity is mostly unexplored due to technical limitations of temporal imaging and gene expression analysis. We have developed a multimodal approach combining advances in mass spectrometry imaging with spatial transcriptomics to explore how plaque age correlates with transcriptional changes in the microenvironment of individual plaques. Furthermore, plaque-associated transcriptomic changes due to mouse age are often a result of increased plaque density. To overcome this problem, we assessed transcriptomic changes around individual plaques at two ages of differing plaque loads.
Methods: Fresh frozen sections were prepared from 10- and 18-month-old *App*$^{NL\text{-}F/NL\text{-}F}$ knock-in mice that had previously been metabolically labelled with a stable isotope-rich diet during the period of initial plaque deposition (6-10 months). In one section, mass spectrometry imaging was used to assess the temporal deposition of plaques by measuring the enrichment of the stable isotope within the Abeta peptides. In the consecutive section, the same individual plaques were identified and analysed using spatial transcriptomics (Nanostring) to assess gene expression in the plaque's immediate vicinity.
Results: Correlating plaque age with expression revealed 343 genes that were significantly correlated with plaque age. Interestingly, positively correlated genes were enriched in mitochondrial modules and genes negatively correlated were associated with neuronal and dendritic spine compartments. Furthermore, by comparing plaque-induced transcriptomic changes in 10- and 18-month-old mice, we found that complement and immune-associated genes increase in expression at individual plaques due to mouse age.
Conclusions: We introduce a novel method of mass spectrometry imaging combined with spatial transcriptomics to assess the impact of plaque age vs mouse age on gene expression. This revealed an association of mitochondrial and synaptic genes with increased plaque age and immune and complement genes with mouse age.

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P0033 / #2584

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

RECAPITULATING THE ADULT ENTORHINAL-HIPPOCAMPAL LOOP IN VITRO TO STUDY EARLY ALZHEIMER'S DISEASE NEUROPATHOLOGY

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Aims: Alzheimer's disease (AD) is a progressive and ultimately fatal disease resulting in memory loss and cognitive impairment. The entorhinal-hippocampal loop, supporting long-term memory, is affected early in the disease process. Among the first neurons to degenerate are reelin positive entorhinal cortex layer II (Re+ ECLII) neurons, which provide a main projection to the hippocampus. Here, we microdissect and culture *adult* rodent Re+ ECLII-neurons, hippocampal DG granular neurons-, CA3 pyramidal neurons-, and CA1 pyramidal neurons from the adult APP/PS1 mouse model.
Methods: We culture each neuronal population in separate chambers of a custom-designed microfluidic microelectrode array (MEA) interface.
Results: The chambers are connected by unidirectional microchannels permissible to neurites, thus enabling the establishment of an anatomically relevant multi-nodal microcircuit with controllable connectivity. In this way, we aim recapitulate the entorhinal-hippocampal loop in an *in vitro* microcircuit. Our preliminary findings indicate that the derived *in vitro* microcircuits become spontaneous active within two weeks, and remain viable for beyond 2 months.
Conclusions: This work may help forward the study the initial AD-related neuropathological changes, and how these changes affect dynamic structure-function relationships within- and between the interconnected neuronal nodes and on the microcircuit as a whole.

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P0034 / #1264

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

NANOSCALE IMAGING OF PT217-TAU IN AGED RHESUS MACAQUE: TRANS-SYNAPTIC PROPAGATION AND SEEDING OF TAU PATHOLOGY IN ENTORHINAL CORTEX

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Aims: Tau pathology in AD propagates from vulnerable entorhinal cortex (ERC) to "seed" pathology throughout the neuronal network. Recent discoveries indicate that tau phosphorylated at threonine-217 (pT217-tau) can be captured in CSF and plasma as an early biomarker. However, role of pT217-tau in tau pathology is unknown, especially as soluble tau species are dephosphorylated postmortem in humans. Rhesus macaques develop the same *qualitative* pattern and sequence of tau/amyloid pathology, with neurofibrillary tangles identical to human AD. We examined the ultrastructural localization of pT217-tau in layer II ERC using perfusion-fixed aged rhesus macaques that preserves phosphorylation state, focusing on potential evidence of propagation between neurons, and exposure to extracellular space.
Methods: We used immunohistochemistry paired with high spatial-resolution immunoelectron microscopy (immunoEM) in aged rhesus macaques (18-31 years) to localize pT217-tau in the stellate cell islands in ERC layer II, which show the earliest signatures of tau pathology in AD.
Results: pT217-tau immunolabeling was predominantly observed in postsynaptic compartments in macaque ERC layer II. pT217-tau accumulated on the calcium-storing smooth endoplasmic reticulum spine apparatus near axospinous asymmetric glutamatergic synapses in dendritic spines. We observed extensive, trans-synaptic pT217-tau trafficking between interconnected neurons within omega-shaped bodies in ERC layer II, specifically near excitatory, but not inhibitory synapses. Within dendritic shafts, pT217-tau aggregated on microtubules often in concordance with autophagic vacuoles indicative of neurite dystrophy.
Conclusions: pT217-tau accumulates in ERC layer II subcompartments known to be the earliest to show pathology in humans. The data provide the first evidence of pT217-tau trafficking between neurons to "seed" tau pathology in higher brain circuits, potentially interfacing with the extracellular space to become readily accessible and captured in CSF and blood as a robust AD biomarker, potentially guiding earlier intervention of therapeutics.

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P0035 / #1093

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

INVOLVEMENT OF THE CELLULAR PRION PROTEIN (PRPC) IN THE RELEASE OF OLIGOMERIC AMYLOID BETA VIA EXOSOMES

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Aims: Oligomeric amyloid beta (oAβ) has been shown to spread between cells via small extracellular vesicles known as exosomes, believed to be crucial for the progression of Alzheimer's disease. Exosomes are generated by two main biogenesis pathways: Endosomal sorting complexes required for transport (ESCRT)-dependent and ESCRT-independent. Aβ can bind to exosomes via prion protein (PrP^C) which is known to be released via the ESCRT-independent pathway. In contrast, the toxic version of PrP (PrP^{Sc}) utilizes the ESCRT-dependent pathway. Given this disparity, we wanted to investigate, the still unknown, exosomal pathway that oAβ utilizes and explore its relationship to PrP^C.
Methods: To study the involvement of PrP^C in the cellular release of oAβ via exosomes, we overexpressed or deleted PrP^C using CRISPR/Cas9 technology in the N2a murine cell line. Cells were then treated with oAβ in the presence or absence of specific exosome biogenesis inhibitors: GW4869 (ESCRT-independent inhibitor) and Manumycin A (ESCRT-dependent inhibitor). oAβ content as well as exosome biogenesis proteins and mRNA were then evaluated.
Results: Our data shows that GW4869 treated cells contain increased levels of oAβ compared to control or Manumycin A treated N2a cells. In addition, lower oAβ levels within the cell medium were also observed indicating a decrease in the re-release of oAβ. Intriguingly, both knockout and overexpression of PrP^C affected several exosome biogenesis-related proteins differently. We also observed, for the first time, that the exosome biogenesis inhibitors had a diminishing effect on the PrP^C mRNA expression.
Conclusions: In contrast to toxic PrP^{Sc}, the release of oAβ through exosomes primarily utilize the ESCRT-independent pathway. Notably, although PrP^C levels affect the expression of several exosome biogenesis-related proteins, our preliminary results indicate no direct impact on oAβ release.

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P0036 / #2258

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

DESIGN OPTIMIZATION OF TAU REPEAT-DOMAIN PROBE ALLOWS DETECTION OF BIOACTIVE TAU IN-SITU IN SYNAPSES AND ASTROCYTES OF ALZHEIMER'S DISEASE BRAIN TISSUES.

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Aims: Prion-like properties of tau protein are a major mechanism in the pathophysiology of tauopathies. Tau seeding bioactivity is usually quantified using a "biosensor" cell line that expresses tau repeat-domain fused to complementary fluorescent proteins. Although this assay is specific/sensitive for quantification of bioactive tau, it is not discriminating for its cellular localization. Recently, we tested the hypothesis that rational design of tau probes aligning the sequence of the probe with amino acid sequence incorporated in the central core of Tau aggregates observed by cryo-EM described in Alzheimer disease (AD) brains could improve the assay's sensitivity. Taking advantage of this design, we aimed to develop a technique that would allow to localize bioactive tau directly on tissue.
Methods: We applied a recombinant Tau fragment with N-terminal Myc-tag on frozen human brain tissue sections, performed immunostaining with Myc, GFAP, Iba1 and synapsin1 antibodies, and imaged the slides with confocal and super-resolution microscopy.
Results: We found that our new tau probes were recruited on AD tissues and that they bound specifically to bioactive tau not only in neurofibrillary tangles, dystrophic neurites and neuritic plaques but also in astrocytes and synapses. In addition, incubation of AD brain sections with formic acid inhibited the recruitment of the probe. Lastly, we did not observe positive staining with the probe on brains from control brains, progressive supranuclear palsy, corticobasal degeneration and Pick disease patients, overall suggesting that the probe detects a unique conformation of tau present in AD tissues only.
Conclusions: Our technique enables to specifically detect AD bioactive tau directly on tissue sections and suggests the presence of bioactive tau in synapses and astrocytes in AD brains.

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P0037 / #483

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

FERRIC AMMONIUM CITRATE MODULTES EXOSOMES SECRETION IN PC12 CELLS

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Aims: Alpha-synuclein (α-syn) pathology plays a central role in Parkinson's disease pathogenesis. It is noteworthy that high levels of iron are present in Lewy bodies of PD postmortem patients, as well as in the substantia nigra (SN) of early stages of PD patients. Previous studies reported that there are close relationships between α-synuclein aggregation and iron deposition in neurons. Although transmission of α-syn between cells is believed to be major driver with α-syn pathology and neurodegeneration, whether and how iron deposition affects α-syn release, especially in an exosomal enriched form, remains unclear.
Methods: Nanoparticle tracking analysis and western blotting were applied.
Results: In this work, we show that ferric ammonium citrate (FAC), an iron overloaded reagent, promotes the expression and aggregation of α-syn in PC12 cells with WT hαsyn or A53T hαsyn over-expression. Although ferroptosis inhibitor ferrostatin-1 could not block iron-induced up-regulation of intracellular α-syn, ferroptosis inducer erastin could further up-regulate α-syn protein levels. The number of exosomes released from FAC treated PC 12 cells is reduced as indicated by nanoparticle tracking analysis, regardless of α-syn overexpression or not. The protein levels of alix and flotillin-1, both exosome specific makers, are decreased in exosome-enriched extracts, supporting that iron deposition diminishes the release of exosomes into culture media. We then observed the protein levels of Rab7, Rab 11 and Rab 35 are unchanged in PC12 cells with or without α-syn overexpression, so we speculate that Rab protein might not be involved in the inhibition of exosome release by iron..
Conclusions: Together, these data suggest that iron deposition promotes α-syn expression and aggregation, while inhibits exosome secretion in PC12 cells.

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P0038 / #232

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

NEUROINFLAMMATION IS A PRIME INITIATOR OF NEURODEGENERATION IN NEURODEGENERATIVE DISEASES.

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Aims: The research identified that the aggregation of protein in neurodegenerative diseases induces immunological responses due to the activation of microglia. The activated microglia produces proinflammatory cytokines and other proinflammators which are responsible for neurodegeneration; invariably, the arrest of the immunological responses could attenuate the progression of the disease.
Methods: Literatures and research addressing the biology of microglia, neurodegeneration, neuroinflammation and protein chemistry in Parkinson's and Alzheimer's Diseases were reviewed in order to assert the connections, gaps and missing links in the biological mechanisms and processes involved in diseases' pathophysiologies.
Results: The neuronal cytoplasmic protein aggregation is majorly connected to neuroinflammation, a process triggered by several biological mechanism and environmental exposures, ranging from air pollution, autoimmunity, aging, systemic toxic metabolism, microbial infections, type 2 diabetes mellitus, atherosclerosis, hypercholesterolemia, obesity, traumatic brain injury and spinal cord injuries. The immunological sentinel of the central nervous system, microglia, in response to these assaults and several pathological attacks, triggers inflammatory reactions in order to protect the brain. However, imbalances in the production of several substances, including cytokines, like interleukin 1&6, tumor necrosis factor-alpha and other proinflammatory biomarkers could trigger some organelles in the neurons, like mitochondria, thereby, initiating compromised bioenergetics in the neuron leading to cell death.
Conclusions: Therefore, understanding the biopathological pathways and interception of proinflammatory responses and/or modifications of microglia activation could intercept the progression of neurodegeneration, hence, mitigate cell loss in neurodegenerative diseases

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P0039 / #519

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

OMEGA-3 FATTY ACID EPA SUPPLEMENTATION RESTORES GUT MICROBIOTA BALANCE IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Neuroinflammation is a major hallmark of Alzheimer's disease (AD) enhanced by inflammatory stimuli of a disturbed balance in the gut microbiota via the gut-brain axis. Dietary polyunsaturated fatty acids (PUFAs) have a high potential to modulate the gut microbiota. The omega-3 PUFA eicosapentaenoic acid (EPA) is metabolized much faster than docosahexaenoic acid (DHA) to lipid mediators with anti-inflammatory effects. Moreover, EPA competes for the same enzymes as arachidonic acid (AA). Thus, promoting EPA metabolism may inhibit the formation of pro-inflammatory omega-6 eicosanoids derived from AA. In this study, we investigate if supplementation with a high dose of EPA and a high EPA/DHA ratio (10:1) reduces neuroinflammation and attenuates gut dysbiosis in the APP-PS1 mouse model.
Methods: APP-PS1 mice (RRID: MMRRC_034829-JAX) and non-transgenic littermates (WT), 13-14 months old, were fed a diet supplemented with 0.3% EPA or control chow for 3 weeks. The hippocampus and blood plasma was used for quantification of eicosanoids. Fecal pellets were analyzed for gut microbiota composition.
Results: APP-PS1 mice had higher hippocampal levels of proinflammatory eicosanoids (e.g. 5-HETE, PGD2) than WT mice. Unexpectedly, WT animals had higher blood levels of 5-HETE. Supplementation with EPA had no effect on brain eicosanoids, but it significantly reduced 5-HETE blood levels in WT mice. Microbiome analysis revealed elevated abundance of Bacteroidetes in the APP-PS1 mice, indicating genotype specific gut microbiota dysbiosis. EPA supplementation decreased the percentage of Bacteroidetes and increased bacteria of the phyla Firmicutes in APP-PS1 and WT mice. The ratio of Firmicutes to Bacteroidetes, which is known to decline in ageing and AD, was significantly increased by EPA-diet.
Conclusions: Short-term EPA supplementation counteracts gut microbiota dysbiosis in the APP-PS1 mouse model, but has no major impact on hippocampal eicosanoid levels.

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P0040 / #1928

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

EFFECT OF MYOCARDIAL INFARCTION IN THE INTERACTION BETWEEN COGNITIVE DYSFUNCTION ON OVERALL MORTALITY

Sri Banerjee
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Aims: Cardiovascular disease (CVD) remains the number one cause of mortality within the United States. Myocardial Infarction is common among CVD individuals which previously has been connected to CVD. The development of this condition on overall mortality among individuals with cognitive dysfunction.
Methods: In the National Health and Nutrition Survey, we used population-based cohort study of 1999-2002 National Health and Nutrition Examination Surveys with mortality data obtained through 2015. Adults aged 60 years or older were assessed for cognitive skills using Digit Symbol Substitution Test (DSST). Outcomes of all-cause mortality were evaluated using Cox regression to test for effect modification in individuals who have experienced a myocardial infarction.
Results: Percent of deaths from low cognitive function among the population (N=1,325) were higher among certain groups than the general population. The mean follow-up was 11.2 years. For all-cause mortality, the overall unadjusted hazard ratio (HR) of low cognitive dysfunction had a hazard ratio of 3.11 (95% confidence interval [CI], 1.95-4.96, $p < 0.001$). Adjusted HR was elevated, 2.69 (CI 1.52-4.76, $p = 0.001$), among male individuals with myocardial infarction (MI but closer to 1.0 (1.82 CI 1.42-2.34, $p < 0.001$) among male individuals without MI, after controlling for medical (obesity, congestive heart failure, and chronic heart disease) and demographic risk factors (age). The same model did not hold true for females who experienced an MI
Conclusions: Cardiovascular disease continues to be a problem as our study especially in conjunction with cognitive dysfunction. However, this differential effect was only found in males and did not exist among females. We found that males were more susceptive to the effect modification of myocardial infarction causing overall mortality than the general population.

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P0041 / #2076

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

CEREBROSPINAL FLUID STREM-2, GFAP AND B-S100 IN SYMPTOMATIC SPORADIC AD: MICROGLIAL, ASTROCYTIC AND APOE CONTRIBUTIONS ALONG THE ALZHEIMER'S CONTINUUM

Chiara Giuseppina Bonomi[1], Martina Assogna[2], Martina Gaia Di Donna[1], Nicola Biagio Mercuri[3], Giacomo Koch[2], Alessandro Martorana[1], Caterina Motta[1]
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Aims: Many transversal mechanisms act synergistically at different time-points in the biological cascade of Alzheimer's Disease (AD), since amyloid (Aβ) deposition, tau-pathology, neuroinflammation and astrogliosis influence each other. We explored non-neuronal contributions – Apolipoprotein E (*APOE*), microglia and astrocytes – in patients with symptomatic sporadic AD stratified according to the ATN system and *APOE*.
Methods: We compared the CSF levels of sTREM-2 and markers of astrocytic activation (GFAP and β-S100) from 71 patients with AD (23 A+T-,48 A+T+; 30 *APOE* ε4, 31 *APOE* ε4) and 14 healthy controls (HC). Then, we performed multivariate regressions and correlation analyses to investigate associations between glial biomarkers, CSF Aβ42 and p-tau in all subgroups.
Results: CSF sTREM-2 was higher in A+T- and A+T+ than in HC ($p<.001$), regardless of *APOE* genotype; CSF GFAP and β-S100 were comparable across groups [see Fig.1]. Considering all patients, sTREM-2 positively associated with Aβ42 ($p=.04$) and p-tau ($=.016$), with the first being retrievable only in the A+T- subgroup ($p=.023$). GFAP positively associated with Aβ42 in all patients ($p=.020$) and in the A+T+ subgroup ($p=.04$). Stratifying by *APOE*, a positive association of sTREM-2 and p-tau was confirmed selectively in carriers of ε4 ($p=.018$). Finally, CSF sTREM-2 positively correlated with β-S100 in all subgroups, and with GFAP in A+T+ ($p=.042$).
Conclusions: Our results confirm the increase of CSF sTREM-2 in AD, which associates with less pathological levels of Aβ42 in A+T-, but not when tauopathy sets in. Moreover, in our cohort, CSF tau levels seem to be influenced by microglia in carriers of *APOE* ε4. Finally, microglial-mediated inflammation is associated with astrocytic reactivity (GFAP) in A+T+, and with the acquisition of a more neurotoxic astrocytic phenotype (β-S100).

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P0042 / #906

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

TLR9 SIGNALING REDUCING INFLAMMATION AND PROMOTING PHAGOCYTIC CLEARANCE OF AB42 OLIGOMERS AS A POTENTIAL PROTECTIVE FACTOR FOR ALZHEIMER'S DISEASE

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Aims: The pathogenesis and progression of Alzheimer's disease (AD) involves central and peripheral immune deregulation. We have previously identified a novel missense variant of TLR9 (p.E317D) co-segregating with early-onset familial AD. In this study we investigated the possible molecular mechanistic links between TLR9 and AD.
Methods: A NF-κB luciferase assay was used to quantify the level of TLR9 activation in response to TLR9 agonist treatment in HEK-293 cell lines expressing either wild type or p.E317D mutant TLR9. Cytokine profiling of human PBMCs in response to TLR7/8/9 agonists were performed using multiplex assays measuring 96 human cytokines/chemokines. Conditioned media from human PBMCs in response to TLR9 agonist were used to treat human iPSC-derived microglia to assess the functional effects of TLR9 signaling-induced cytokines. Microarray transcriptome analysis was applied to identify the molecular pathways underlying the effects of TLR9 signaling-induced cytokines.
Results: The p.E317D variant caused 50% reduction in TLR9 activation in the NF-κB luciferase assay indicating that p.E317D is a loss-of-function mutation. Cytokine profiling of human PBMCs upon TLR9 activation revealed a predominantly anti-inflammatory response in contrast to the inflammatory responses from TLR7/8 activation. The cytokines released upon TLR9 activation suppressed inflammation and promoted phagocytosis of $A\beta_{42}$ oligomers in human iPSC-derived microglia. Transcriptome analysis identified upregulation of AXL, RUBICON and associated signaling pathways, which may underline the effects of TLR9 signaling-induced cytokines in regulating the inflammatory status and phagocytic property of microglia.
Conclusions: TLR9 activation releases cytokines that provide predominantly anti-inflammatory effects and promote phagocytic clearance of $A\beta_{42}$ oligomers. We suggest a protective effect of TLR9 in AD pathogenesis and hypothesize that reduced signaling, caused by specific mutations, could contribute to increase of neuroinflammation and Aβ accumulation.

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P0043 / #570

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

"MODULATION OF STAT1 SIGNAL TRANSDUCTION IN AN ALZHEIMER'S DISEASE TRANSGENIC MOUSE MODEL"

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Aims: Established transgenic mouse models such as 5xFAD allow for exploration of various major symptomatic hallmarks of Alzheimer's disease (AD), mainly focussing on amyloid-ß deposition, development of astro- and microgliosis, neuron loss and behavioural deficits. Histopathologically, activated microglia cluster around β-amyloid deposits, suggesting that phagocytosis by these cells is important for either the formation or clearance of amyloid plaques. Chronic inflammatory activation of microglia (e.g. by interferon-alpha or -gamma signalling) and associated cytokine production is largely mediated through STAT ("Signal Transducer and Activator of Transcription")-dependent transcriptional regulation of inflammation-associated genes. By crossing 5xFAD mice with STAT1-deficient mice ($STAT1^{-/-}$), we aimed at studying a presumed inflammation-modulating effect of a loss of interferon-alpha and -gamma signalling, with regard to chronic microglial activation, amyloid plaque pathology and behavioural deficits as pivotal symptoms of the disease.
Methods: After comprehensive behavioural analysis with established motor and memory tasks (such as rotarod, Morris water maze, elevated plus maze or novel object recognition tasks), immunohistochemical analyses with antibodies directed against various Aß-peptide species and inflammatory markers were conducted on 5xFAD and 5xFAD/$STAT1^{-/-}$ brain material. Neuropathological analyses were complemented with ELISA assays and gene expression analyses (such as real-time quantitative PCR for selected inflammation-associated genes) in isolated brain regions (cortex/hippocampus).
Results: STAT1 deficiency significantly ameliorated learning and memory deficits in certain memory tasks and partially restored the wildtype-typical anxiety phenotype. Immunohistochemical analysis revealed an unchanged total Aß-plaque load but altered Aß-peptide composition. RT-qPCR analysis demonstrated significantly altered expression levels for candidate genes associated with specific microglial activation stages.
Conclusions: These findings highlight the crucial role of inflammatory mechanisms in the pathogenesis of AD and specifically point to microglia as a potential target for therapeutical intervention

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P0044 / #2416

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

ROLES OF COMPLEMENT DYSREGULATION AND MEMBRANE ATTACK COMPLEX FORMATION IN DEVELOPMENTAL SYNAPSE LOSS

Sarah Carpanini, Megan Torvell, Lewis Watkins, Ryan Bevan, Robert Byrne, Nikoleta Daskoulidou, Timothy Hughes, Wioleta Zelek, B.Paul Morgan
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Aims: Complement is involved in developmental synaptic pruning and pathological synapse loss in Alzheimer's disease (AD). Our recently published work identified complement dysregulation in AD mice involving the activation (C1q; C3b/iC3b) and terminal membrane attack complex (MAC) pathways. Inhibition or ablation of MAC formation reduced synapse loss in two AD mouse models, demonstrating that MAC formation is a driver of pathological synapse loss; however, the precise mechanism of MAC induced synapse loss and its relevance to developmental synaptic pruning remains to be elucidated.
Methods: We explored whether complement dysregulation and MAC formation occurred during developmental synaptic pruning and contributed to synapse loss. Novel ELISA methods were used to quantify C1q, C3 fragments and MAC in total brain homogenates from WT and complement deficient (C1q, C3 and C7) mouse brains at 8, 15, 28 and 40 days after birth. Synapse density was assessed across this time-course in order to measure the impact of complement deficiencies on developmental synaptic pruning.
Results: Complement activation products were present in WT brain homogenates across the developmental period examined, suggesting ongoing complement dysregulation. In each of the complement deficient lines, complement activation product levels were decreased, demonstrating the specificity of the assays. Initial analyses suggested that synapse density was altered compared to WT in each of the complement deficient lines.
Conclusions: We show that complement dysregulation occurs in the brain during the period of highest synaptic remodelling. Early or late complement component deficiencies reduced complement activation in the brain and synapse loss, implicating complement and the MAC in the process.

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P0045 / #468

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

EXPLORATORY STUDY ON THE NEUROINFLAMMATORY PROFILES OF TG-ARCSWE AND APP-NL-G-F MICE.

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Aims: The pathophysiological processes of Alzheimer's disease (AD) have yet to be determined. Among several factors, neuroinflammation has been suggested to contribute to the progressive neurodegeneration. Capturing neuroinflammation through *in vivo* imaging, e.g. with PET radioligands, could therefore carry great diagnostic potential for AD patients, and further, be used in clinical trials of new anti-inflammatory drug candidates to evaluate effects at the target site. In a first step towards achieving this, the current project sought to explore the neuroinflammatory profiles of aged transgenic mice with AD pathology.
Methods: *Ex vivo* investigations were carried out using cryosections and extracts from brains of tg-ArcSwe, APP^{NL-G-F}, and wild-type mice (aged 12-23 months). Initial screenings of inflammatory proteins were performed using fluorescent immunohistochemistry. Protein levels in TBS- and SDS-soluble fractions were further analysed with enzyme linked immunosorbent assays.
Results: CD22 (Siglec 2), Galectin-3 and the P2X7 receptor were selected as inflammatory proteins of interest as the levels tended to be higher in tg-ArcSwe and APP^{NL-G-F} mice, than in wild type mice. Moreover, an age-dependent increase in inflammatory protein load appeared to be present in all three animal groups.
Conclusions: Further evaluation of CD22, Galectin-3 and the P2X7 receptor will be necessary to determine each protein's suitability as a future target for antibody-based PET radioligands in AD diagnostics.

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P0046 / #227

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

IS THERE RELATIONSHIP BETWEEN TOXOPLASMA GONDII IGG SEROPOSITIVITY AND IDIOPATHIC PARKINSONISM AND DOES IT HAVE CORRELATION WITH CORTISOL BLOOD LEVEL ?

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Aims: Background: some researches linked between latent Toxoplasmosis and neurological diseases, now the main interest is the propable relation between toxoplasmosis and neurological diseasesas epilepsy and Parkinsonism.
Aim: To detect the incidence of Toxoplasma gondii infection in patients idiopathic Parkinsonism and correlate it to their blood level of cortisol.
Methods: Materials and Methods: This study was conducted on 30 idiopathic Parkinson's Patients, 30 psychiatric Patients, 30 apparently healthy individuals. All subjects were submitted to a questionnaire, detection of ant-Toxoplasma IgM, anti-Toxoplasma IgG and cortisol level by ELISA.
Results: of the 90 cases; 41.11% and 1.11% were positive for ant-Toxoplasma IgM and IgG, respectively. The percentage of positive anti-Toxoplasma IgG cases was in healthy group (46.67%.) followed by Parkinsonism group (43.3%). Mean cortisol level higher in Pakinson's group than other groups but still within normal levels. Contact to cats, drinking unfiltered water and consuming unwashed raw vegetables were significantly higher in Toxoplsma IgG seropositive Parkinson's patients. Highest anti-Toxoplasma IgG positive casaes in Parkinson's group were detected in stage 3 of the disease .
Conclusions: Conclusion: A high Toxoplasma seropositivity in association with Parkinsonim. Toxoplasma gondii oocyst may be was the most propable main mode of transmission of Toxoplasma gondii in idiopathic Parkinson's patients. Toxoplasma gondii may worsen idiopathic Parkinsonism. Cortisol level was higher in Parkinson's patients, still it showed no significant relationship with Toxoplasma gondii seropositivity.

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P0047 / #2138

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

INTRACEREBROVENTRICULAR (ICV) ADMINISTRATION OF MTOR-INHIBITORS TO RE-ESTABLISH TOLERANCE TOWARDS AUTOIMMUNITY IN MULTIPLE SCLEROSIS: A PILOT STUDY IN THE EAE MODEL.

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Aims: We aim to replicate, in a larger and translational preclinical study, what was observed in a pilot experiment on RR-EAE: The ICV administration of everolimus for 10 days, started at the symptoms' onset, resulted in a complete and long-lasting remission of relapses (Fig 1). After Mohammad et al., JCI 2014, we know that the murine brain is patrolled by a continuous flow of dendritic cells. It has long been known that dendritic cells, after processing an alloantigen in vitro in the presence of rapamycin, once injected intravenously back in the animal, migrate to the secondary lymphoid organs where they generate Treg (hence tolerance) towards said antigen. The extreme thermolability at Body Temperature of all mTOR inhibitors made any following in vivo investigation difficult to reproduce and made it mandatory to create a thermostable formulation of mTOR inhibitors.

Methods: .

Everolimus was loaded in distearoylphosphatidylethanolamine-polyethyleneglycole 2000 (DSPE-PEG2000) micelles by the thin layer method. The compounds were dissolved in chloroform. The solvent was evaporated at r.t. under nitrogen stream and vacuum dried for 1 hour. Micelle formation was obtained by hydration of the thin layer with an Everolimus physiologic solution.

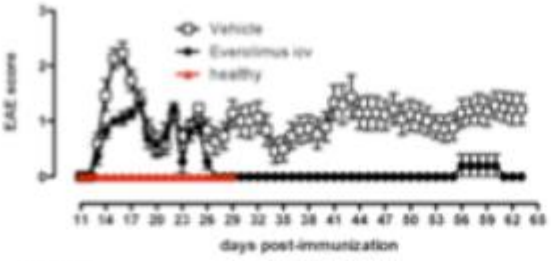

Fig. 1

Fig. 1. Starting the DMSO- Everolimus solution administration at clinical onset, the severity of the first attack was always decreased. Surprisingly, EAE did not relapsed after the third attack.

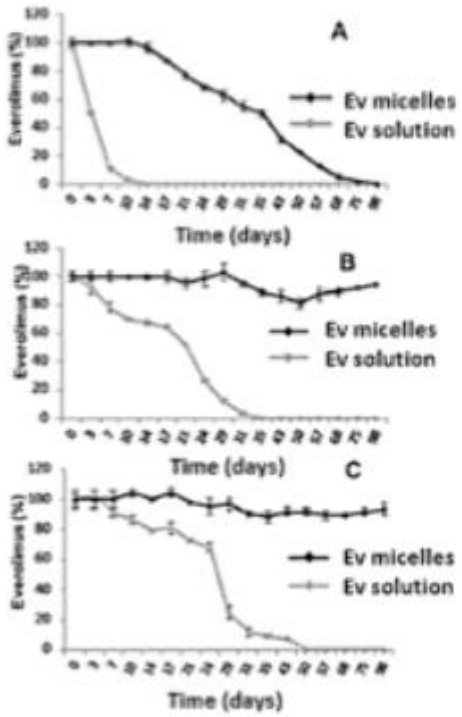

Fig. 2: A. Everolimus decay in DMSO solution (grey) and in micelles (black) at Body Temperature (37° C). **B.** At Room Temperature (25° C). **C.** At 4° C

Results:
We have developed a micellar formulation stable at body temperature (see Fig 2) (PCT: WO 2021205297A1). Moreover, the already known biocompatibility, its ease of production, storage (in powder form), and preparation for use are also interesting features.
Conclusions: With this thermostable formulation it will be possible to deepen, in a fully translational framework, the restoration of tolerance through the ICV administration strategy of rapamycin in autoimmune neurological pathologies: only in this way can the tolerogenic conditioning of DCs be obtained avoiding systemic immunosuppression, which cancels the reactivity of the immune system.

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P0048 / #2204

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

CONDITIONAL C3 KNOCKOUT MICE TO STUDY THE IMPACT OF COMPLEMENT DEFICIENCY ON NEUROINFLAMMATION AND ALZHEIMER'S DISEASE PATHOLOGY

Pieter Dujardin[1,2], Marlies Burgelman[1,2], Elien Van Wonterghem[1,2], Griet Van Imschoot[1,2], Tino Hochepied[1,2], Charysse Vandendriessche[1,2], Roosmarijn Vandenbroucke[1,2]
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Aims: The complement system represents an important part of innate immunity and comprises a hub-like network that converges on the cleavage of the central complement protein C3, which can then lead to the formation of the membrane attack complex, phagocytosis, and recruitment of immune cells. Compelling evidence indicates that complement activation occurs and plays a key role in Alzheimer's disease (AD). Previously, we could show that the intracerebroventricular (icv) injection of amyloid beta oligomers in mice induces the upregulation of C3 in the choroid plexus (CP) (Vandendriessche et al., 2021). However, a better understanding of the exact role, source, and mechanisms of complement activation in AD is required. In this project, we aim to further study the impact of the complement system on neuroinflammation and AD pathology using conditional C3 knock-out ($C3^{fl/fl}$) mice.
Methods: $C3^{fl/fl}$ mice were generated from mouse embryonic stem cells obtained via the European Conditional Mouse Mutagenesis program (EUCOMM). Next, $C3^{fl/fl}$ mice were crossed with Rosa26-CreERT2, Cx3Cr1-CreERT2, GFAP-Cre, and LysM-Cre mouse lines, to obtain inducible full body, inducible microglial, astrocytic, and myeloid cell specific C3 knockout mice, respectively. To achieve CP specific C3 knock-out, TAT-Cre is icv injected in the $C3^{fl/fl}$ mice.
Results: C3 deficiency in our different $C3^{fl/fl}$ mouse lines was validated by deflox PCR, western blot, ELISA and immunostaining. Our different $C3^{fl/fl}$ mouse lines are currently being crossed with APP^{NL-G-F} mice and studied in mouse models of LPS induced systemic inflammation and neuroinflammation. As such, we will examine the effects of conditional C3 knock-out on cognitive impairment, amyloid beta plaque load, neurodegeneration and microglial/astrocytic activation.
Conclusions: Using conditional C3 knock-out mice crossed with different Cre(ERT2) driver lines, we further unravel the role of the complement system in AD and neuroinflammation.

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P0049 / #1892

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

IL6 AS A RISK FACTOR FOR ELEVATED BETA AMYLOID IN THE SERUM OF PATIENTS WITH PREMATURE OVARIAN FAILURE

Milena Erić Jovičić[1], Svetlana Jovičić[2], Natalija Pavlovic[3], Svetlana Vujovic[3]
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Aims: Women are at greater risk than men for developing Alzheimer's disease during their lifetime. The aim of our study is to determine the relationship between IL6 and beta amyloid in the serum of patients with premature ovarian failure.
Methods: In the serum of affected patients, IL6 and beta amyloid were determined using the Elisa technique.
Results: The results of our study conducted on 78 patients with POF and 75 controls showed that there is a positive correlation between IL6 and beta amyloid levels in the serum.
Conclusions: From this we can conclude that IL6 can be a target for testing therapy in patients and opens a new avenue.

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P0050 / #1898

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

CORRELATION OF TNF ALPHA AND BETA AMYLOID IN THE SERUM OF PATIENTS WITH PREMATURE OVARIAN FAILURE

Milena Erić Jovičić[1], Svetlana Jovičić[2], Natalija Pavlovic[3], Svetlana Vujovic[3]
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Aims: Women are at greater risk than men for developing Alzheimer's disease during their lifetime. The aim of our study is to determine the relationship between TNF alpha and beta amyloid in the serum of patients suffering from premature ovarian failure.
Methods: In the serum of affected patients, TNF alpha and beta amyloid was determined using the Elisa technique.
Results: The results of our study conducted on 78 POF patients and 75 controls showed that there is a positive correlation between TNF alpha and beta amyloid levels in the serum.
Conclusions: The results of our study conducted on 78 POF patients and 75 controls showed that there is a positive correlation between TNF alpha and beta amyloid levels in the serum.

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P0051 / #1819

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

A ROLE FOR B CELLS IN ALZHEIMER DISEASE

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Aims: We recently reported that inflammaging activates monocytes to convert innate B1a cells into pathogenic 4-1BBL^{+} TNFα^{+} MHC-I^{High} B cells (termed 4BL cells), which then induce cytolytic CD8^{+} T cells and insulin resistance in elderly humans, macaques, and mice. However, the role of these or other activated B cells in aging-associated diseases, such as Alzheimer's disease (AD) remains unknown.
Methods: Methods J_HT mice (B6.129P2-*Igh-J*^{tm1Cgn}/J), which do not develop functional B cells in the circulation due to the immunoglobulin J_H locus deletion[26], were separately bred with either congenic 3×TgAD mice (with three human genes associated with familial AD, B6;129-Psen1^{tm1Mpm} Tg(APPSwe,tauP301L)1 Lfa/Mmjax))[24,25], APP/PS1 mice (B6.Cg-Tg(APPswe,PSEN1DE9) 85Dbo/J)[16] or 5×FAD mice expressing mutant human APP and PSEN1 genes (B6.Cg-Tg;APPSwFILon,PSEN1*M146L*L286V)[21]. The effect of B cell deficiency was assessed on Amyloid-beta plaque formation, microglial cell activation and behavioral deficits.
Results: Results Herein, we provide counterintuitive evidence that the AD progression requires B cells. Despite expression of the AD-fostering transgenes, the loss of B cells alone is sufficient to reduce Aβ plaque burden and disease-associated microglia. It reverses behavioral and memory deficits and restores TGFβ^{+} microglia, respectively. Moreover, therapeutic depletion of B cells at the onset of the disease retards AD progression in mice, suggesting that targeting B cells may also benefit AD patients.
Conclusions: Conclusions Taken together, we provide evidence for a "dark" side of B cells—they exacerbate manifestation of AD-like symptoms in addition to producing potentially beneficial Aβ plaque-reducing immunoglobulins and expressing AD-ameliorating cytokines.

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P0052 / #1284

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

TARGETING THE NLRP3 INFLAMMASOME IN PARKINSON'S DISEASE VIA BRUTON'S TYROSINE KINASE (BTK)

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Aims: Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. PD is characterised by a progressive loss of nigrostriatal dopaminergic neurons and the accumulation of α-synuclein aggregates for which there are currently no effective treatments to slow disease progression. Neuroinflammation can be observed early in the disease process and thus been closely linked to disease progression based on accumulating evidence from clinical studies and experimental models. Inhibition of the NLRP3 inflammasome has recently been shown to prevent α-synuclein pathology and dopaminergic neurodegeneration. The aim of the study was to examine if Bruton's Tyrosine Kinase (BTK) is activated in experimental PD and determine if inhibition of this kinase leads to improved outcomes.
Methods: We utilised human patient samples, primary microglia and human peripheral blood monocyte cultures for BTK activation and inhibition studies. For our in vivo studies - two established preclinical models of PD, the 6-OHDA model and alpha synuclein pre-formed fibril (PFF) model were used with once daily oral inhibiton of BTK inhibitors.
Results: We demonstrate that BTK is activated by pathological synuclein and triggers NLRP3 inflammasome activation in microglia. BTK is also activated in the nigrostriatal system of experimental PD models at the same timepoints as NLRP3 activation. Pharmacological inhibition of BTK signalling prevented inflammasome activation in vitro. Interestingly, we demonstrate that pharmacological inhibition of BTK ameliorates markers of neurotoxic astrocytes in PD experimental models. Additionally, daily oral dosing with BTK inhibitors effectively reduces NLRP3 inflammasome activation markers and neuropathology in pre-clinical models of PD and improves dopaminergic neuron survival.
Conclusions: Together, our results suggest that BTK drives inflammasome activation and neuropathology in PD and that BTK is a druggable therapeutic target for neuroprotection in PD.

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P0053 / #2150

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

CONSORTIUM FOR COLLECTION AND DISTRIBUTION OF BRAIN TISSUE AND ASSOCIATED FLUIDS FROM INDIVIDUALS WITH DOWN SYNDROME

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Aims: Individuals with Down syndrome (DS) develop Alzheimer's disease (AD) with almost complete penetrance at an early age. One reason for a lack of pharmaceutical investment in this population is the paucity of information regarding biological mechanisms, disease progression, and neuropathology in DS-AD. The Down Syndrome Biobank Consortium, DSBC, is a group consisting of 12 international brain banks focused on DS research and providing high-quality samples to scientists. By studying this vulnerable population, we will be able to generate novel data to be used for both prevention and intervention, not only for DS but also sporadic AD.
Methods: A novel infrastructure grant from the BrightFocus Foundation offsets costs for brain donation, transportation, and processing in each brain bank site, enabling the collection of valuable tissues for research. DSBC training sessions for brain procurement allow harmonized procedures. DSBC has developed a website and a database for sample inventory and medical information and provided tissues to researchers both in the USA and Europe.
Results: During the initial years, the consortium collected brain donations from 30 DS brain donations, some with a very low *postmortem* interval and associated medical information. Due to a heightened interest in neuropathological effects of SARS-CoV-2, we had several young and old DS brain donors who succumbed to COVID-19. The resultant networking activities within DSBC are invaluable for the future of DS and AD research.
Conclusions: The DSBC collection has allowed unprecedented access to high quality tissues for many scientists in the DS and AD research fields. Here, we will describe the auspices of the consortium and provide novel neuropathological data. ***Funding****: We are grateful for the funding from the BrightFocus Foundation Bold Initiatives*.

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P0054 / #1715

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

EFFECT OF BONE MARROW-DERIVED CELL TRANSPLANT IN CHIMERIC MICE IMMUNOPHENOTYPE, AND INVOLVEMENT IN ALZHEIMER'S-LIKE COGNITIVE IMPAIRMENT

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Aims: The complex interplay between the peripheral immune and central nervous systems has implications for Alzheimer's disease (AD) that correlates with cognitive function. Transplantation of bone marrow (BM) provides neuroprotection through the improvement of the neuroinflammatory features of AD and cognitive decline in mice. We hypothesize that whole BM allogeneic transplantation from WT or 5XFAD donors into either WT or 5XFAD recipient mice influences the host's immune signature and causally affects cognition, respectively.
Methods: BM from female WT and 5XFAD mice donor animals, 7-9-months old, was collected. WT and 5XFAD heterozygous male recipient animals, 2 months old, were total-body-irradiated. BM-derived cells were intravascularly delivered to the superficial temporal vein in anesthetized recipient animals. *Zfy1* gene expression was monitored and correlated with successful chimerism in blood. Neurobehavioral assessment using Y-maze, Novel Object Recognition, and Light/Dark behavioral tests were used to measure cognitive and mood performance. Mass Cytometry (CyTOF) analysis was used to examine the immune profile in all the newly generated chimeric mouse lines.
Results: Chimerism was confirmed by *Zfy1* gene expression. WT mice transplanted with 5XFAD BM exhibited significant impairment of spatial working memory, short-term, and long-term recognition memory after 4, 6, and 8 months post-BM transplantation, respectively, compared to WT mice engrafted with WT BM. Ongoing CyTOF immune probing will confirm selective immunological signatures in chimeric WT mice recipient mice following engrafting of BM from 5XFAD mice.
Conclusions: Chimeras of 5XFAD in WT mice may acquire AD-type phenotype following engraftment. We hypothesize that the mechanism could be explained by the integration of hematopoietic and mesenchymal stem cell cells carrying genetic susceptibility genes from 5XFAD, and therefore, the pro-inflammatory signature found selectively in these donor mice.

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P0055 / #1982

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

DEVELOPMENT OF A PLATFORM FOR CRISPR/CAS9 SCREENING AND ENGINEERING OF IPSC-DERIVED HUMAN MICROGLIA-LIKE CELLS TO VALIDATE NEUROINFLAMMATION DRUG TARGETS IN ALZHEIMER'S DISEASE

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Aims: Microglia are the innate immune cells of the brain and play a critical role in neurological disorders, including Alzheimer's disease (AD). Genome-wide association studies (GWAS) have identified several genes that are preferentially expressed by microglia and are associated with increased risk of developing late-onset AD, such as triggering receptor expressed on myeloid cells 2 (*TREM2*), myeloid cell surface antigen CD33 (*CD33*), and inositol polyphosphate-5-phosphatase (*INPP5D*). Designing reverse genetic experiments to ascertain the function of microglial AD-associated genes is hindered by the inability to obtain and manipulate postmortem tissue from AD patients. Human-induced pluripotent stem cell (hiPSC)-derived microglia cells represent a novel strategy to examine the relationship between genetic risk factors and late-onset AD. Recently, several groups have independently demonstrated that patient-derived hiPSCs can be differentiated into human microglia *in vitro* by providing cues that mimic the environment present in the developing embryo.
Methods: Using iPSC-derived hematopoietic progenitor cells, we replicated the protocol published by Abud *et al*. (*Neuron* **94,** 278-293, 2017) to generate induced microglial-like cells ("iMGLs") and confirmed relevant phenotypes by whole-transcriptome, flow cytometry and immunocytochemical analysis. Functional analysis of iMGLs reveals that they secrete cytokines in response to inflammatory stimuli and CNS substrates, including Aβ fibrils.
Results: The ability to precisely introduce genetic disease-associated mutations in hiPSC-derived microglia cells using CRISPR/Cas9 technology will help define the contribution and function of genes associated with late-onset AD. We present a method to facilitate high-throughput gene activation and knockout studies of gene function via chemically inducible Cas9 and dCas9-fusion proteins.
Conclusions: We present a method to facilitate high-throughput gene activation and knockout studies of gene function via chemically inducible Cas9 and dCas9-fusion proteins.

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P0056 / #1359

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

NON-INVASIVE IN VIVO IMAGING OF CASPASE-1 ACTIVATION ENABLES RAPID AND SPATIOTEMPORAL DETECTION OF ALZHEIMER'S DISEASE

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Aims: Inflammasome plays a critical role in diverse inflammatory disorders, including cancers and Alzheimer's disease. It is induced by various pathogenic insults and activates caspase-1, a hallmark executor of inflammasome. Here, we aimed to develop a non-invaseive probe for deagnosing Alzheimer's disease at earlier stage.
Methods: The caspase-1 activatable (Cas-1) probe was synthesized by conjugating Cy5.5 and BHQ-3 to caspase-1 substrate (G-W-E-H-D-G-K). In Alzheimer disease model imaging, 5xFAD mice (three to six months old) were analyzed each month. The Cas-1 probe was intravenously injected and *in vivo* images were taken every 30 min by eXplore Optix system starting at 2 h after probe injection. Animals were also humanely sacrificed and collected brains and lymph nodes were imaged by an IVIS-Lumina system. For non-invasive imaging, animals were shaved before imaging process by IVIS-Lumina system. In case of head imaging in AD model by eXplore Optix system, we partially cut the skin to expose mouse skull.
Results: The caspase-1 probe that we developed is biocompatible, efficiently delivered into cells and tissues, and specifically emits fluorescence upon caspase-1 activation as assessed in in vitro and in vivo models of inflammatory conditions. We demonstrated efficient in vivo imaging of caspase-1 activation in early stages of various inflammatory conditions of mice models, including endotoxin shock, inflammatory bowel disorder, transplanted cancer, and Alzheimer's disease. Notably, the caspase-1 probe enables detection of neuroinflammation in vivo two months earlier than cognitive impairments occur in Alzheimer's disease model. We detected significant fluorescence emitted from inflamed sites, as well as their draining lymph nodes, by macroscopic imaging analysis within 30 min after systemic injection of the probe.
Conclusions: This novel synthetic probe could be applied for efficient and rapid detection of caspase-1 activity in a spatiotemporal way by non-invasive imaging.

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P0057 / #466

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

PHLOROGLUCINOL DERIVATIVES EXERT ANTI-INFLAMMATORY EFFECTS AND ATTENUATE COGNITIVE IMPAIRMENT IN LPS-INDUCED MOUSE MODEL

Jushin Kim[1], Ji Won Choi[1], Hyeon Jeong Kim[2], Sun Jun Park[2], Byungeun Kim[2], Yoowon Kim[2], Elijah Hwejin Lee[2], Rium Kim[2], Jaehwan Kim[2], Jong-Hyun Park[2], Ki Duk Park[2]
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Aims: Neuroinflammation is an inflammatory immune response that arises in the central nervous system. It is one of the primary causes of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Phloroglucinol (PG) is a natural product contained in extract of *Ecklonia cava*, a marine brown algae, and is reported to be antioxidant and anti-inflammatory agent. In this study, we synthesized PG derivatives to enhance their antioxidant and anti-inflammatory activity.
Methods: PG derivatives were synthesized by Claisen–Schmidt condensation of PG structure based acetophenones with aldehydes containing various substituents. We performed some *in vitro* experiments such as Griess assay to confirm the antioxidant and anti-inflammatory effects in LPS-stimulated BV-2 microglial cells. In addition, we conducted *in vivo* behavioral experiments in the LPS-induced model of neuroinflammation and immunofluorescence staining in the brain of the model.
Results: Among PG derivatives, **6a** suppressed pro-oxidative and inflammatory molecule nitric oxide (NO) production more effectively than PG. Moreover, **6a** dose-dependently reduced the expression of proinflammatory cytokines such as IL-6, IL-1β, TNF-α, and NO producing enzyme iNOS in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells. Additionally, we confirmed that **6a** alleviated cognitive impairment and glial activation in mouse model of LPS-induced neuroinflammation.
Conclusions: These findings suggest that novel PG derivative, **6a**, is a potential treatment for neurodegenrative diseases.

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P0058 / #1034

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

INTERFERON HYPERSENSITIVITY OCCURS IN THE BRAIN OF PRECLINICAL MODELS OF DOWN SYNDROME

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Aims: Down syndrome (DS) is caused by trisomy of chromosome 21 (Hsa21). People with DS have an abnormal peripheral immune system including an over-activated interferon response, which is likely due to four genes encoding interferon receptors being located on Hsa21. How this interferon hypersensitivity affects inflammation in the brain is unknown. We generated organotypic brain slice cultures (OBSCs) from DS preclinical mouse models which contain three-copies of the interferon receptor genes and treated slices with interferon-β to investigate if DS mouse models exhibited a hypersensitive interferon response in the brain.
Methods: The Dp2Tyb (Dp(16Mis18a-Runx1)2TybEmcf, MGI:5703800) and Dp1Tyb (Dp(16Lipi-Zbtb21)1TybEmcf, MGI:5703798) mouse strains were used. Dp1Tyb mice have three-copies of ~148 Hsa21 orthologous genes, including the four interferon receptor genes. Dp2Tyb mice have a subregion of ~32 of those Hsa21 orthologous genes in three-copies, still including the four interferon receptor genes. Cortico-hippocampal OBSCs were prepared from pups at age P7-P9, maintained in culture and treated at DIV14 with interferon-β for 24-hours. Slices were collected for western blotting or qPCR, and conditioned media for CXCL10 ELISA.
Results: Both Dp1Tyb and Dp2Tyb OBSCs had a hypersensitive response to interferon-β treatment compared to treated wild-type OBSCs, with higher expression of interferon-stimulated genes in lysed slices and higher levels of CXCL10 protein secreted into the media.
Conclusions: We found that OBSCs from DS preclinical models displayed a hypersensitive interferon response, indicating that interferon hypersensitivity may occur in the brain of individuals with DS and is likely due to having three-copies of the interferon receptor genes encoded on Hsa21. How this interferon hypersensitivity effects neuroinflammation in the presence of amyloid pathology is unknown. To investigate this, next we will cross the Dp2Tyb with the *App*$^{NL\text{-}G\text{-}F}$ mouse model of amyloid pathology.

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P0059 / #2414

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

LEUCINE-RICH REPEAT KINASE 2 (LRRK2) AS A POSSIBLE HUB IN THE NEUROINFLAMMATORY PROCESS OF ALZHEIMER' AND PARKINSON'S DISEASE

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Aims: Chronic neuroinflammation plays a crucial role in the progression of several neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). Intriguingly, Leucine-rich repeat kinase-2 (LRRK2), a gene mutated in familial and sporadic PD, has been identified and corroborated as a mediator of neuroinflammation upon different challenges. Although accumulating evidence suggests overlapping pathways between AD and PD, the contribution of LRRK2-related inflammation in AD is still unknown. In this context, our *in vitro* results showed that LRRK2 kinase inhibition decreases neuroinflammation mediated by β-amyloid ($A\beta_{1–42}$) fibrils. Based on these observations, in this study, we investigate if LRRK2 kinase activity controls $A\beta_{1–42}$-mediated neuroinflammation *in vivo*and whether LRRK2-related neuroinflammation may represent a common signal shared by these two neurodegenerative diseases (NDs).
Methods: As AD animal model, we inoculated $A\beta_{1–42}$ fibrils in the lateral ventricle, and to explore the contribution of LRRK2 to neuroinflammation we intraperitoneally injected two different LRRK2 kinase inhibitors.
Results: Our findings reported that $A\beta_{1–42}$ fibrils induced increased levels of Ser935-LRRK2 phosphorylation, gliosis, inflammatory cytokine IL-1β, and caspase-3 activation. Interestingly, the treatment of both LRRK2 kinase inhibitors can lower the neuroinflammatory state, suggesting that LRRK2 kinase activity controls AD-related inflammation and might contribute to AD pathogenesis. In addition, we are currently exploring whether the inhibition of LRRK2 kinase activity attenuates neuroinflammation in our a-synuclein pffs-based PD mouse model.
Conclusions: Overall, our results will help to clarify whether LRRK2- mediated neuroinflammation is a pathway shared by these two NDs and thus might be a therapeutic target to be considered in NDs with an inflammatory component.

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P0060 / #1685

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

TSPO-PET BRAIN INFLAMMATION IMAGING: A TRANS-DIAGNOSTIC SYSTEMATIC REVIEW AND META-ANALYSIS OF 156 CASE-CONTROL STUDIES

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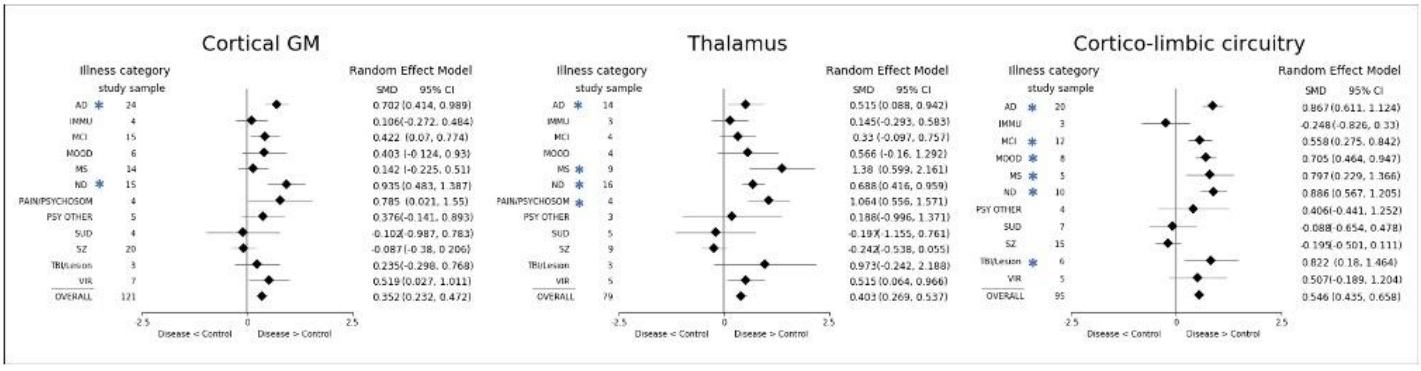
Aims: We conducted a transdiagnostic systematic review and meta-analysis of all in-vivo human TSPO-PET case-control studies in the central nervous system. We investigated the direction and strength of the TSPO-PET signal across disorders and brain regions, and explored the demographic and methodological sources of heterogeneity.
Methods: We applied a random-effects meta-analysis to estimate case-control standardized mean differences of the TSPO-PET signal in the lobar/whole-brain cortical grey matter (cGM), thalamus, and cortico-limbic circuitry between illness categories. We explored heterogeneity using I^2-statistic, and subgroup and meta-regression analyses for radioligand generation, PET quantification method (V_T or reference region-based), age, sex, and publication year.
Results: 156 individual case-control studies were included in the systematic review (2381 healthy controls and 2626 patients). Across 12 illness categories, we observed higher TSPO-PET signal in cases compared to controls for cGM (P_{FDR}<0.001, I^2=69%), with a significant difference between illness categories (P=0.005). cGM increases were significant only for Alzheimer's and other neurodegenerative disorders (**Fig.1**). Cortico-limbic increases were most prominent for neurodegenerative and mood disorders, with additional hippocampal increases in multiple sclerosis and TBI. Thalamic involvement was observed for Alzheimer's and other neurodegenerative disorders, multiple sclerosis, and chronic pain/functional disorders. Main outcomes for systemic immunological disorders, viral infections, substance use disorders, schizophrenia and other psychiatric disorders were not significant. We identified quantification method as the highest source of between-study variability, followed by age and radioligand generation.



Conclusions: We present the first overarching transdiagnostic meta-analysis of case-control TSPO-PET findings in humans. We observed TSPO-PET increases for specific types of disorders, which were widespread particularly in neurodegenerative diseases. Our results can support future studies to optimize experimental design and power calculations, by taking into account the type of disorder, brain region-of-interest, radioligand, and quantification method.

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P0061 / #623

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

MOLECULAR CHARACTERISATION OF THE ROLE OF SYSTEMIC INFECTIONS IN ALZHEIMER'S DISEASE BRAIN

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Aims: The main aim of the project is to investigate the molecular mechanisms involved in systemic inflammation in AD through the integration of different layers of omics data. The study was divided into four steps to accomplish this objective: - analyse gene expression changes among the sub-cohorts - analyse the miRNA changes among the 4 sub-cohorts - perform integrated multi-omics analysis of SNPs, DNA methylation, gene expression and miRNA - identify drug compounds that can prevent the side effects caused by inflammation in AD The results presented in this abstract will refer to the first step of the project.
Methods: The cohort of patients selected for the study is composed of 243 post-mortem prefrontal cortex brain samples. The cohort is divided as follows: 67 AD samples and 47 controls that died with infection, 64 AD patients and 65 controls without infection at the time of the death. The infections included in the analysis were mostly represented by lung infections (i.e. pneumonia), urinary and chest infections. Following RNA sequencing, a two-way ANOVA analysis was performed to test for associations among the four sub-cohorts.
Results: These results identified 142 statistically significant genes ($p < 0.01$). The top resulting gene was *KIF3B*, which was reported to have a role in lung inflammation in rat model and a component of kinesin II involved in the axonal transport.
Conclusions: This analysis laid the foundations for further investigations into gene expression changes associated with AD and infection. Future work will include a WGCNA (weighted correlation network analysis) to identify the co-expressed genes and a pathway enrichment analysis on the statistically significant genes and the resulting modules from the WGCNA. These results will be used in the following steps of the project.

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P0062 / #1702

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

INTERACTION BETWEEN SYNAPTIC, NEURONAL AND INFLAMMATORY CEREBROSPINAL FLUID MARKERS IN ALZHEIMER'S DISEASE

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Aims: Synaptic dysfunction is an important early mechanism involved in Alzheimer's disease (AD) but its correlation with neuronal, glial and inflammatory markers is still debated. Aim the study is to evaluate the levels of synaptic markers Neurogranin, SNAP25 and CAP2 in cerebrospinal fluid of AD and their correlation with neuronal, glial and inflammatory markers in vivo.
Methods: twenty AD patients and 20 age-matched controls underwent CSF analyses for neurogranin, SNAP-25, CAP2, Tau, P-tau and Abeta amyloid, NfL, and an extensive cognitive, behavioral and motor assessment. CAP2 levels were assessed using standard CSF ELISA. Correlations between CSF biomarkers were evaluated using partial correlation adjusted for the effect of age, sex and disease duration.
Results: AD patients exhibited higher synaptic markers namely neurogranin, SNAP-25 and CAP2 levels compared to controls. SNAP-25 showed a stronger correlation with the Neuronal marker NfL compared to neurogranin and CAP2. The inflammatory marker IL-6 did not correlated with any synaptic marker but NfL in partial correlation analyses.
Conclusions: this study confirmed the increased levels of synaptic markers. The preliminary findings indicate lack of correlation between synaptic markers and inflammation in AD, whereas neuronal loss might be related to mild inflammatory alterations in CSF.

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P0063 / #2427

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

1C7: AN IMMUNE GENE ENCODED IN MHC CLUSTER IS IMMUNOPROTECTIVE AGAINS NEUROINFLAMMATION IN ALZHEMER'S DISEASE AND DOWN SYNDROME DEMENTIA

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Aims: Dysfunction of APP processing and amyloid β (Aβ) accumulation are key factors in the pathogenesis of Alzheimer's disease (AD) in Down syndrome (DS). Another factor involved in AD/DS is neuroinflammation. The major histocompatibility complex (MHC) is an extended gene cluster encoding a remarkable number of proteins important for immune protection, i.e., *HLA-DR, 1C7,* complement components (C4, C2), and *TREM2.* 1C7, a member of the immunoglobulin gene superfamily (IgSF), has been identified and involved in inflammation. We reported that TREM2 (R47H) mutation causes severe phenotype in DS subjects. To investigate 1C7 as a candidate gene for DS, gene variation and protein expression were analysed.
Methods: DS (n=50), AD (n=50) participants and age matched controls (n=50) were genotyped for *TREM2*, *HLA-DR* 1C7 *and ApoE* by SNPs analysis, and mutations assessed by DNA sequencing. The corresponding plasma protein levels were measured by ELISA. Post-mortem brains from DS, AD and controls (n=18) were analysed by immunohistochemistry.
Results: The human 1C7 has three alternate splice forms with mRNA expression in the spleen, tonsils, B and NK cells. Two mutations were detected in exon 3 in AD/DS subjects (C/T, coded for Leucine to Phenylalanine) and (C/A, a change from Alanine to Aspartate). Additionally, a single nucleotide C/T polymorphism was detected in intron 3, ratio 2:1 between AD/DS and control subjects. Soluble (s1C7) protein expressed in the microglia, oligodendrocytes close to senile plaques, in the blood vessels and in choroid plexus. 1C7 protein levels declined with age and with disease progression in DS and AD serum.
Conclusions: This data indicated that 1C7 is an important protein and mutation in the gene may impair the immune protection that influences the neurodegeneration.

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P0064 / #1009

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

THE IMPACT OF CHRONIC NEUROINFLAMMATION ON THE CHOLINERGIC SYSTEM AND THE THERAPEUTIC POTENTIAL OF MERIVA CURCUMIN

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Aims: One of the major features of Alzheimer's disease is the degeneration and loss of cholinergic neurons located in the medial septum of the basal forebrain, however, the underlying mechanisms leading to their vulnerability are still unclear. Several studies indicated the key role of chronic neuroinflammation through microglial and astrocytic activation. Hence, the aim of this study is to assess if the glial activity affects the excitability profile of cholinergic neurons. Additionally, we investigated the effect of an anti-inflammatory food supplement, called Meriva curcumin (Indena, Italy), in ameliorating the impact of chronic neuroinflammation on the cholinergic system.
Methods: We have bred a new mice model called IL6-ChAT-eGFP starting from the GFAP-IL6 mouse model for chronic neuroinflammation and the ChAT-eGFP line, where cholinergic neurons are labelled with the green fluorescent protein. We assessed the excitability profile of cholinergic neurons in the medial septum through whole-cell patch-clamp recordings from acute brain slices and the number of microglia through immunohistochemistry.
Results: Cellular recordings of cholinergic neurons in the medial septum of IL6-ChAT mice showed significant alterations in their excitability profile at 9-10 months old compared to 3-4 due to chronic neuroinflammation and ageing. In addition, the number of TREM2 positive microglial cells was increased in the IL6-ChAT mice compared to the WT at 9-10 months old in the medial septum. Moreover, we observed the effect of a long-lasting feeding with Meriva Curcumin on both the cholinergic neurons and the number of TREM2 positive microglial cells, which was decreased.
Conclusions: Our results indicate that chronic inflammation can affect the excitability profile of cholinergic neurons, which might make them more susceptible to degeneration. However, this effect can be ameliorated by an anti-inflammatory curcumin treatment that interferes with glial activation.

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P0065 / #1766

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

ROLE OF BIOACTIVE LIPIDS IN ALZHEIMER'S DISEASE

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Aims: Chronic inflammation is part of Alzheimer's disease (AD) pathology, indicating that the resolution process that terminates inflammation is impaired in AD, which is supported by the reduced levels of mediators of resolution, so called specialized pro-resolving lipid mediators (SPMs) and altered levels of their receptors in AD brain. The goal is to develop a novel strategy for treatment of AD based on resolution of inflammation. Specific aims are to analyse effects of SPMs on neurons and microglia in relation to AD neuropathology, and to pave the way for future human treatment in a mouse AD model, and to analyse bioactive LMs including SPMs in CSF samples from patients with AD, MCI and subjective cognitive impairment (SCI) to investigate if these molecules reflect the stage of disease in conjunction with inflammatory proteins.
Methods: *In vitro:* analyse inflammatory phenotype in microglia (cellular/secreted markers) upon incubation with amyloid β (Aβ) peptide with and without SPMs. *In vivo:* effects of SPMs on memory impairment in mouse AD model. Human CSF samples: analysis of pro-resolving and pro-inflammatory lipids, and pro- and anti-inflammatory cytokines and chemokines
Results: Our data show reduced SPM levels in CSF from AD and MCI compared to SCI, whereas pro-inflammatory lipids were increased. In microglial cultures we find that SPMs stimulate Aβ phagocytosis and reduce Aβ-induced pro-inflammatory phenotype, NF-κB activation and NLRP3-inflammasome activation. SPMs also reduced neuronal cell death. Studies in the mouse AD model (*App*$^{NL\text{-}G\text{-}F}$) showed that intranasal administration of SPMs improved cognitive function and decreased neuroinflammation, as well as restored gamma oscillation deficits.
Conclusions: The data support that targeting the dysfunctional resolution of inflammation in AD is a potential future treatment option.

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P0066 / #2263

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

GLUCOCORTICOID INDUCED LEUCINE ZIPPER IS A MOLECULAR LINK BETWEEN NEUROINFLAMMATION AND PD/AD.

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Aims: Correlative associations between circadian timing, glucocorticoid secretion and neuroinflammation contribute to the pathogenesis of neurodegenerative diseases including Parkinson's disease and Alzheimer's disease. Brain specific or global deficiency of core circadian trans-activator BMAL1 or that of the transrepressor REV-ERBβ, impaired motor ability and cognitive performance in rodents. Consistently, transcripts of inflammatory cytokines and host immune responses exhibit diurnal variation. Glucocorticoids exhibiting circadian rhythm similar to the core clock transactivator BMAL1 are critical for controlling neuroinflammation. Both glucocorticoids and the core clock components suppress nuclear factor-kappa B (NF-κB) transactivation and suppress inflammation in the brain. The aim is to determine evidence for interactions between the circadian clock, glucocorticoids and NF-κB and propose glucocorticoid induced leucine zipper (GILZ) encoded by Tsc22d3, as a molecular link that connects all three pathways in CNS homeostasis as well as in the pathogenesis of neuroinflammation-neurodegeneration.
Methods: Considerable evidence supports neuroinflammation as common basis for neuroinflammation leading to neurodegeneration. Cross talk between the NF-κB pathway and glucocorticoid signaling maintains the homeostasis in CNS health. Literature mining was performed to evaluate GILZ as a potential link between the NF-κB signaling pathway, glucocorticoid signaling and circadian oscillations.
Results: In health, the autoregulatory clock loop and the endogenous GC synergistically prime glial cells to patrol for danger signals and activate NF-κB p65 for optimal response. Disruption of the rhythmic release of GC in phase with CLOCK-BMAL1 transcripts affect the autoregulatory feedback loop, precipitate GR resistance, promote persistent activation of NF-κB p65 and lead to exaggerated inflammatory responses.
Conclusions: Given the correlation between plasma and brain cortisol and GILZ expression in the periphery, it is conceivable that GILZ could represent a candidate molecule in regulating time-of-day dependent glucocorticoid and NF-**k**B responses in the CNS

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P0067 / #978

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

SINGLE CELL SEQUENCE-BASED EXPLORATION OF CHANGES IN BRAIN-CELL SUBPOPULATIONS IN ACCELERATED AGING MICE

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Aims: Aging is defined as the progressive accumulation of changes over time, that lead to senescence or declining biological functions. These changes may be a predominant risk factor for the development of neurodegenerative diseases such as Alzheimer's or Parkinson's disease. Which specific age-related factors predispose some individuals to the development of these common neurodegenerative diseases is still enigmatic. Therefore, we aimed at investigating the effects of aging on CNS cell subpopulations. To this end, we performed an exploratory analysis comparing an accelerated aging mouse model with equally aged control mice.
Methods: Senescence Accelerated Mouse-Prone 8 (SAMP8) mice were subjected to various motor tests to assess an age-related frailty index. 3-month-old SAMP8 mice already showed a limited amount of decline, while 10-month-old mice revealed severe motor deterioration and low vitality. Based on a frailty index both groups display an accelerated aging phenotype compared to their corresponding control group from the Senescence resistant SAMR1 mouse line. For this reason, these four groups were subjected to single-cell sequencing.
Results: We applied the Adult Brain Dissociation mouse and rat Kit from Miltenyi Biotec to dissociate mouse forebrain and removed contaminants such as myelin debris and red blood cells while maintaining cell viability above 87% using a trehalose treatment based on a previous publication[1]. The high viability enabled successful generation of cDNA libraries from approximately 10,000 cells per animal brain. This allowed an accurate resolution of even smaller cell subpopulations.
Conclusions: Ultimately, this study will provide insights into age-related changes in brain cell populations and will help to unravel the correlation of Alzheimer's and Parkinson's disease with age-related changes on distinct brain cell populations.

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P0068 / #303

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

SUBTYPES OF INTERFERONS ASSOCIATION WITH ALZHEIMER'S DISEASE IN CANDI COHORT STUDY

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Aims: The principal type of interferons related to cognitive impairment in Alzheimer's disease remain unclear, although interferon pathway are reported to be relvant with Alzheimer's disease in animal models and human brain tissues.
Methods: Using our Mesoscale Discovery-derived U-PLEX multi-array platform, we detected changes in type I (interferon α-2a and interferon-β) and type II (interferon-γ) interferons with interferon-related cytokines, including tumor necrosis factor alpha, interleukin-6, interleukin-10, monocyte chemoattractant protein-1, and C-X-C Motif Chemokine Ligand 10, in the CSF and paired serum from patients with Alzheimer's disease, mild cognitive impairment due to Alzheimer's disease, non-Alzheimer's disease-related cognitive impairment and age-sex-matched cognitively normal participants.
Results: Only interferon-β in CSF was significantly elevated in Alzheimer's continuum groups, while interferon-β, interferon-γ, tumour necrosis factor alpha, and IL-6 were significantly elevated in the serum of patients with Alzheimer's disease than that seen in cognitively normal or non- Alzheimer's disease-related cognitive impairment. Moreover, interferon-β was significantly associated with Alzheimer's
disease core biomarkers (Aβ42, Aβ42/Aβ40 ratio, P-tau, and T-tau) and cognitive performance. The CSF interferon-β levels were also significantly higher in APOE ε4 carriers than in non-carriers, while including the CSF P-tau, T-tau, and plasma P-tau as co-variables changed this difference, but not by the Aβ42/ Aβ40 ratio.
Conclusions: In conclusion, our findings demonstrate that interferon-β levels, especially in the CSF, are significantly associated with the pathology and disease progression of Alzheimer's disease, making it a potential therapeutic target and promising biomarker for Alzheimer's disease.

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POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

PERIPHERAL BLOOD INFLAMMATORY MARKERS AND THEIR CORRELATION WITH SEVERAL CLINICAL ASPECTS OF PARKINSON'S DISEASE.

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Aims: Objectives: The pathogenesis of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease (PD), is significantly influenced by their immunological basis. Studies on the serum level of tumor necrosis factor-α (TNF-a) in PD are contradictory. Additionally, based on our research, no article has ever examined the serum level of CC chemokine ligand 2 (CCL2) in PD. We examined if the severity and clinical phenotype of PD and those variables' serum levels are related in this study.
Methods: Patients and methods:130 patients with Parkinson's disease (PD) and 70 healthy volunteers were included in this case-control study. The diagnosis was made in accordance with the clinical diagnostic standards of the UK Parkinson's Disease Society Brain Bank. The severity of PD was assessed using the modified Hoehn and Yahr (H and Y) scale and Unified PD Rating Scale (UPDRS). Cognitive assessment was done using Addenbrooke's Cognitive Examination (ACE-III) and Mini Mental State of Examination (MMSE). Patients were categorized into three distinct clinical phenotypes: tremor dominant, intermediate and postural instability gait difficulty. We measured the levels of TNF-a and CCL2 in the serum with Enzyme-linked Immunosorbent Assay (ELISA). The correlation of several clinical aspects of Parkinson's disease patients to these cytokine and chemokine serum levels was examined.
Results: Mean serum TNF-α and CCL2 levels were not significantly different in PD patients as compared to controls. TNF-a serum levels were significantly correlated with the Hoehn and Yare scale and UPDRS. More specifically, serum TNF-a levels were shown to be higher in the more advanced clinical stages of the disorder p=0,0003).
Conclusions: Our work has shown that serum levels of TNF-a may serve as significant predictive biomarkers for Parkinson's disease severity.

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POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

STRESS SUSCEPTIBILITY-RELATED IMMUNE RESPONSE HETEROGENEITY INFLUENCES COGNITIVE IMPAIRMENT IN A MODEL OF ALZHEIMER'S DISEASE

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Aims: Meta-analysis studies have showed strong correlations between individuals' histories of early-life depression induced by stress and their risk of developing AD later in life. While stress is crucial for survival, its response can become maladaptive and cause various disease conditions. However, it is not known if maladaptive stress response may cause an acceleration of the onset and/or exacerbation of cognitive decline in a transgenic mouse model of AD.
Methods: We used 8-week-old WT and 5xFAD mouse model with AD type phenotype. Repeated social defeat stress (RSDS) paradigm was performed to promote social stress-induced anxiety or depression like behaviors in rodents for 2 weeks. Following RSDS, novel object recognition test was performed to measure cognitive function. CyTOF was used to profile homeostasis of peripheral immune cells.
Results: We found that following RSDS exposure, 39.4% of total WT mice showed significant social avoidance behavior (susceptible mice). Interestingly, 61.2% of total 5xFAD mice were significantly more 'susceptible', suggesting a heterogeneous maladaptive stress response in 11-weeks-old AD mice. Excitingly, we found that only susceptible 5XFAD mice, exhibited significantly impaired cognitive functions, relative to non-stressed 5xFAD mice which is a pre-pathological stage of AD ($p<0.05$). There was no statistically significant difference in cognitive impairment among susceptible, resilient and non-stressed WT mice, respectively. To understand potential underlying mechanisms, we performed CyTOF and identified alteration of certain immune cell subtypes in blood of susceptible 5xFAD mice compare with resilient 5xFAD mice.
Conclusions: Our study elucidated how the heterogeneity of immune response differentiates in stress susceptible 5xFAD mice accelerated cognitive impairments. These data may provide insight into disease progression and the effects of drug treatments, tailored to the individual condition in transgenic mouse model of AD.

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P0071 / #2695

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

BIOLOGICAL VARIATION OF PLASMA SNAP-25 LEVELS IN 23 HEALTHY VOLUNTEERS

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Aims: Plasma biomarkers such as ptau181, $A\beta_{42/40}$ and neurofilament light (NfL) are being considered for several context-of-use applications in the Alzheimer's disease (AD) field, while synaptic markers such as β-synuclein and SNAP-25 in plasma are still in their discovery phase. In this study, we explored individual biomarker stability over a seven months period in follow-up plasma samples and evaluated age-dependency of SNAP-25, NfL, $A\beta_{42/40}$ and ptau181 levels in 23 healthy volunteers.
Methods: All markers were quantified with homebrew immunoassays on the Quanterix Simoa platform which have been previously described for $A\beta_{42/40}$ and ptau181, while NfL and SNAP-25 were recently developed in-house.
Results: Plasma SNAP-25 levels ranged from 0,47-1,5 pg/mL, while the median and interquartile range are 0,80 (0,64-0,92) pg/mL. The levels of the other three markers are comparable to control groups from previous studies. The age of healthy volunteers ranged from 22 to 69 years and a clear age-dependency of plasma NfL was observed in these healthy volunteers (Rho=0,71(CI 0,54-0,83), p<0,0001). SNAP-25, ptau181 and $A\beta_{42/40}$ did not show an age-dependent effect in this cohort. Also, no clear correlation could be observed between any of these markers. Measuring all four plasma biomarkers in follow-up samples of seven months from these healthy volunteers demonstrate that all these biomarkers remain stable over time taking confounders, such as age and sex into consideration.
Conclusions: In contrast to NfL, SNAP-25 levels were not associated with age. Furthermore SNAP-25 levels were stable over seven months, which is relevant for consideration of SNAP-25 as a target-engagement biomarker if confirmed in AD patients. Finally, this pilot study indicates that SNAP-25 levels did not correlate with other AD plasma markers.

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P0072 / #1048

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

DISRUPTION OF CYTOSKELETAL ACTIN-PSD95 INTERACTION AT THE SYNAPSE IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Aims: Dynamic regulation of actin mediated by actin interacting proteins is critical for synaptic functions such as neurotransmission and synaptic plasticity. F-actin levels at the synapse are significantly decreased in APP/PS1 mice as early as 1 month of age. Therefore, we aim to characterize synaptosomal actin interactome from wildtype (WT) and APP/PS1 mice.
Methods: Synaptosomes were isolated from cerebral cortex of age matched wildtype and APP/PS1 mice. Immunoprecipitation was performed using anti-actin polyclonal antibody. Immunoprecipitated elutes were resolved on SDS PAGE gels, digested and subjected to LC-MS/MS analysis. The MS data was validated by immunoprecipitation using anti PSD-95 antibody followed by immunoblotting against β-actin in synaptosomes from both WT and APP/PS1.
Results: We detected 232 proteins in WT and 231 proteins in APP/PS1 mice interacting with actin in the synaptosome at the age of 6 months. We identified 166 proteins common to both WT and APP/PS1, while 66 and 65 proteins were specific to WT and APP/PS1 mice, respectively. Our proteomic analysis revealed several actin interacting proteins critical for synaptic functions, protein translation and energy metabolism. We identified PSD-95, a scaffolding protein to several neurotransmitters and signal transduction component, to associate with actin in WT and APP/PS1 mice. We have validated PSD-95 actin interaction in synaptosomes isolated from adolescent and middle-aged WT and APP/PS1 mouse brain cortex. PSD95 association is detected with actin and is significantly decreased in middle-aged APP/PS1 mice compared with WT while it remains unaffected in the F-actin fraction of synaptosomes in APP/PS1 mice.
Conclusions: Our results demonstrate the synaptosomal actin interactome in WT and APP/PS1 mice and identified critical interactions that may delineate synaptic dysfunctions associated with AD.

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P0073 / #539

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

SERUM LEVELS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) ARE INCREASED IN ALZHEIMER'S DISEASE AND MCI PATIENTS AND CORRELATE WITH COGNITIVE DEFICITS

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Aims: Alzheimer's disease (AD) is a central nervous system (CNS) disease characterized by loss of cognitive functions and neurodegeneration. Plasmin is an enzyme degrading many plasma proteins. In the CNS, plasmin may reduce the accumulation of Aβ, and have other actions relevant to AD pathophysiology. Brain plasmin synthesis is regulated by two enzymes: one activating, the tissue *plasminogen* activator (*tPA*), and the other inhibiting, *the plasminogen activator inhibitor-1* (*PAI-1*). We investigated whether tPA and PAI-1 serum levels in AD patients are altered compared to cognitively healthy controls. Moreover, we examined the PAI-1/tPA ratio in these patient groups.
Methods: In total, 40 patients with dementia due to AD , 40 patients with amnestic mild cognitive impairment (aMCI) due to AD, and 10 healthy controls were recruited from Czech Brain Aging Study. Venous blood was collected, and PAI-1 and tPA serum concentrations were quantified by sandwich ELISAs.
Results: The results showed that PAI-1 levels increased in patients with dementia and aMCI due to AD. This increase negatively correlated with cognitive deficit measured by MMSE. Similarly, the ratio between tPA and PAI-1 gradually increases in patients with aMCI and dementia.
Conclusions: This study demonstrates that patients with dementia and aMCI due to AD have altered PAI-1 serum levels and PAI-1/tPA ratio. Since these enzymes are CNS regulators of plasmin, PAI-1 serum levels could be a marker reflecting the cognitive decline in AD.

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P0074 / #2334

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

TRANSLATIONAL POTENTIAL OF SYNAPTIC ALTERATIONS IN ALZHEIMER`S DISEASE PATIENTS AND APP KNOCK-IN MICE

Erika Bereczki[1], Dina Medina-Vera[2], Daniela Enache[1], Simone Tambaro[1], Ethar Abuhashish[1], Cristina Rosell-Valle[2], Bengt Winblad[1], Fernando Rodriguez De Fonseca[2], Per Nilsson[1]
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Aims: Post-mortem studies suggest that alterations in synaptic proteins such as zinc transporter protein 3 (ZnT3), dynamin1 (Dyn1) and AMPA glutamate receptor 3 (GluA3) are associated with cognitive decline in AD. We aimed to measure the concentration of ZnT3, Dyn1 and GluA3 in CSF of subjects with mild cognitive impairment and AD patients and compared the levels to cognitively and neurologically healthy controls. We also aim to assess the translational potential of these synaptic proteins in two established App knock-in AD animal models by assessing the CSF, hippocampal and cortical synaptic protein concentrations.
Methods: We have used ELISA to measure these three proteins in CSF and/or brain of 12-and 24-months old App^{NL-F} and App^{NL-G-F} knock-in mice and App^{Wt} control mice. Regional distribution and expression of these proteins upon ageing is explored by quantitative immunofluorescence microscopy.
Results: We found a significant increase in concentrations of ZnT3 and GluA3 in CSF of both MCI and AD patients compared to cognitively and neurologically healthy controls. MCI patients who converted to AD exhibited elevated baseline CSF ZnT3 concentrations compared to MCI non-converter patients. Similar to the alterations in AD subjects, CSF GluA3 concentration was significantly higher in AppNL-G-F knock-in mice as compared to wild-type controls. Notably, all the three CSF synaptic protein concentrations correlated negatively with concentrations in hippocampal lysates.
Conclusions: The elevated ZnT3 concentrations in the CSF of MCI-Cv versus MCI-nCv group of patients suggests a prospective role of ZnT3 in differentiating dementia patients of the biological continuum of AD. The increased CSF concentrations of synaptic proteins in both MCI and AD subjects, potentially reflecting synaptic alterations in the brain, were similarly observed in the App knock-in mouse models highlighting the translational potential of these proteins as markers for synaptic alterations.

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P0075 / #2107

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

QUANTITATIVE SYNAPTIC PROTEOMICS: A TOOL TO MEASURE DISEASE PROGRESSION AND INVESTIGATING THE DYNAMICS OF SYNAPTIC DYSFUNCTION IN NEURODEGENERATIVE DISEASES

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Aims: Synaptic dysfunction is a key pathogenic event in neurodegenerative and psychiatric diseases. Biomarkers reflecting synaptic integrity could be highly valuable tools to monitor synaptic dysfunction directly in individual patients during treatment or disease progression.
Methods: Immunoprecipitation was performed on a KingFisher™ Flex Purification System (96 well format). Isotopically labeled standards were added and the enriched proteins were digested with trypsin or trypsin/Lys-C. MS based quantification was performed either with LC-PRM-MS on a Q Exactive/Ultimate 3000 system or LC-MRM-MS on a 6495 Triple Quadrupole LC/MS system.
Results: CSF levels of SNAP-25 and SYT-1 are significantly increased in AD patients with dementia compared with Ab-negative controls and MCI patients, but also compared with Ab-positive controls. In PD and FTD, there is generally a trend to decreased levels compared to controls. In this study the IP-MS assay is expanded to a two-step immunoprecipitation where proteins are simultaneously enrich with antibodies from different species. Employing this novel method, we have been able to, besides SNAP-25 and SYT-1, quantify both complexin-1 which is primarily present in glutamatergic terminals and complexin-2, which is more highly represented in inhibitory terminals. Preliminary data show CSF levels of both complexins increased in AD compared to controls. Additionally, we perform characterization as well as simultaneous quantitation of co-immunoprecipitated proteins. This method could be an alternative to sandwich ELISAs with capture and detection antibodies recognizing different proteins. Preliminary results include quantitation of several SNARE associated proteins co-immunoprecipitated with SNAP25 in post-mortem brain tissue from patients with AD, and several tauopathies.
Conclusions: Combining robust and high-throughput selective protein enrichment with quantitative mass spectrometry is a promising novel method for investigating synaptic dysfunction.

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POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

THE MK2 CASCADE MEDIATES TRANSIENT ALTERATION IN MGLUR-LTD AND SPATIAL LEARNING IN A MURINE MODEL OF ALZHEIMER'S DISEASE

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Aims: Early deficits in long-term potentiation (LTP) are associated with the accumulation of amyloid beta and learning impairment in the APP_{swe}/PS1dE9 (APP/PS1) mouse model of Alzheimer's disease. However, less is known about how mGluR-mediated long-term depression (mGluR-LTD) is affected. The aim of this study was to investigate whether mGluR-p38 MAPK-MAP kinase-activated protein kinase 2 (MK2) signalling contributes to the depressed synapse dynamic range and cognitive dysfunction seen in these mice.
Methods: To address this question we generated a novel APP/PS1 x MK2 knockout mouse combined with several experimental approaches such as the Barnes maze behavioural testing combined with field excitatory postsynaptic potential recordings at Shaffer collateral-CA1 hippocampal synapses and biochemical analysis.
Results: In this study, we have found that mGluR-LTD is enhanced in the APP/PS1 mouse at 7 months but returns to wild-type levels at 13 months of age when compared to wild-type littermates mice. This transient over-activation of mGluR signalling is coupled with impaired LTP and shifts the dynamic range of synapses towards depression. These alterations in synaptic plasticity are associated with an inability to utilise cues in a spatial learning task. This transient dysregulation of plasticity can be prevented by deletion of the MK2, a substrate of p38 MAPK.
Conclusions: These findings demonstrated that manipulating the mGluR-p38 MAPK-MK2 cascade at 7 months can prevent the shift in synaptic dynamic range. Our work reveals the MK2 cascade as a potential pharmacological target to correct the over-activation of mGluR signalling and revert synaptic plasticity to wild-type levels. This work was supported by the Wellcome Trust Grant 200646/Z/16/Z and MMU Strategic Opportunity Funding to SALC.

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P0077 / #1601

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

A SPATIOTEMPORAL EXPLORATION OF CHANGES IN SYNAPTIC TRANSMISSION AND GENE EXPRESSION IN APP NL-F X TREM2-R47H MICE

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Aims: We have previously reported in *App*$^{NL-F/NL-F}$ knock-in mice that, in microglia touching plaques, expression of *Trem2*, along with phagocytic and lysosomal genes is greatly increased. This effect is prevented by the *Trem2*$^{R47H/R47H}$ risk factor mutation (https://www.biorxiv.org/content/10.1101/2022.01.26.477873v1). Here, we explore how this *Trem2* mutation affects synaptic function and transmission.
Methods: Spatial transcriptomics was used to investigate changes in the hippocampal expression of synaptic genes in relation to plaques in 18-month-old *App*$^{NL-F/NL-F}$ and *App*$^{NL-F/NL-F}$/*Trem2*$^{R47H/R47H}$ mice. Patch-clamp and field potential electrophysiological recordings from CA3-CA1 hippocampal synapses were obtained to study the effect of the inclusion of the *Trem2*$^{R47H/R47H}$ mutation on basal synaptic transmission and long-term plasticity in wildtype and *App*$^{NL-F/N-LF}$ mice.
Results: Spatial analyses revealed a downregulation in the expression of synaptic genes in and near plaques in the *App*$^{NL-F/NL-F}$ mice. Patch-clamp recordings confirmed an increase in glutamate release probability in *App*$^{NL-F/NL-F}$ compared to wildtype animals at 7, 18 and 30 months of age (P<0.0001). The magnitude of long-term depression was greater in *App*$^{NL-F/NL-F}$ than wildtype mice. However, there were no additional effects of the *Trem2*$^{R47H/R47H}$ mutation for the electrophysiological findings while some but not all of the downregulation of synaptic genes depended on the *Trem2*$^{R47H/R47H}$ mutation.
Conclusions: TREM2-dependent effects are largely plaque dependent. The downregulation of synaptic gene expression in regions in the immediate vicinity of plaques in *App*$^{NL-F/NL-F}$ mice is likely due to microglia phagocytosing unhealthy synapses damaged by the high concentration of amyloid-beta around plaques. For some genes, this loss is decreased in the *App*$^{NL-F/NL-F}$/*Trem2*$^{R47H/R47H}$ mice, in which phagocytosis is impaired. At an electrophysiological level, synaptic changes were not exacerbated by the *Trem2*$^{R47H/R47H}$ mutation as the synapses recorded were likely far from plaques.

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P0078 / #1128

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

SOLUBLE AMYLOID-BETA ALTER ULTRASTRUCTURE OF GLUTAMATERGIC SYNAPSES AND PRE-SYNAPTIC MITOCHONDRIA IN THE HIPPOCAMPUS

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Aims: Synaptic dysfunction is a pathological hallmark of Alzheimer's disease (AD) that begins in the preclinical stages of (AD) along with changes in cognitive function. Soluble oligomers of amyloid β (oAβ) have been detected in AD brains and oAβ levels within synaptosomes could differentiate subjects with early AD from cognitively intact controls with AD pathology. Our study aims to provide evidence for the effect of soluble oAβ on synapse and mitochondria pathology and function in the absence of Aβ plaques.
Methods: We used transgenic mice expressing the Dutch APP E693Q mutation (DU) that produce only oAβ and do not develop Aβ plaques. We used Western blot to measure GluR2/3 protein expresison. We next quantified density and morphology of excitatory synapses and presynaptic mitochondria in the CA1 region of the hippocampus in DU mice compared to wild type (WT) mice, using electron microscopy (EM). We also performed immunogold EM to examine the density and morphology of CA1 GluR2/3+ synapses.
Results: There was no change in GluR-2/3 expression between WT and DU mice. Total synapse density, as well as the density of non-perforated and perforated synapses, and the density and distribution of GluR-2/3 receptors at the synapse in DU mice were similar to those in WT. When we assessed perforated and non-perforated GluR-2/3+ synapses, GluR-2/3+ non-perforated synapses showed larger area of post-synaptic densities (PSD) in DU mice compared to WT. Mitochondrial density and size was also decreased in DU mice compared to WT.
Conclusions: Our observations of altered PSD area at GluR-2/3 + synapses and decreased mitochondrial density at axon terminals in the CA1 of DU mice point towards a presynaptic role of oAβ in contributing to the cognitive deficits observed in these mice.

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P0079 / #1794

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

POLYPHARMACY THERAPIES DIFFERENTIALLY AFFECT FUNCTIONAL AND COGNITIVE OUTCOMES IN A MOUSE MODEL OF ALZHEIMER´S DISEASE DEPENDING ON SEX AND MULTIPLE-DRUG COMBINATION

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Aims: The concurrent use of five or more medications (polypharmacy) is associated with a greater risk of developing adverse drug events and cognitive decline in older people. In this context, people suffering from dementia are particularly susceptible to unexpected events secondary to polypharmacy. Here we investigate the effects of long-term administration of two different multiple-drug regimens in the APP^{NL-G-F} knock-in (APP KI) mouse model of Alzheimer´s Disease (AD), and whether this could affect the disease progression at early stages. Gaining knowledge of benefits and harms associated with multi-medication use would help in designing more personalized therapies.
Methods: APP KI mice were fed for 2 months with a control or polypharmacy diet (including anti-hypertensive, lipid lowering and psychotropic drugs, in two different combinations) based on the most used medications by older adults in Sweden. Animals were assessed for locomotion, cognition, and anxiety-like behavior. Brain tissues were collected for molecular biology experiments, while blood was analyzed by GC/LC-MS to measure serum metabolomics.
Results: We found that polypharmacy in AD mice differentially affected essential functions such as locomotion, and distinct types of memory, depending on sex and multiple-drug combination. APP KI male mice treated with combination#1 exhibited a rescue of cognitive deficits compared to controls, which we didn´t observe in females. These findings positively correlate with the significant reduction of cortical Aβ plaques observed in treated APP KI males. Conversely, combination#2 didn´t exert a positive effect on the cognitive abilities of the mice.
Conclusions: We show that multi-medication therapies may impact the progression of AD pathophysiology, supporting the importance of understanding mechanisms of polypharmacy that can help in defining more individualized therapies in aging and AD, taking the gender into special consideration.

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P0080 / #1575

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

ALTERED SYNAPTIC PATTERN OF NMDAR IN ALZHEIMER'S HUMAN BRAIN

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Aims: NMDA receptor (NMDAR) malfunctioning has been claimed to be a crucial event in Alzheimer's disease (AD), the most common form of dementia. While synaptic NMDAR activation leads to synaptic plasticity, extrasynaptic NMDAR activation leads to excitotoxicity, mitochondrial toxicity and cell death. Our aim is to shed light on the synaptic vs extrasynaptic NMDAR distribution in the Alzheimer's Disease brain.
Methods: We isolated synaptic and extrasynaptic membranes from frontal cortex of AD and non-demented subjects. We studied the levels of NMDAR subunits GluN1, GluN2B and GluN2A. We also evaluated the GluN2B phosphorylation at sites Y1472 and Y1336, associated to synaptic and extrasynaptic membranes, respectively. Furthermore, to reach our aim we are using two different AD mice models: TAUP301S and APPswe/PS1dE9.
Results: We found lower levels of GluN1, GluN2B, Glun2A and pY1472-GluN2B at synaptic membranes in AD respect to non-demented patients. At extrasynaptic membranes, an increase of GluN2B levels and a reduction in Y1336-GluN2B phosphorylation were observed. Altered GluN2B phosphorylation was also replicated in APPswe/PS1dE9 mice.
Conclusions: We found that in AD synaptic-NMDAR levels are lower, while extrasynaptic GluN2B levels are higher compared to non-demented individuals. However, the phosphorylation of both GluN2B Y1472 and Y1336 is lower in AD.

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P0081 / #1552

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

SARS-COV-2 SPIKE PROTEIN INDUCES LONG-TERM TLR4-MEDIATED SYNAPSE AND COGNITIVE LOSS RECAPITULATING POST-COVID SYNDROME

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Aims: To develop a mouse model of intracerebroventricular (icv) SARS-CoV-2 Spike protein exposure to understand the role of this protein in cognitive and synapse impairment of NeuroCOVID.
Methods: The objective of this study was to assess the direct impact of SARS-CoV-2 S protein on cognitive function, and to gain insight into the mechanisms underlying COVID-19 long-term brain effects, thereby identifying new avenues for therapeutic intervention. Dissection of the underlying mechanisms was performed using qPCR, ELISA, SIMOA, behavioral, and immunohistochemical approaches in mice subjected to pharmacological inhibition of C1q or TLR4, with the role of TLR4 being confirmed using a knockout mouse line. Additionally, the direct impact of spike in different brain cell types was assessed using murine BV-2, and primary neuronal cortical cell cultures. Finally, to support the translational relevance of our results, we investigated two *TLR4* SNPs in a cohort of recovered COVID-19 patients with cognitive impairment.
Results: Here, we demonstrate that brain infusion of S protein in mice induces late cognitive impairment and increases serum levels of neurofilament light chain (NFL), which recapitulates post-COVID features. Neuroinflammation, hippocampal microgliosis and synapse loss are induced by S protein. Increased engulfment of hippocampal presynaptic terminals late after S protein brain infusion was found to temporally correlate with cognitive deficit in mice. Blockage of TLR4 signaling prevented S-associated detrimental effects on synapse and memory loss. In a cohort of 86 patients recovered from mild COVID-19, genotype GG TLR4 -2604G>A (rs10759931) was associated with poor cognitive outcome.
Conclusions: Collectively, these findings indicate that S protein directly impacts the brain and suggest that TLR4 is a potential target to prevent post-COVID cognitive dysfunction.

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P0082 / #913

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

SCREENING ALZHEIMER'S GENETIC RISK FACTORS AGAINST AMYLOID-BETA SYNAPTOTOXICITY

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Aims: Synapse degeneration is one of the earliest events in Alzheimer's disease (AD) and toxic oligomers of amyloid-beta (Aβ) peptide, cleavage products of APP, is suggested to play a major role in this process. Genome-wide association studies recently reported 75 genomic risk loci for developing AD, but if and how the potential risk genes contribute to AD remains unknown. We conducted a high-content shRNA screening to assess the impact of 200 neuronal risk genes on synapses. This project aims to determine the role of AD risk factors in Aβ-induced synaptotoxicity.
Methods: Top 10% genes with highest impact on synapses when silenced were shortlisted for a medium-throughput screening to assess their capacity to block Aβ-induced synaptotoxicity. Synaptotoxicity was modelled in microfluidic coculture devices that expose primary neurons to Aβ1-42 oligomers secreted by model cell lines overexpressing wild-type or mutant (V717I; London) APP. We will modulate the expression of target genes either in pre- or postsynaptic neurons and assess its impact on synaptic connectivity.
Results: Based on the shRNA screening, we shortlisted 17 detrimental genes, for which we obtained overexpression vectors packed in lentiviruses, and 6 protective genes. We have developed a medium-throughput co-culture device that permits screening twelve genes per imaging session using the INCell 6000 automated microscope, as well as an automated image analysis workflow for detecting and assigning presynaptic to postsynaptic puncta based on their relative proximity.
Conclusions: We have developed a microfluidic co-culture model to rapidly and systematically interrogate genetic risk factors for their impact on synaptic connectivity. The medium-throughput screen will help us identify AD genetic risk factors with a potential to block Aβ-induced synaptotoxicity *in vitro*. Hit genes will be functionally validated via microelectrode array recordings.

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P0083 / #907

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

ASSESSING MOLECULAR MECHANISMS OF SYNAPTIC DYSFUNCTION IN FRONTOTEMPORAL DEMENTIA PATIENT-DERIVED NEURONS

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Aims: Objectives: Frontotemporal dementia (FTD) is characterized by progressive neurodegeneration in the frontal and temporal lobes associated with personal and behavioral changes, problems with executive functions as well as language impairment. The major genetic cause underlying FTD and amyotrophic lateral sclerosis is a *C9orf72* GGGGCC hexanucleotide repeat expansion (C9-HRE). Impaired synaptic function is suggested to play a significant role in FTD. Patients commonly show alterations in the glutamatergic and GABAergic neurotransmitter systems. However, not much is known of the molecular mechanisms of these synaptic changes so far.
Methods: Methods: Human induced pluripotent stem cells (iPSCs) were generated from FTD patients and healthy individuals from a genetically and clinically well-characterized cohort of Finnish FTD patients containing both C9-HRE carriers and non-carriers. The iPSCs were differentiated to cortical neurons using the dual SMAD inhibition approach. The identity of the iPSC-neurons and disease-specific alterations were assessed by using different neuronal markers by qPCR and immunohistochemistry.
Results: Results: The obtained cortical iPSC-neuron cultures contain both glutamatergic and GABAergic neurons and express markers of the six cortical layers, and thus they model well the neuronal complexity of human cortex. The C9-HRE-carrying iPSC-neurons were found to display the C9-HRE-associated pathological RNA foci. All FTD iPSC-neurons also showed changes in TDP-43 and p62 proteins. Initial analyses of dendritic spines suggested decreased number of spines in FTD iPSC-neurons. Next, we will examine if the FTD iPSC-neurons show alterations in different synaptic proteins or synaptic activity.
Conclusions: Conclusion: These studies deciphering underlying mechanisms of synaptic dysfunction in FTD may help in identifying novel therapeutic options or biomarker candidates. Using cells from individuals harboring different genetic backgrounds enables identifying specific disease mechanisms that are C9-HRE-dependent or common in all FTD patients.

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P0084 / #1199

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

ASSESSING FUNCTIONAL CHANGES TO SYNAPTIC ACTIVITY IN ORGANOTYPIC HIPPOCAMPAL SLICES CULTURES, PREPARED FROM TGCRND8 APP TRANSGENIC MICE.

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Aims: OHSCs prepared from TgCRND8 mice develop phenotypic changes that are relevant to early changes in human AD, including increased amyloid beta and progressive loss of the presynaptic protein synaptophysin; however, direct analysis of functional changes in this model has not yet been achieved. This project aims to develop the use of patch clamp electrophysiology to investigate the impact of overexpressed mutant APP in TgCRND8 OHSCs on synapse function, and to further apply this technique to other OHSC models of neurodegeneration and inflammation.
Methods: Brains from P6-9 CRND8 mice (overexpressing human APP with the Swedish and Indiana mutations), and their WT litter mates, were dissected; sagittal brains slices were cut at 350μm using a vibratome. Organotypic hippomcapal slice cultures (OHSCs) were cultured for up to 8 weeks. At 2, 4, 6 and 8 weeks in vitro in vitro patch clamp recordings were taken from neurones in area CA1 of the OHSCs. Following gap free recording in voltage clamp, 1uM tetrodotoxin was used to record miniature excitatory and inhibatory postsynaptic currents (mEPSCs). Slices were collected for westernblot and assayed for synaptic proteins.
Results: Preliminary data shows subthreshold inhibitory and excitatory synaptic activity, and action potentials, recorded from OHSCs up to 8 weeks in vitro. The frequency of mEPSPs and mIPSPs is correlated with the amount of synaptophysin protein detected in OHSCs.
Conclusions: This preliminary data demonstrates the functional viability of the OHSCs up to 8 weeks in vitros. We are able to measure the size and frequency of action potential evoked post-synaptic responses, and mEPSPs, and compare to the levels of synaptic proteins. This can be used to determine the nature of the earliest functional changes in the OHSCs, alongside their temporal relationship to structural changes.

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P0086 / #1247

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

PERTURBATION OF AKT/MTOR SIGNALING PATHWAY IN HIPPOCAMPUS OF ALZHEIMER'S DISEASE MOUSE MODEL

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Aims: Akt and mechanistic target of rapamycin (mTOR) signaling pathways are implicated in AD pathology. Our aim is to understand the molecular mechanisms prior to manifestation of pathological symptoms by examining the Akt1 and mTOR signaling cascades and new protein synthesis in hippocampus of WT and APP/PS1 male mice.
Methods: We isolated post nuclear supernatant (PNS) and synaptosomes from brain cortices of WT and APP/PS1 mice at different ages. Synaptosomes and PNS were resolved on SDS-PAGE and immunoblotted against respective antibodies. Further, synaptoneurosomes were also prepared from hippocampus and we performed ^{35}S methionine incorporation assay without or with KCl stimulation. Statistical comparisons were performed using two-way ANOVA followed by Tukey's post-hoc test or two-tailed Mann-Whitney U test.
Results: We observed that pAkt1, pGSK3β, pmTOR, pS6 ribosomal protein, p4E-BP1 levels are significantly decreased in both post nuclear supernatant (PNS) and synaptosomal fractions isolated from hippocampus of one month old (presymptomatic) APP/PS1 compared to WT male mice. Further, activity dependent new protein synthesis at the synapse was significantly impaired in synaptoneurosomes isolated from hippocampus of presymptomatic APP/PS1 mice, and this deficit is sustained at young adults (three months). However, no impairment was observed in basal protein synthesis at both ages in hippocampus of APP/PS1 compared to WT male mice. Down regulation of Akt1 precludes synaptic activity dependent protein translation at the dendrites but not in the soma in hippocampal neurons from APP/PS1 mice compared to WT mice.
Conclusions: Our finding demonstrate that the dysregulation of Akt1/mTOR and its downstream signaling molecules in hippocampus contributes to synaptic dysfunction in AD through loss of activity dependent new protein synthesis at the synapse in hippocampus which is essential for synaptic plasticity and maintenance.

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P0087 / #2395

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

ROLE OF RNF10 IN ALZHEIMER'S DISEASE SYNAPTIC FAILURE

Laura D'Andrea, Stefano Musardo, Nicolò Carrano, Silvia Pelucchi, Ramona Stringhi, Filippo La Greca, Ana Ribeiro, Matteo Audano, Francesca Genova, Nico Mitro, Diego Scheggia, Fabrizio Gardoni, Monica Diluca, Elena Marcello
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Aims: Synaptonuclear messengers translate synaptic signaling into changes in gene transcription, thus modulating long-term functional modifications of the synapto-dendritic input. Alterations of such proteins lead to synaptic failure, suggesting a contribution to synaptopathies such as Alzheimer's Disease (AD). During AD early stages, the amyloid-β peptide (Aβ) oligomers trigger the disruption of mechanisms of neuronal plasticity, eventually resulting in synapse loss and in cognitive deficits. In this frame, the synaptonuclear messenger RING Finger Protein 10 (RNF10) operates as a mobile hub that docks NMDA receptor-derived signalosomes to nuclear target sites, regulating genes involved in spine morphology and AD pathogenesis. We aimed at investigating the potential involvement of RNF10 in AD-synaptic dysfunction.
Methods: We used several imaging and biochemical approaches to investigate RNF10 pathway in AD in vitro and in vivo models.
Results: RNF10 expression and localization are altered in AD patients' hippocampi at the earlier stages of the disease. In the hippocampus of APP/PS1 mice, a mouse model of AD, we detected an upregulation of RNF10 signaling in the initial stages of the pathology. The RNF10 downregulation in the hippocampus of APP/PS1 mice before the onset of the pathology can restore cognitive function in AD mice. To investigate the RNF10-triggered neuronal pathways in AD, we exposed primary hippocampal cultures to Aβ oligomers. Aβ triggers a calcium-dependent NMDA receptor-induced RNF10 nuclear translocation. RNASeq data show that RNF10 silencing prevents the Aβ oligomers-driven changes in the expression of genes implicated in synaptic and mitochondrial function. In line with these results, RNF10 down-regulation prevents Aβ oligomers-triggered mitochondrial defects in neuronal cultures.
Conclusions: Our findings suggest that RNF10 can play a key role in translating Aβ-induced signaling into synaptic and mitochondrial dysfunction, thus contributing to AD cognitive deficits.

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P0088 / #2129

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

EXCESSIVE VESICLE CLUSTERING BY E46K-AMPLIFIED '3K' ALPHA-SYNUCLEIN UNDERLIES EARLY-DISEASE HIPPOCAMPAL SYNAPTIC DEFICITS IN A MOUSE MODEL OF SYNUCLEINOPATHY

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Aims: A large proportion of people with Parkinson's Disease (PD) develop PD dementia over time, which is associated with elevated levels of insoluble alpha-synuclein (aS) in the hippocampus. Better understanding of early aS-associated hippocampal pathologies may contribute to new therapies that delay the progression of dementia in PD. This study aims to characterize early synaptic changes in the hippocampus of transgenic mice expressing wild-type (WT)/mutant aS proteoforms, including familial PD-causing G51D and E46K mutations, and E46K's phenotypic amplification '3K' aS.
Methods: We studied aS distribution and biophysical properties at synaptic vesicle (SV) clusters in hippocampal tissue and synaptosomes from WT/mutant mice by immuno-electron microscopy, super-resolution microscopy, and photobleaching approaches. Hippocampal synaptic plasticity parameters were obtained by electrophysiology. aS mobility at synapses is studied using FRAP on synaptosomes from WT/mutant mice electroporated with Alexa488-coupled aS.
Results: We found that disturbed hippocampal long-term potentiation and paired-pulse facilitation are early pathological events in mice with moderate (~1-fold) overexpression of 3K aS, which was accompanied by aS accumulation at SV clusters, alterations in SV distribution and density, and increased clathrin-coated SVs. E46K/3K aS at SV clusters exhibited increased resistance to photobleaching compared to WT and -more prominently– to G51D aS. This gradient suggests that enhanced membrane-association of aS partially arrests its dynamics at SV clusters. To confirm this, we are currently conducting FRAP experiments to study WT/mutant aS mobility in synaptosomes. In parallel, we are characterizing synaptic function in E46K/G51D mice to further dissect different possible routes leading to aS-related synaptic dysfunction.
Conclusions: Our preliminary dataset provides evidence for a role of excessive vesicle interaction by 'K' aS mutations in early hippocampal synaptic impairment, implying increased membrane-phospholipid-association of familial PD E46K-type mutant aS may promote pathological phase-separation at SVs.

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P0089 / #1883

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

THE SIGNIFICANCE OF THE CEREBROSPINAL FLUID POSTSYNAPTIC PROTEIN LEVELS IN THE PATIENTS WITH DEMENTIA

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Aims: Alzheimer's disease (AD) is a progressive and incurable neurodegenerative disorder. One of the earliest and most important symptoms is cognitive decline. Early deficits of memory and dysfunction of other cognitive symptoms seem to be closely related to dysfunctions of the neurons and synaptic plasticity. Interestingly, synaptic pathology appears to have an important meaning in AD. One of the postsynaptic proteins that reflects the synaptic pathology and is detected in human cerebrospinal fluid (CSF) is neurogranin. Ng is mainly located in dendrites and spines in brain structures like the hippocampus. It is suggested that this protein plays an essential role in synaptic transmission and modulation of memory processes. Ng is engaged in the induction of LTP by binding to calmodulin (CaM) in response to low Ca2+ levels. Therefore, the purpose of our investigation was the quantitive assessment of Ng in the CSF and comparison with core CSF biomarkers in the spectrum of AD.
Methods: The CSF levels of neurogranin and classical AD biomarkers, such as Aβ-42, Aβ-42/Aβ-40, hTau, and pTau181 were measured by immunoenzyme assays. The study group included patients with mild cognitive impairment (MCI), Alzheimer's disease and non-demented controls (CTRL).
Results: We observed significantly elevated concentrations of Ng in CSF of AD and MCI patients compared to non-demented controls. However, the highest difference was observed between AD and CTRL. Moreover, increased CSF levels of Ng correlated with age, Tau and pTau181 in the AD group.
Conclusions: Our results suggest that Ng could be a useful and valuable biomarker of the dementia spectrum.

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POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

THE POST-SYNAPTIC MARKER CYCLASE-ASSOCIATED PROTEIN (CAP2) IS SIGNIFICANTLY ASSOCIATED WITH ALZHEIMER DISEASE ACROSS SEVERITY STAGES AND CORRELATES WITH TAU-RELATED PATHOLOGY

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Aims: Several pre and post synaptic proteins have been identified in AD, thus arguing for synaptic biomarkers as an adjunctive measure for characterize AD in vivo. The Cyclase-associated protein 2 (CAP2) is known to play a role in synaptic plasticity in AD. Aim of the study was to evaluate whether CAP2 CSF levels are significantly associated to AD across severity stages and whether specifically correlate with tau and amyloid related biomarkers.
Methods: one-hundred ten AD patients, 20 dementia with Lewy bodies (DLB), 20 frontotemporal dementia (FTD) and 40 healthy controls (HC) underwent CSF analyses for h-tau, p-tau and Aß42 and a standardized neurological and cognitive behavioral assessment. CAP2 levels in CSF were assessed by using standard ELISA. Between-groups differences and correlations between CSF biomarkers were evaluated using non-parametric comparisons and partial correlation analyses adjusted for the effect of age, sex and disease duration.
Results: AD group, including either MCI and dementia patients, exhibited higher CSF CAP2 levels compared to controls or non-AD patients (p=0.001). Partial correlation CSF analyses showed a positive correlation between CAP2 levels and Tau (r=0.43, p=0.001), P-tau (r=0.41, p=0.001) and P-tau/ Aβ42 ratio (r=0.34, p=0.007). CAP2/ Aβ42 ratio was also significantly associated with a diagnosis of AD (r=0.38, p=0.0001) and exhibited a discrimination accuracy of 0.93 (CI95% 0.88-0.97%). CSF CAP2 levels were significantly either in MCI due to AD (p=0.0001) and in mild dementia due to AD (p=0.0001).
Conclusions: CAP2 levels in the CSF were increased in AD patients, since its early stages, and were associated with tau pathology in presence of amyloid pathology. These data strongly support the role of synaptic alteration in AD and its potential role as a surrogate marker for diagnose and assess pharmacological intervention

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POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

EXITABILITY CHANGES IN HIPPOCAMPAL NEURONS IN THE RODENT MODELS OF ALZHEIMER'S DISEASE AND A WAY TO PREVENT IT

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Aims: Early hippocampal hyperexcitability is known to be present in patients and different transgenic Alzheimer's models. Cellular and intracellular cascades and processes of this phenomenon are poorly understood.
Methods: Intrinsic neuronal excitability was investigated in CA1 hippocampal neurons *in vitro* in McGill-APP-rats and TBA2.1 mice. Additionally, in TBA2.1 mice we performed Nitarsone treatment (50 mg/kg) over a period of six weeks *in vivo* and compared intrinsic excitability with control groups.
Results: We observed increased intrinsic excitability of pyramidal neurons in McGill-APP-rats and TBA2.1 mice, as well as disruption of positive correlation between input resistance and action potential half width duration in disease conditions. Feeding of transgenic mice with Nitarsone, a small compound which restores CREB transcriptional activity, despite the presence of amyloid pathology, rescues this positive correlation.
Conclusions: Our data suggest that prevention of the CREB shut-off in AD models might be an effective way to slow down early synaptic failure in AD.

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POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

AMYLOID-BETA SHIFTS THE AGE-DEPENDENCE OF LOW FREQUENCY STIMULATION-INDUCED TAU PHOSPHORYLATION IN LIVE RATS

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Aims: Accumulating evidence suggests synergism between amyloid-β and tau, the two hallmark proteins of Alzheimer's disease (AD), but the detailed mechanisms are still poorly understood. Recent studies indicate that tau hyperphosphorylation caused by either Aβ or long-term depression (LTD), a form of synaptic weakening involved in learning and memory, share similar mechanisms. Very recently we reported that LTD-inducing low frequency stimulation (LFS) enhances pospho-Tau181 and pospho-Tau217, particular sensitive biomarkers in preclinical AD, in the hippocampus of live aged rats (Zhang, *et al.*, 2022). Having found that Aβ facilitates LTD in young rats *in vivo* (Hu, *et al.*, 2014), we wondered whether Aβ can promote LFS-induced phosphorylation of tau in live young rats. Here we investigated the role of Aβ in LFS-induced phosphorylation of tau in the hippocampus of young live rats.
Methods: Soluble synthetic $A\beta_{1-42}$ or vehicle was injected intracerebroventricularly and LTD was induced by LFS in the CA1 area of urethane-anaesthetized adult male Sprague Dawley rats. Phosphorylation of tau on several sites and the expression of related kinases were detected by Western blot and immunofluorescence staining.
Results: We found that: (i) LTD-inducing LFS in $A\beta_{1-42}$ pre-injected young rats significantly increased the levels of p-Tau181, p-Tau217 and p-Tau202/205 in the hippocampus. (ii) When applied alone, neither LFS nor acute $A\beta_{1-42}$ injection altered the expression levels of the investigated p-tau species under the same experimental conditions. (iii) The expression levels of p-GSK3α, p-GSK3β and Cdk5 were not significantly changed.
Conclusions: Our results indicate that Aβ promotes LFS-induced phosphorylation of tau in the hippocampus of young live rats in a manner that appears not to be mediated by GSK3 or Cdk5.

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P0093 / #2509

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

THE AMYLOID PRECURSOR PROTEIN INTRACELLULAR DOMAIN (AICD) ACTIVATES THE CK2/MAPK KINASE PATHWAY AFFECTING AXONAL TRANSPORT CHARACTERISTICS

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Aims: Deficits in axonal transport (AT) are well known early deficits in age-related neurodegenerative diseases such as Alzheimer's Disease (AD). Those changes in AT are mostly consequences of kinase activation that are due to early pathologic changes. Here, we wanted to address the question, if increased generation of APP intracellular domain (AICD), released after gamma-secretase cleavage, might activate different signalling pathways that in turn contribute to axonal transport deficits.
Methods: The impact of AICD on overall-vesicle movement was assessed using a vesicle motility assay on isolated squid axoplasm preparations in combination with different pharmacological and biochemical approaches. Moreover, live cell imaging of mouse neurons expressing fluorescently-labelled variants of APP and other transport vesicle cargos were used to investigate the role of AICD on AT.
Results: We found that the perfusion of axoplasm with AICD causes a reduced anterograde transport velocity associated with increased phosphorylation of conventional kinesin. Notably, AICD lacking the NPTY motif did not affect AT, indicating that PTB containing scaffolding proteins, involved in the regulation of kinase activity might mediate the AT defect. Indeed, treatment with JNK and p38 inhibitors abolished the impact of AICD on AT, whereas other kinase inhibitors such as GSK3beta had no influence or were just able to relieve the effect of AICD as shown for CK2. Together, this study shows that AICD affects anterograde AT by activating the CK2/MAPK pathway that might also be implicated in AT perturbations observed in AD.
Conclusions: Altogether, our results revealed novel effects of AICD on kinase activity and AT suggesting that alterations in AICD production might contribute to AT deficits observed in early AD stages. Further on, the presence of an Fe65-like protein in squid was predicted for the first time.

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P0094 / #164

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

THE ROLE OF MADECASSOSIDE IN REGULATING NF-_B SIGNALING PATHWAY IN BETA-AMYLOID INDUCED BV2 MICROGLIAL CELLS

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Aims: This study aims to determine the anti-neuroinflammatory effects of madecassoside on beta amyloid stimulated BV2 microglial cells via NF-κB signalling pathway.
Methods: The BV2 microglial cells were treated with madecassoside at MNTD (9.50 µg/mL) and ½ MNTD (4.75 µg/mL) and incubated for 3 hours. Upon the 3 hour pre-treatment, the cells were stimulated by beta amyloid (12 µM) and incubated for 24 hours. The BV2 microglial cells were then harvested and subjected for the determination of mitochondrial membrane potential, cell death assay and determination of the expressions of key proteins involved in NF-κB signalling proteins *via* Western Blot.
Results: The percentage of BV2 cells with high MMP was increased for the MNTD group with exogenous Aβ. It was suggested that the untreated and ½ MNTD treatment group decreased in the percentage of cells with high MMP upon stimulation with Aβ for 24 hours could be associated with staticity of ROS production in BV2 cells. Madecassoside was observed to reduce the percentage of early apoptotic cells significantly ($p<0.05$) at MNTD compared to the untreated cells. Comparison between MNTD and MNTD with Aβ; and ½ MNTD and ½ MNTD with Aβ groups where upon stimulation with Aβ, the early apoptotic cells were increased significantly. Based on the present findings, madecassoside was suggested to play a role in the regulation of the NF-κB signalling pathway through upregulation of IKKβ and the downregulation of NF-κB and phosphor-IKK.
Conclusions: Madecassoside was observed to regulate IKKβ, NF-κB and phosphor-IKK proteins in the NF-κB signalling pathway indicating potential anti-neuroinflammatory responses towards beta amyloid stimulation of BV2 microglial cells.

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P0095 / #591

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

INCREASED NEURONAL NITRIC OXIDE SYNTHASE IN ALZHEIMER'S DISEASE MEDIATES ABERRANT GLUTAMATERGIC CALCIUM RESPONSES THAT CAN BE REVERSED BY BLOCKING NNOS FUNCTION OR SCAVENGING NITRIC OXIDE

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Aims: Nitric oxide (NO) is an important neuromodulator and regulator of neuronal calcium signaling. Nitrosative stress, mediated by NO, is a feature of Alzheimer's disease (AD), however the underlying mechanism(s) driving nitrosative stress and the impact of NO on glutamatergic calcium signaling during AD is still largely unknown. The aim of this research was to assess neuronal nitric oxide synthase (nNOS) protein levels in late-onset Alzheimer's disease (LOAD) *post mortem* tissue and cognitively normal individuals and assess the impact of nNOS on glutamatergic calcium signalling in induced pluripotent stem cell (iPSC)-derived neurons from LOAD patients compared to controls.
Methods: Quantification of nNOS expression was performed using immunostaining and western blotting in post mortem tissue from four areas of the brain that are differentially affected by AD pathology in LOAD patients and healthy individuals (n=19) and in iPSC derived neurons. The impact of nNOS activity was assessed in iPSC derived neurons by calcium imaging.
Results: Significant increases in nNOS amount in both LOAD *post mortem* tissue and iPSC-derived neurons were identified, compared to healthy donors. nNOS levels were increased in early and severely affected regions of LOAD brains, but not late and mildly affected regions. Ca^{2+} imaging demonstrated that inhibition of nNOS activity, or scavenging of endogenous NO, significantly decreased aberrant spontaneous calcium signaling in LOAD neurons.
Conclusions: Together these data show that NO modulation of glutamatergic calcium signaling may be neuroprotective under non-pathogenic conditions, with increased nNOS and NO contributing to pathogenic signaling changes during AD. Importantly, aberrant glutamatergic calcium responses could be reversed by blocking nNOS function or scavenging NO, indicating a central role for NO in the dysfunctional calcium signalling in AD.

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P0095a / #3103

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

THE ROLE OF IMPAIRED RECEPTOR TRAFFICKING IN MEDIATING THE PATHOLOGICAL EFFECTS OF APOE4 IN ALZHEIMER DISEASE

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Aims: This study aims to examine the role of receptor levels and intracellular recycling in mediating the pathological effects of apoE4. Specifically, we focus on examining the effects of *APOE* -genotype on the levels and compartmentation of apoE receptors; apoER2 and LRP-1 and growth-factor receptors; InsulinR and VEGFR in primary neuronal cultures.
Methods: A primary neuronal cultured were prepared from either apoE3 or apoE4 transgenic mice. After purification, these cultures were double-stained utilizing immunofluorescence method for a receptor and intra-cellular compartment. The stained cells were then captured using confocal microscopy and analyzed for the receptors' levels, the compartments' levels and the extend of co-localization between the two stains. Additionally, to assess the levels of membranal receptors a biotinylation assay was used following ELISA measurements of the different receptors on the external membrane.
Results: Comparisons of the receptors' levels in apoE4 and apoE3 primary neuronal cultures, revealed that apoE4 is associated with lower levels of the four receptors, specifically in the external membrane. Additionally, apoE4 affects the intracellular localization of these receptors in two main patterns: the first pattern was observed with LRP-1 and was associated with decreased receptor levels in numerous intracellular compartments. The second pattern, which was obtained with the other receptors, was associated with their accumulation in early endosomes combined with a decrease of their levels in the late endosomes.
Conclusions: These results provide a unifying mechanism, in which apoE4 drives the down regulation of various receptors, which plays important roles in distinct apoE4 related pathological processes.

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P0096 / #2616

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

GENE MODULATION AND ER STRESS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE INDUCED AT DIFFERENT AGES BY INTRACEREBROVENTRICULAR INJECTION OF B-AMYLOID OLIGOMERS.

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Aims: The present project aims to study the role of UPR and ER stress in AD, evaluating also the mechanisms that are significantly deregulated in the pathology and aging process.
Methods: Mice C57BL76 were injected intracerebroventricularly with β-amyloid oligomers ($A\beta_{1-42}$) at 3 and 18 months. After 10 days, animals performed behavioral tests before being sacrificed. RNA sequencing was carried out. The expression of each gene was assessed for different age and treated and not treated mice (3 $A\beta_{1-42}$/18 $A\beta_{1-42}$, 3 Sham/18 $A\beta_{1-42}$/ 18 Sham/18 $A\beta_{1-42}$) by their log2 fold change (log2FC) from the basal-state to investigate the UPR, oxidative stress, inflammation and cell death on hippocampal samples.
Results: Our data showed as the impairment induced by $A\beta_{1-42}$ injection worsen in aging, underlying the involvement of the inflammatory response and UPR. 124 genes were common between all groups and 47 are involved in important pathways as "Alzheimer disease-amyloid secretase", "Inflammation mediated by chemokine and cytokine signaling pathway" and "Neurodegenerative disorders".
Conclusions: The $A\beta_{1-42}$ oligomers injection in young and aged mice activates cellular pathways involved in the cellular response to stress and in the regulation of cellular death. Among them, the involvement of the ER stress and the UPR seem to play a role not only in relation to the presence of $A\beta_{1-42}$ oligomers but also to the aging process. More investigations need to be addressed, but these results suggest the deep relation among ER stress, aging process and Alzheimer's disease. Supported by PRIN 2017 (Prot.2017MYJ5TH) and PRIN 2020 (Prot.20202THZAW).

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P0097 / #1624

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

PIKFYVE AND PI(3,5)P2: REGULATORS OF THE INTRA LYSOSOMAL NETWORK REQUIRED FOR APP HOMEOSTASIS IN NEURONS

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Aims: In Alzheimer's disease (AD), endolysosomal dysfunctions are amongst the earliest cellular features to appear. Each organelle of the endolysosomal system, from the multivesicular body (MVB) to the lysosome, contributes to the homeostasis of amyloid precursor protein (APP) and its cleavage products including ß-amyloid (Aß) peptides. Yet little is known about the relevance of the endolysosomal dynamic and associated trafficking processes in the regulation of APP processing. Our former reports showed the role of the PIKfyve complex, which regulates PI(3,5)P2 level, in the lysosomal reformation process and in the generation of physiological PMEL-derived amyloids. We reasoned that the PIKfyve complex, already associated to severe neurodegenerative diseases, could also play a central role in APP processing and AD.
Methods: In the present study, we took advantage of the inhibition of the PIKfyve to modulate endolysosomal dynamic in neuronal cellular models and to study the relevance of the endolysosomal dynamic for APP homeostasis and for AD pathogenesis .
Results: We observed by biochemical and immunofluorescence analysis that PIKfyve inhibition in neurons induces early and late endosome/lysosome defects and is associated to an impaired APP processing. This impairment was correlated to an altered trafficking of APP/APP fragments and its endolysosomal secretases, BACE1 and PSEN2. Detailed analysis by live cell imaging revealed active vesicular exchange of the transmembrane secretase, PSEN2, as well as soluble proteases between endolysosomal compartments.
Conclusions: Altogether, these results propose the existence of an intracellular lysosomal network connecting hundreds of endolysosomes through PIKfyve/PI(3,5)P2 dependent tubulations and regulating the global lysosomal proteostasis load, which is of prime importance for APP homeostasis.

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P0098 / #1908

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

V-ATPASE-HYALURONIDASE AXIS ORCHESTRATES LYSOSOMAL DYSFUNCTION IN ALZHEIMER DISEASE

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Aims: Impaired activities and abnormally enlarged structures of lysosomes are frequently observed in Alzheimer disease (AD) brains. However, little is known about whether and how lysosomal dysregulation is triggered and associated with AD. Here, we show that vacuolar ATPase (V-ATPase) is a hub that mediates proteopathy of oligomeric amyloid-beta (Aβ) and hyperphosphorylated tau (p-tau).
Methods: In this study, we examined the detrimental effect of Aβ and tau on lysosomal function in AD model *in vivo* and *in vitro*. In addition, we performed a human protein chip array, genome-wide gain-of-functional screening for lysosomal regulators. Further, we investigated the molecular mechanism of how the novel genes are involved in lysosome-related pathophysiology in AD.
Results: Lysosomal integrity was largely destructed in Aβ-overloaded or p-tau-positive neurons in culture and AD brains, which was a necessary step for triggering neurotoxicity, and treatments with acidic nanoparticles or endocytosis inhibitors rescued the lysosomal impairment and neurotoxicity. Interestingly, we found that the luminal ATP6V0C and cytosolic ATP6V1B2 subunits of V-ATPase complex bound to the internalized Aβ and cytosolic PHF-1 tau, respectively. Their interactions disrupted V-ATPase activity and accompanying lysosomal activity *in vitro* and induced neurodegeneration. Using a genome-wide functional screen, we isolated a genetic suppressor, a hyaluronidase (HYAL), which reversed the lysosomal dysfunction and proteopathy and alleviated the memory impairment in 3xTg-AD mice. Further, we found that its metabolite hyaluronic acid (HA) and HA receptor CD44 attenuated neurotoxicity in affected neurons via V-ATPase.
Conclusions: We propose that lysosomal V-ATPase is a bona fide proteotoxic receptor that binds to pathogenic proteins and deteriorates lysosomal function in AD, leading to neurodegeneration in proteopathy.

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P0099 / #544

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

THE NOXIOUS CROSS-TALK BETWEEN REDOX HOMEOSTASIS AND PROTEIN QUALITY CONTROL SYSTEMS IN ALZHEIMER-LIKE PATHOLOGY

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Aims: Increased oxidative stress (OS), due to mitochondrial dysfunction and the failure of antioxidant responses, represents an early signature of Alzheimer Disease (AD) neuropathology, triggering protein oxidative modification and the build-up of toxic aggregates. Protein quality control (PQC) systems are involved in the surveillance of protein folding/degradation, and reduce the accumulation of neurotoxic damaged proteins. Data from our laboratory demonstrated in Down syndrome (DS) and AD brain the impairment of PQC systems, including the ubiquitin proteasome system (UPS) and autophagy, that may promote the escape of unfolded/misfolded proteins from protein homeostasis mechanisms favoring aberrant protein aggregation.
Methods: Recently we analyzed the aberrant induction of the unfolded protein response (UPR) during the neurodegenerative process to demonstrate that the increased oxidation of BiP may lead to the selective detrimental over-induction of the PERK branch of the UPR in AD-like neuropathology. Further we seek to understand the fine tuning between PQC systems and antioxidant responses.
Results: We reported in AD and DS brain that the dysregulation of the PERK branch of the UPR was associated on one side with the reduction of translation and in the other with the depletion of antioxidant responses, due to the uncoupling between PERK and NRF2. Furthermore, such alterations correlated with metabolic defects observed on DS and AD brain. In agreement, the pharmacological partial inhibition of the PERK pathway was able to rescue proteostasis, reduce the build-up of oxidative damage and ameliorate metabolic dsysfunctions.
Conclusions: Our results suggest that the failure to regulate the PERK pathway as effect of altered redox homeostais and metabolic failure is an essential step in promoting aberrant proteostasis in AD-like pathologies. Therefore, its therapeutic rescue may represent a valuable option against AD-like neurodegeneration.

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P0100 / #1788

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

ALTERATIONS IN INTRACELLULAR ABETA ACCUMULATION AND AGGREGATION BEFORE PLAQUE FORMATION

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Aims: Immunohistochemical findings of endosomal dysfunction and intraneuronal Aβ accumulation preceding amyloid pathology support that extracellular plaques may originate intraneuronally. However, biochemical evidence that the conformational transition of soluble Aβ into aggregated species can take place intracellularly *in vivo* is still lacking. Using TgCRND8 mice as a model of AD-like β-amyloidosis, we provide a detailed analysis of the dynamics of intracellular Aβ accumulation and aggregation, before extracellular plaque formation.
Methods: RIPA soluble and insoluble extracts of brain intracellular vesicles and exosomes obtained from TgCRND8 mice were used to quantify Aβ species. Levels of monomeric Aβ and oligomers were measured by sandwich ELISA. Fibrillar Aβ was quantified by dot blot using the OC antibody. By immunohistochemistry, SH-SY5Y cells overexpressing wild type APP were used to determine the intracellular localization of fibrillar Aβ.
Results: Intracellular Aβ oligomers and fibrillar Aβ were already detectable at the earliest age analyzed (3 weeks), and long before the onset of extracellular amyloid deposition. From that point, there was a progressive loss of RIPA soluble intracellular Aβ species, and intravesicular insoluble Aβ42 levels began to rise precipitously at ~8 weeks. Plaque formation started at around 10 weeks of age, when intracellular insoluble Aβ42 was near maximal. At this time-point, fibrillar Aβ was also detectable in exosomes, suggesting an association of aggregates with endosomal membranes before secretion. Co-localization studies and super-resolution Airyscan imaging further confirmed that intracellularly-formed fibrils localize to endosomal membranes.
Conclusions: Loss of Aβ42 solubility in endosomal vesicles, and the acquisition of a fibrillar conformation appear as a key event for the emergence of extracellular amyloid deposition. Our results provide further evidence for the intraneuronal origin of amyloid plaques.

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P0101 / #2604

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

FLUORANTHENE INDUCED NEURONAL DEGENERATION, IMPAIRED BEHAVIOUR AND ACTIVATED UPREGULATION OF SKN-1 EXPRESSION IN CAENORHABDITIS ELEGANS

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Aims: In this study, we investigated the neurotoxicity of Fluoranthene via its effects on cholinergic, dopaminergic and GABAergic neurons, behaviour and genes linked to antioxidant defense system in Caenorhabditis elegans
Methods: Wild-type worms and worms expressing green fluorescent protein (GFP) in either cholinergic, dopaminergic or GABAergic neurons were treated with Fluoranthene (50 – 1000 µM) for 48 h at the fourth larval (L4) stage and survival rate was determined. The median lethal dose obtained was used for further experiment. Neurodegeneration were monitored in the worms after treatment with fluoranthene using confocal microscope and scored for both treated and untreated groups. Alteration in behavioural activities were monitored using the basal slow response and locomotion speed assays and compared to the control (untreated group). Data obtained were analysed using worm lab software. Quantitative polymerase chain reaction was used to assess the expression of genes (skn-1, gst-4 and cat-1) linked to neurodegeneration in treated and untreated worms.
Results: Fluoranthene (50 – 1000 µM) significantly ($P < 0.05$) reduced the survival of the worms after 48 h with a median lethal dose (LD50) of 223.4 µM compared to the control. Fluorescent micrographs revealed that fluoranthene induced degeneration of cholinergic, dopaminergic and GABAergic neurons with increasing concentrations. Fluoranthene also reduced locomotor behaviour (basal slowing response and locomotion speed via forward speed) of the worms. Real-time polymerase chain reaction data showed a significant increase in skn-1 (a homolog of Nrf2), gst-4 and cat-1 expression after exposure to Fluoranthene.
Conclusions: Our findings revealed that Fluoranthene induced oxidative stress which may contribute to degeneration of cholinergic, dopaminergic and GABAergic neurons and altered locomotor behaviour. Hence, exposure to polluted air, smoke or aquatic animals with high concentration of fluoranthene may induce neurodegeneration.

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P0102 / #2670

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

THE ROLE OF AGE-RELATED MITOCHONDRIA IMPAIRMENT IN PROTEOSTASIS DISRUPTION IN HEALTHY AGEING AND ALZHEIMER'S DISEASE

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Aims: The objective of this work is to elucidate the importance of mitochondria disfunction in response to oxidative stress, particularly proteostasis, differentiating healthy and pathological ageing.
Methods: Healthy and pathological ageing were studied using fibroblasts from differently aged human healthy donors and AD patients, using pharmacological tools. Mitochondria network homeostasis was assessed by live confocal imaging. Protein aggregation was studied using specific dyes, and the insoluble protein fraction was analysed by mass spectrometry.
Results: relate oxidative stress and mitochondria disruption to ageing-associated diseases. This work shows that flavonoid antioxidative agents reduce protein aggregation, particularly in cells from older donors, supporting their antioxidant properties as a good therapeutic strategy for age-related diseases. Cells from old donors show higher susceptibility to oxidative stress, either in terms of protein aggregation, cell viability, or mitochondria homeostasis. Analysis of the insoluble protein fraction identified potential therapeutic targets, that are differently expressed with ageing and in AD patients.
Conclusions: Aged cells are more susceptible to oxidative stress, reflecred in proteostasis and mitochondrial status. Given their protective effect, flavonoids can be of strategic therapeutic value for protein-aggregation related diseases. However, the role of the newly identified metabolic remains unknown, and more studies in this area are necessary.

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P0103 / #1918

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

APOE4-MEDIATED DISRUPTION OF THE L-CARNITINE SYSTEM IN ALZHEIMER'S DISEASE

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Aims: The L-carnitine system plays an important role in mitochondrial fatty acid metabolism. Recent studies suggest that in addition to being a risk factor for Alzheimer's disease (AD), the apolipoprotein E (APOE) E4 allele also modifies fatty acid (FA) transport and metabolism. We, therefore, hypothesize that APOE genotypes will differentially modulate the blood and brain L-carnitine system in AD.
Methods: Using Hydrophilic interaction chromatography/mass spectrometry, plasma and brain L-carnitine, L-carnitine metabolites, and acylcarnitines were measured in controls and AD patients and in mice with targeted replacement of mouse APOE with human APOE isoforms (APOE-TR). Complementary proteomic and molecular biology studies were applied to identify pathways associated with L-carnitine disturbances in the brain.
Results: In human plasma from E4 carriers, high Trimethylamine N-oxide (TMAO) and low acylcarnitines were associated with AD diagnosis. Among E4 carriers, brain medium-chain acylcarnitines (MCA) and long-chain acylcarnitine (LCA) were high in AD compared to controls. Brain levels of L-carnitine and its metabolites and acylcarnitines are differentially affected by APOE genotypes and cerebrovascular, amyloid and tau pathologies. Compared to non-E4-TR mice, MCA and LCA decreased with age within the cerebrovasculature but not in the brain parenchyma of E4-TR mice. Proteins associated with glucose metabolism and FA oxidation (FAO) were differenetially modulated within the cerebrovasculature and the parenchyma of E4-TR mice. Levels of malonyl-CoA, that allosterically modulate carnitine palmitoyltransferase-1 (CPT1) activity, were decreased in the cerebrovasculature of E4-TR mice compared to non-E4-TR mice.
Conclusions: The APOE genotypes modify the association between the L-carnitine system and AD. Pathways that link glucose sensing with L-carnitine-mediated FAO are affected by APOE genotypes. Understanding the influence of APOE genotypes on L-carnitine-mediated bioenergetics pathways is required for developing novel preventative/therapeutic strategies for AD.

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P0104 / #213

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

HOW LOCALISED IS BRAIN DAMAGE IN PARKINSON'S DISEASE?

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Aims: Dopaminergic neurodegeneration within the substantia nigra pars compacta (SNpc) is the principle histopathological hallmark of Parkinson's disease (PD) and is linked to the motor deficits experienced by PD patients. However, damage and neurodegeneration of other brain regions may contribute to disease aetiology and explain some of the non-motor symptoms associated with PD. The aim was to investigate whether the protein repair enzyme, protein L-isoaspartate methyltransferase (PIMT) and the enzyme responsible for L-Dopa formation, tyrosine hydroxylase (TH), were similarly expressed in the caudate nucleus (CN), prefrontal cortex (PFC) and SN tissue from patients with PD when compared with matched control subjects.
Methods: *Post-mortem* brain tissue from 10 PD patients and 10 matched controls were resolved by gel electrophoresis. Relative protein levels were quantified by Western immunoblotting.
Results: In PD patients, there was a reduced expression of both PIMT in the SN (p= 0.0460) and TH in the PFC (p=0.0096).
Conclusions: Alpha-synuclein is a known target of repair by PIMT. Downregulated expression of this in the SN could contribute to elevated levels of damaged and aggregated alpha-synuclein, the major protein that accumulates in Lewy bodies. The reduced TH expression in the PFC suggests the potential for reduced dopamine activity within this brain region, an area linked to behaviour and executive function.

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P0105 / #115

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

THE NAD+-BOOSTER NICOTINAMIDE RIBOSIDE IMPROVES MITOCHONDRIAL FUNCTION AND MITIGATES OXIDATIVE STRESS IN EXPERIMENTAL MODELS OF PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

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Aims: Impaired mitochondrial function has been associated with the etiopathogenesis of neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD). Sustained alterations in mitochondrial electron transport chain complexes lead to mitochondrial dysfunction and downstream neurodegenerative processes. Variations in nicotinamide adenine dinucleotide (NAD^+) concentration have been related with aging and play a key role in both health and life span. Nicotinamide riboside (NR), a source of vitamin B3, is a precursor of NAD^+ that induces mitochondrial biogenesis and potentiates the activity of sirtuins, which are a family of NAD^+-dependent protein deacetylases that dynamically regulate transcription, metabolism, and cellular stress response. We investigated whether boosting NAD^+ cellular levels confer neuroprotection by improving mitochondrial function and decreasing oxidative damage in experimental models of PD and AD.
Methods: We used cell cultures to assess cell viability, glutathione levels, and ATP synthesis. For *in vivo* studies, we used mice to evaluate functional outcome, NAD^+ content, Aβ deposition, intracellular advanced glycation end products (AGEs), lipid peroxidation and protein nitration, and both GFAP and Iba1 levels. In both cells and brain tissue, we measured mRNA levels of SIRT1, SIRT3, PGC-1α, and downstream mitochondrial genes.
Results: Our results demonstrated that NR treatment has beneficial properties in PD and AD. Long-term dietary supplementation with NR improved behavioral phenotype and increased NAD^+ brain content in Tg19959 AD mice, thereby ameliorating the cardinal features of neurodegenerative diseases, including mitochondrial damage, oxidative insult, and inflammation. We have also provided new insights into the molecular mechanism underlying the neuroprotective effects of NR, which increases SIRT1, SIRT3, PGC-1α, and SOD2 gene expression and protein levels, and promotes mitochondrial biogenesis and function.
Conclusions: Our findings provide important evidence that NR might be beneficial to the treatment of neurodegenerative diseases.

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P0106 / #1539

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

THE RELATION BETWEEN AMYLOID BETA 1-42, TFAM AND MITOCHONDRIAL DNA

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Aims: Mitochondrial dysfunction is considered one of the early emerging features of Alzheimer's Disease(AD). Amyloid beta 1-42(Aβ1-42), the primary AD peptide, has been shown to be found in mitochondria. However, very little is known about the functions of Aβ1-42 in mitochondria. Furthermore, it has been demonstrated that Aβ1-42 can localize in the nucleus, bind to particular genes' promoter regions, and regulate their expression. Mitochondrial transcription factor A(TFAM) plays a role in the packaging and replication of mtDNA. However, there is still a lack of information about the connection between TFAM and AD. So, we reasoned that Aβ1-42 could affect the regulation of mitochondrial gene expression via altering TFAM's ability to bind to mtDNA. For this purpose, the localization of endogenous Aβ1-42 in mitochondria in SH-SY5Y cells was investigated under physiological conditions.
Methods: The co-localization of endogenous Aβ1-42-mtDNA was then examined using an immunofluorescence-based BrdU(5-bromo-2 deoxyuridine) assay.We used a chromatin-immunoprecipitation(ChIP) assay from SH-SY5Y cells treated with two different dosages of Aβ1-42 to determine the effects of Aβ1-42 on TFAM-mtDNA binding ability.Eluted DNA fragments were analyzed with qPCR using mtDNA-Displacement Loop(D-loop) specific primers.
Results: We demonstrated the co-localization of Aβ with mtDNA under physiological conditions based on the outcomes of the BrdU assay. Our results showed that in 0,1μM Aβ1-42 treatment, the mtDNA binding signal of TFAM decreased through the D-loop region. Additionally, we demonstrated that only two areas of the D-loop region had an increase in TFAM binding signal after treatment with 5μM Aβ1-42.
Conclusions: According to our results, Aβ1-42 has the potential to regulate mtDNA transcription and stability by affecting TFAM-mtDNA binding capacity. Our study is the first to demonstrate that Aβ1-42 alters TFAM's ability to bind to mtDNA.
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P0107 / #284

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

PROTEIN O-GLCNACYLATION AND REGULATION OF MITOCHONDRIAL FUNCTION

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Aims: Mitochondrial dysfunction plays an important role in Alzheimer's and Parkinson's diseases. Our overall objective is to investigate how post-translational O-GlcNAcylation plays a role in regulating mitochondrial function in Alzheimer's disease pathogenesis and contribute to therapeutic interventions against Alzheimer's and Parkinson's diseases.
Methods: Using primary neuronal cultures and in vivo mouse models, as well as human postmortem samples, we investigated the impact of disease on regulating protein O-GlcNAcylation, and on autophagy, mitophagy, mitochondrial function, and their network associations.
Results: We have demonstrated that in primary neuronal cultures, elevation of O-GlcNAcylation resulted in attenuated autophagy and elevation of alpha-synuclein. In vivo, we found that key factors in regulation of O-GlcNAcylation are correlated with mitochondrial electron transport activities and proteins in mice. In human postmortem samples, we found elevated O-GlcNAcylation in Alzheimer's and Parkinson's diseases post-mortem brain samples. Current studies are dissecting roles of O-GlcNAcylation in glial cells in Alzheimer's and Parkinson's disease mouse models.
Conclusions: Together, our study demonstrated a key role of O-GlcNAcylation in neurodegenerative disease models.

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P0108 / #2734

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

BODY MASS INDEX IS RELATED TO FATTY ACID LEVELS IN PATIENTS WITH ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA

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Aims: We aimed to explore the relationship between BMI and FA in patients diagnosed with dementia with Lewy Bodies and Alzheimer`s disease.
Methods: This is a secondary cross-sectional analysis from the Dementia Study of Western Norway. Body Mass Index and Fatty acid concentrations were obtained in 124 patients with mild dementia, gas chromatography flame ionization was used to measure FA in plasma. Linear regression models adjusted for age, sex, and diagnosis were used to explore the relationship between Body Mass Index and each of the Fatty Acid concentration metrics.
Results: 59% of participants were female, the mean age of both groups was 74.60 ± 7.03. Monounsaturated fatty acids and Oleic acid relative concentrations related positively to Body Mass Index. While α linolenic acid related positively to BMI, both Eicosapentaenoic acid, Docosahexaenoic acid related negatively to Body Mass Index. The Omega-6 intermediates Gamma-Linolenic acid, Arachidonic acid, Adrenic acid correlated to positively to Body Mass Index.
Conclusions: We found Omega-3 metabolites to relate with lower BMI, and Omega-6 metabolites to relate with higher BMI (in the DLB group with statistically significant estimates). FA intake may be a relevant mediator in body composition and inflammatory responses, making them potential therapeutical targets for cognitive decline and dementia.

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P0109 / #734

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

UNRAVELLING AMYLOID BETA PLAQUE PATHOLOGY ASSOCIATED LIPID PATTERNS IN GENETIC ALZHEIMER'S DISEASE MOUSE MODELS

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Aims: The primary goal of this project is to employ advanced chemical imaging to unravel the exact lipid-Aβ plaque interactions in various AD model systems.
Methods: Here, we employed a multimodal imaging paradigm combining matrix assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS) and fluorescent amyloid staining. Tri-modal MALDI-IMS under negative- and positive ion mode lipid analysis and subsequent peptide/protein ion imaging were performed at 10 µm spatial resolution on the same tissue section from tgAPP$_{Swe}$, tgAPP$_{ArcSwe}$ and tgAPP$_{UppSwe}$ mouse brains. Furthermore, employed LCO-based, hyperspectral, fluorescent amyloid microscopy paradigm provided the insights into degree of Aβ aggregation associated with plaque polymorphism. Multivariate statistical analysis was used to interrogate the IMS datasets and region-specific differences in Aβ peptide pattern were correlated with changes in lipid distributions revealed by MALDI-IMS lipid analysis.
Results: MALDI-IMS and fluorescent amyloid staining revealed chemical features associated with heterogeneous distributions of different individual Aβ deposits. For the tgAPP$_{Swe}$ mouse model, it was primarily the wild type peptides that aggregated in Aβ plaques including both diffuse and core formation. For the tgAPP$_{ArcSwe}$ mouse model, there were massive, cored plaques containing primarily the C-terminally truncated peptides. Meanwhile, there were smaller and diffused plaques containing primarily AβUpp peptides in the tgAPP$_{UppSwe}$ mouse model. Furthermore, heterogeneous distributions of lipids were revealed by high-spatial resolution MALDI-IMS. GM1 aggregated at the core region of Aβ plaques, while arachidonic acid (AA) conjugated phosphatidylinositols (PI) and their corresponding degradation product, lysophosphatidylinositols (LPI) were located to the periphery of the plaques in the tgAPP$_{Swe}$ and tgAPP$_{ArcSwe}$ mouse models.
Conclusions: Here, multimodal imaging was monitored to delineate lipid patterns associated with Aβ plaque pathology. The results highlight the heterogeneous metabolism of neuronal lipid is associated with amyloid plaque polymorphism.

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P0109a / #3101

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

STRUCTURAL AND FUNCTIONAL DIFFERENCES BETWEEN APOE3 AND APOE4 PARTICLES.

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Aims: Objectives: This work was aimed at characterizing the structural and functional differences between apoE4-particles, and apoE3-particles. In order to study specific particles, we separated apoE3 and apoE4 astrocytic conditioned media (ACM) on a density gradient, and characterize their weight, lipids' composition, and ability to transport cholesterol.
Methods: Methods: Sucrose-gradient-ultracentrifugation was used to separate ACMs to fractions. Native gels were used to measure apoE-particles' weight. Cholesterol levels were measured by Amplex red. Phosphatidylcholine (PC) and triacylglycerol (TAG) were measured by lipidomics utilizing LC-MS. Cholesterol efflux, and absorption, were measured to assess the function of these particles.
Results: Results: Following density separation, the apoE3-containing-fractions had higher levels and higher molecular weights per density compared to apoE4-containing-fractions. E4-ACM had fewer lipids than E3-ACM, but the lipids' levels per apoE molecule were higher in E4-fractions. E4-fractions and E3-fractions also differ in their lipid composition, such that TAGs, specifically long-chain-polyunsaturated-TAGs, showed higher levels in low density E4-fractions, and lower levels in the high density E4-fractions, compare to E3-fractions. PCs levels were higher in E4-fractions, specifically in the high-density fractions. Functional analysis showed that the ability of E3-particles to induce cholesterol efflux from astrocytes was higher than E4-particles in the low density fractions, and lower than E4-particles in the high density fractions. This was inversely correlated with long-chain-polyunsaturated-TAGs levels. E3-particles' ability to absorb cholesterol into neurons was decreased at the high density fractions, while E4-particles lacked the ability throughout all fractions. The reasons remain to be investigated.
Conclusions: Conclusions: This work has shown differences in structure, composition, and function, between E3- and E4-particles of different densities, and that the long-chain-polyunsaturated-TAGs, are inversely correlated with cholesterol efflux. Additionally, it showed the inability of E4-particles to give lipids to neurons.

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P0111 / #1361

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

IMPACT OF THE ANTIOXIDANT FUNCTION OF APOD IN ALZHEIMER´S DISEASE

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Aims: Objectives: This project aims at elucidating how the glial neuroprotective glycoprotein Apolipoprotein D (ApoD) affects the pathological situation in Alzheimer´s disease (AD) patients. Our hypothesis states that ApoD, through its interaction with membranes and its lipid-reducing Met93-dependent activity, maintains the correct structure of membrane domains, promoting the non-amyloidogenic processing of amyloid precursor protein (APP), and thus reducing amyloid beta (Aβ) accumulation.
Methods: Methods: We use the SH-SY5Y APP695swe cell line as a pathogenic neuronal model, after differentiation with retinoic acid (RA), followed by exposure to experimental oxidative stress treatment with paraquat (PQ). We are studying ApoD and APP subcellular location by immunocytochemistry, and membrane subdomains location after isolation of Triton X-100 and X-114 detergent-resistant membranes (DRM) domains. We have created stably-transfected HeLa cells expressing the ApoD wildtype or Met93-mutant versions to use as an ApoD source after protein purification. Cell viability is assayed by MTT assay, and lipid peroxidation is estimated by TBARS assay and 4-HNE quantitative immunofluorescence.
Results: Results: ApoD and APP appear to colocalize in SH-SY5Y APP695swe-differentiated neurons and co-fractionate in Triton X-114 DRMs known to contain both plasma membrane and endosomal-lysosomal lipid rafts. We are testing the effects of exogenously-added ApoD on viability and lipid peroxidation levels in pathogenic SH-SY5Y cells, and exploring whether the Met93 mutant version of ApoD produces the same effects.
Conclusions: Conclusions: Although the project is at an early phase, our strategy is providing promising data that will contribute to the understanding of the neuroprotective response of ApoD in AD and the contribution of its antioxidant mechanism to an anti-amyloidogenic mechanism.

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P0112 / #1235

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

EXTRACELLULAR VESICLES MEDIATE THE CROSSTALK BETWEEN WHITE ADIPOSE TISSUE AND THE BRAIN IN OBESITY-INDUCED ALZHEIMER'S DISEASE

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Aims: Obesity accompanied with the ectopic lipid accumulation in multi-organs as the main manifestation is tightly associated with a four-fold increased risk of Alzheimer's disease (AD). White adipose tissues play an important role in this cognitive impairment process, and weight loss interventions targeting obesity improve memory and executive function. Mechanisms explaining the link between adipose tissue and the brain are elusive.
Methods: In addition to lipidomic study for the whole adipose tissues, we extracted the extracellular vesicles (EVs) from human subcutaneous adipocytes and visceral adipocytes for lipidomic and transcriptomic profiling. To predict and validate Food and Drug Administration (FDA) approved drugs targeting lipid related pathways and suppressing Amyloid β (Aβ)/phosphorylated tau (ptau) elevation in mice exposed to obese adipocyte-derived EVs, we applied *in silico* prediction to reposition known drugs targeting critical signaling pathways identified by our in-house modeling software, CCCExplorer.
Results: We demonstrated adipose tissue-derived EVs fuse with lipid droplets *in vitro* using cryo-electron microscopy. Moreover, the lipidomic study for the white adipose tissue and its derived EVs displayed globe lipid composition changes between lean and obese patients. Importantly, we found that adipocyte-derived EVs from obese mice markedly increased the abundance and size of lipid droplets in microglia, the major site of lipid droplet accumulation in AD brain, and the deposition of Aβ and ptau in brains of 5XFAD mice.
Conclusions: Our experimental findings suggest that white adipose tissue originated EVs may impact not only neuroinflammation induced by ectopic lipid droplet accumulation in microglia, but also neural-glial crosstalk during the onset and progression of AD. The system biologic modeling for the dialogue between white adipose tissue and the brain revealed that increased AD pathological proteins can be suppressed by repositioning certain FDA approved drugs.

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P0113 / #2591

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

CHARACTERIZATION OF MICROGLIAL ACTIVATION STATES IN MURINE MODELS OF ALZHEIMER'S DISEASE USING NOVEL RABBIT MONOCLONAL ANTIBODIES

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Aims: Neuroinflammation is an important feature of Alzheimer's disease (AD) pathology, but the precise contribution of neuroinflammation on disease progression is poorly understood. Microglia, the resident macrophages of the brain, are likely to contribute to the initiation and maintenance of neuroinflammatory responses that contribute directly or indirectly to AD pathogenesis. Single-cell RNA sequencing (scRNA-seq) studies identified multiple microglia-enriched genes that are upregulated in the context of disease, both in human AD tissue as well as AD mouse models. Development of tools to detect these specific genes or gene products can be used to identify disease-associated microglial states and further our understanding of how neuroinflammatory responses contribute to disease. We sought to develop and validate a cohort of rabbit monoclonal antibodies to detect microglial gene products that might reflect various disease-associated stages of microglia identity in a mouse model of AD.
Methods: Recombinant rabbit monoclonal antibodies against identified genes enriched or uniquely expressed in microglia were analyzed on a mouse model of AD by immunofluorescence using established protocols. Samples were multiplexed using a combination of direct and indirect detection and a sequential labeling strategy. High-resolution images were captured using a Leica SP8 confocal microscope.
Results: Using rabbit monoclonal antibodies, we identified several gene products including ASC/TMS1, GPNMB, TMEM119, Galectin-3, and Cathepsin D that stain microglia in mouse models of AD.
Conclusions: We continue to develop a comprehensive portfolio of monoclonal antibodies that can be used to characterize microglia cellular processes and activation states to understand the role of microglia in neurodegenerative diseases.

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P0114 / #2592

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

CHARACTERIZATION OF SYK PHOSPHORYLATION AS A READOUT FOR TREM2-DEPENDENT SIGNALING PATHWAYS USING NOVEL TREM2 ACTIVATING RABBIT MONOCLONAL ANTIBODIES

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Aims: Triggering receptor expressed on myeloid cells 2 (TREM2), a single-pass type 1 transmembrane glycoprotein expressed by microglia, is genetically linked to, and considered a therapeutic target for Alzheimer's disease (AD). TREM2 activates a diverse set of cell signaling pathways, driving several microglial functions that can either ameliorate or accelerate AD progression. Characterization of TREM2 signaling pathways mediating these functions, however, is incomplete. We aimed to develop research tools to specifically stimulate TREM2 to examine signaling events downstream.
Methods: We generated a library of rabbit host monoclonal antibodies specific to either human or mouse TREM2. We initially screened this library by western blot to identify clones that were specific to TREM2. Antibodies were then used to stimulate human and mouse TREM2 *in vitro*. Cell extracts were generated by direct lysing of cells at treatment end points. Extracts were then analyzed by western blot for treatment-driven modulation of proteins downstream of TREM2. In order to confirm that downstream targets were altered in a TREM2-dependent manner, we generated a TREM2 -/- mouse cell line to be treated and analyzed in the same manner.
Results: We identified several clones that could activate cell signaling pathways downstream of TREM2, including spleen tyrosine kinase (Syk). Syk activation was characterized using phospho-specific Syk monoclonal antibodies. Based on our findings, we suggest that Syk phosphorylation may be a reliable readout for TREM2-dependent microglia activation.
Conclusions: The antibodies generated and validated in this study can be leveraged to further characterize additional signaling cascades and cellular responses (phagocytosis, inflammation, proliferation, etc.) downstream of TREM2 using both biased and unbiased approaches.

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P0115 / #2684

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

ASSOCIATIONS BETWEEN METABOLIC RISK FACTORS AND GLIAL REACTIVITY IN THE BRAIN IN AN ELDERLY POPULATION – A 5-YEAR FOLLOW-UP STUDY WITH [11C]PBR28 PET IMAGING

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Aims: Low-grade inflammation, commonly associated with the metabolic syndrome, has been associated with poorer cognitive performance. The activation of glial cells as a marker of neuroinflammation appears to play role in the pathogenesis of Alzheimer's disease (AD) Our objective was to examine the associations between metabolic risk factors for AD and glial activation assessed with positron emission tomography (PET) and translocator protein (TSPO) binding tracer [^{11}C]PBR28.
Methods: We examined 40 volunteers (median age at follow-up 74,2, 55% women, APOEε4 carriers 50%) at two timepoints, in 2014-2016 and 2019-2021. Data on participants' high sensitivity CRP (hs-CRP), insulin resistance and body mass index (BMI) was obtained at baseline and follow-up. Participants underwent [^{11}C]PBR28 PET both at baseline and follow-up. [^{11}C]PBR28 binding was quantified using ratio analysis with respect to cerebellar cortex, and measured from a composite region-of-interest consisting of brain regions where beta-amyloid accumulation is commonly first seen in AD. Linear regression model adjusted to age, sex and TSPO genotype was used to analyse the association between metabolic risk factors for AD and [^{11}C]PBR28 binding. Blood samples were obtained at baseline and follow-up. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated to evaluate insulin resistance.
Results: A higher BMI was associated with [^{11}C]PBR28 binding at follow-up (slope 0.008, p=0.01 for baseline BMI, slope 0.007, p=0.01 for follow-up BMI). No association was seen between BMI and change in [^{11}C]PBR28. Higher baseline, but not follow-up HOMA-IR was associated with higher [^{11}C]PBR28 binding but not with the change in [^{11}C]PBR28 binding. Hs-CRP was not associated with [^{11}C]PBR28 binding.
Conclusions: While we did not find association between other evaluated risk factors for AD, BMI seems to be associated with glial reactivity regardless of the time of measurement of the BMI.

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P0116 / #1446

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

HIGH VOLUME MICROGLIA STAINING IN THE PRESENCE OF DISEASE PATHOLOGY

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Aims: Despite the variations in clinical manifestation, many age-related neurodegenerative diseases share similar pathological features, such as neurofibrillary tangles (NFT) comprised of abnormally phosphorylated tau protein and extracellular plaques containing amyloid-beta (Aβ) proteins. Microglial changes are also believed to be associated with the neurodegenerative disease as well. Despite the continued innovation of techniques such as scRNA-Seq, histological examination of stained tissue remains the most robust and reliable method to visualize pathology topographically in FFPE archived brains. Using various combinations of antibodies in tandem allows for visualization of potential sub-populations of microglia. Traditionally, immunofluorescence has been one of the most widely used methods to visualize multiple proteins of interest within a cell, although this method is often limited in its efficacy and the number of targets that can be detected.
Methods: Using a recently developed method of multiplex staining, we visualized the spatial and morphological changes taking place in microglia with more than 10 different makers in the presence of disease-associated pathology. We tested how loss of homeostatic microglial markers directly associate with disease pathology as opposed to cells not in direct proximity to pathology.
Results: Using multiplex staining in FFPE samples of human mid-temporal gyrus and well-characterized and commercially available antibodies, we investigated changes in immunoreactivity and microglial morphology at various distances from plaque and tangle pathology associated with Alzheimer's disease. Our working hypothesis is that loss of homeostatic microglial markers and changes in microglial morphology are related to their proximity to pathology.
Conclusions: Understanding the changes occurring in microglia and their spatial association to disease pathology may allow for a better insight to the role of microglia in disease.

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P0117 / #964

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

EFFECTS OF PATHOLOGICAL PROTEIN AGGREGATES ON THE ACUTE TRANSITION IN MICROGLIAL PHENOTYPES

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Aims: The resident immune cells called microglia in the brain are the first ones to react to stress or damage and are the principal immune response mediator in the brain. Both in homeostatic and pathological conditions, microglia displayed a variety of multifunctional roles. Increasing amounts of data point to the idea that activated microglia enhance neuroinflammation and ultimately exacerbate certain diseases. Despite the fact that microglial activation has traditionally been defined as any morphological or biochemical alteration from the naive state, recent research has revealed that the microglial response is heterogeneous with possible neuro-toxic subtypes. The molecular mechanisms causing disease-associated microglial transition are still not completely understood, despite their significant involvement in neuropathology. Given the diversity of the characteristics of disease-associated microglia (DAM), we hypothesized that pathogenic protein aggregation might cause the change of microglia to a disease-specific state. In this research, we addressed the issues of how microglia react to pathological protein aggregates and whether disease-specific aggregates have an effect on the microglial transition.
Methods: We analyzed the acute transition of microglia after treating them with neuronal cell-derived α-synuclein or tau aggregates.
Results: Microglia that have been exposed to either α-synuclein or tau aggregates have shown an increase in both the population of inflammasome- and TLR-activated microglia. It's interesting to note that pathological protein aggregates reduced less-differentiated early microglia and homeostatic microglia. We discovered that pathological protein aggregates activated inflammasomes in homeostatic microglia, causing this population to change into DAM-like microglia.
Conclusions: Collectively, our findings imply that pathological proteins hasten neuroinflammation by encouraging homeostatic microglia to undergo a DAM-like shift.

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P0118 / #757

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

MICROGLIA DRIVE ACCELERATED AMYLOID PLAQUE ACCUMULATION IN PERI-INFARCT TISSUE AFTER STROKE

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Aims: Numerous lines of evidence have implicated vascular dysfunction and concomitant damage to the blood brain barrier (BBB) as a pathomechanistic step towards augmented amyloid beta (Aβ) production in tandem with impaired Aβ clearance. These changes create a favourable environment for the accumulation of Aβ plaques (a hallmark of Alzheimer's disease (AD)) within the brain parenchyma. In contrast, comparatively few studies have aimed to delineate the effect of ischaemia on AD, despite the fact that AD increases the risk of both ischaemic and haemorrhagic stroke in patients under 80 years old (Tolppanen et al., 2013).
Methods: To dissect the interactions between ischemic stroke and AD we utilized the APP/PS1 mouse line (a well-established model of Aβ deposition) in combination with ischaemic stroke (photothrombosis).
Results: Using this approach, we found that Aβ plaques are cleared from the infarct core, yet dramatically increase in number within the peri-infarct region three weeks after stroke. Surprisingly, we further found that these Aβ plaques are relatively inert (as evident by reduced plaque-associated axonal dystrophy) and are encapsulated by an overabundance of plaque-associated microglia.
Conclusions: Taken together, we demonstrate that the pathological milieu created by ischaemic stroke triggers a functional change in microglia that allows for the formation of - relatively inert - dense core Aβ plaques, despite age- and disease-associated deterioration in microglial function in AD.

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P0119 / #2409

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

COMPLEMENT RECEPTOR 1 IS EXPRESSED ON BRAIN CELLS AND IMPACTS ROLES OF MICROGLIA RELEVANT TO ALZHEIMER'S DISEASE

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Aims: Genome-wide association studies (GWAS) in Alzheimer's disease (AD) have highlighted the importance of the complement cascade in pathogenesis. Complement receptor 1 (CR1; CD35) is a top AD-associated GWAS hit; the long variant of CR1 is associated with increased risk. Roles of CR1 in brain health and disease are poorly understood; indeed, CR1 expression in brain is controversial. Our aim was to resolve this controversy by investigating CR1 expression in brain cells and testing whether the AD-associated length polymorphism impacted CR1 expression and function.
Methods: Two well-characterised human microglial cell lines, iPSC-derived microglia from two sources (donor-derived and KOLF2) and post-mortem human brain tissue obtained from AD cases and age- and sex-matched controls were used in this study. Cells and tissue were stained with in-house CR1-specific antibodies and analysed by immunofluorescence. RNA and protein were extracted and subjected to qRT-PCR and western blotting respectively. Functional differences of microglia expressing long and short CR1 variants were tested in phagocytosis assays using diverse targets (E.coli bioparticles, synaptoneurosomes, amyloid β) either unopsonised or opsonised with human serum.
Results: CR1 mRNA was detected in microglial lines, iPSC-derived microglia and brain tissue using qRT-PCR. CR1 protein was demonstrated using western blotting and immunofluorescence in cell lines and iPSC-derived microglia expressing long or short variant CR1 and on microglia and astrocytes in situ on brain tissue. Both mRNA and protein expression were significantly increased in the AD samples. Phagocytosis of serum-opsonised targets was significantly different in iPSC-microglia expressing the risk or non-risk variants.
Conclusions: CR1 is expressed in the human brain. CR1 expression is an important component of microglial phagocytic activity; expression of the long (risk) variant of CR1 impacts phagocytosis, perhaps explaining its association with AD risk.

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P0120 / #458

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

IMPACT OF MICROGLIAL AND ASTROCYTIC APOE GENOTYPE ON MICROGLIA PHENOTYPE

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Aims: This project aims to elucidate differences in APOE genotype and isoforms between glia in the CNS. **Aim 1: Differences between microglial and astrocytic APOE's contribution to microglia phenotype.** Our lab uses monocyte-derived microglia-like cells (MDMi) to create microglia cultures from human blood monocytes. MDMi are genotyped for APOE risk/protective AD variants. APOE protein can be processed differently between cell types and may induce differential effects on the immune response and amyloid beta clearance. This aim will determine the influence of astrocyte APOE genotype on microglia phenotype. **Aim 2: Microglia age, sex, and ethnicity interaction with APOE genotype.** Donor demographics are available for MDMi. This aim will determine if sex, age, or ethnicity differences between individuals contribute to the MDMi outcomes modulated by APOE genotype.
Methods: Microglia: Peripheral blood mononuclear cells (PBMCs) are isolated and microbead separation is used to further purify monocytes. These monocytes are cultured with a cytokine cocktail for 10-14 days to induce differentiation into MDMi. **Astrocytes:** P1 mouse brains are isolated and dissociated into a single cell suspension. O4 and CD11B microbeads are used to preclear oligodendrocytes and microglia from the single cell suspension. GLAST positive microbead separation is then used to isolate purified mouse astrocytes. We used this method to isolate astrocytes from mouse lines expressing human APOE 2, APOE 3, or APOE 4. Supernatants from mouse astrocytes expressing human APOE 2, 3, or 4 are added to MDMi.
Results: We found that astrocyte APOE genotype can modulate microglia phenotype independent of microglia APOE genotype, and continue to explore the impact of MDMi intrinsic properties on these outcomes.
Conclusions: Both astrocytes and microglia produce APOE, which can independently influence microglia phenotype, which may be relevant to susceptibility to Alzheimer's.

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P0121 / #1474

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

LOSS OF IRHOM2 IN MICROGLIA INDUCES POTENTIAL NEUROPROTECTIVE EFFECTS IN ALZHEIMER'S DISEASE

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Aims: Neuroinflammation, induced by Abeta deposition, plays a key role in Alzheimer's Disease (AD) pathogenesis. Subsequently, microglia start to release pro-inflammatory cytokines, such as TNFα, cleaved by the protease ADAM17. Immature ADAM17 is localized to the membrane of the ER. Inactive rhomboid 2 (iRhom2, RHBDF2) is an essential upstream regulator of ADAM17 and necessary for its trafficking and maturation in microglia. iRhom2 has recently been identified as an epigenetic risk factor for AD. A genetic inactivation of iRhom2 may prevent the activation of ADAM17 in microglia and thus, the release of pro-inflammatory cytokines.
Methods: We investigated the effect of iRhom2 deficiency in APP/PS1 mice. We analysed number and size of plaques, number and activation pattern of microglia and the area of plaque associated dystrophic neurites, as well as the amount of Abeta in brain homogenates.
Results: The histological results indicate a beneficial effect on AD pathology caused by the heterozygous knockout of iRhom2 (iR2(+/-);APP/PS1). This effect was characterized by a reduced number of diffuse and dense core amyloid plaques, determined by Abeta stainings. Additionally, the number of microglia cells was reduced, indicating an attenuated neuroinflammation. The area of the dystrophic neurites was significantly reduced within the hippocampus especially in male iR2+/-;APP/PS1 mice compared to females and the other genotype groups. The decreased protein levels of insoluble Abeta40 and especially of the toxic Abeta42 correlated with the estimated number of congophilic plaques within the iR2(+/-);APP/PS1 genotype group and thus strengthen our histological data.
Conclusions: Taken together, the partial loss of iRhom2 due to a heterozygous knockout of the *Rhbdf2* gene harbours potential neuroprotective functions in an AD mouse model. Our findings provide an encouraging approach for testing iRhom2 as a potential AD drug target.

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P0122 / #1341

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

PHAGOCYTIC AND NEUROINFLAMAMTORY RESPONSE OF HUMAN DIFFERENTIATED MICROGLIA FROM HEALTHY AND ALZHEIMER'S DISEASE PATIENT

Izaskun Itxaso[1,2], Tina Loeffler[1], Irene Schilcher[1], Stefanie Flunkert[1], Boris Chagnaud[2], Manuela Prokesch[1]
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Aims: Microglia are the innate immune cells of the central nervous system (CNS) playing an important role for the homeostasis of the brain. Microglia dysfunction has been identified as a hallmark of Alzheimer's disease (AD). Here, we analyzed the phagocytic and inflammatory responses of human differentiated microglia from healthy and diseased donors. Results will help to better understand pathological features of AD.
Methods: Differentiated iPSC-derived human microglia from healthy and Alzheimer's disease patients of different vendors were cultivated. To test the phagocytic abilities, cells were treated with 4 µM pHrodo Red-labelled Abeta1-42 and monitored via live-cell imaging over time to measure lysosomal uptake of Abeta1-42 as increased fluorescence. For the neuroinflammatory response, cells were stimulated with LPS and 10 µM Abeta1-42 in the presence and absence of anti-inflammatory agents (e. g. dexamethasone) for 24 h. Cytokine release was measured in the cells' supernatant via immunosorbent assays.
Results: All tested cells of healthy donors showed the ability to phagocytose Abeta1-42 and responded to inflammatory stimuli. Currently data of AD patient-derived microglia are generated and analyzed.
Conclusions: Human iPSC-derived microglia are a valuable tool to study neuroinflammatory processes and alterations. The ability to use healthy and diseased cells opens a great opportunity to test the response of microglia-targeted treatments *in vitro*.

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P0123 / #2336

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

TITLE: THE ROLE OF CHOLESTEROL IN THE REGULATION OF MICROGLIA FUNCTION AND ITS RELEVANCE IN AD

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Aims: Project Objective: Examine the interaction of genetically associated proteins with cholesterol pathways in AD and how alterations in cholesterol impact on microglia responses in the context of AD Aim 1: Effect of modulating cholesterol uptake and turnover in microglia cells. We are using monocyte-derived microglia-like cells (MDMi) to create microglia cultures from human blood monocytes. This aim will investigate how knocking down genes involved in cholesterol uptake and transport affect microglia gene expression and function using MDMi. Aim 2: Investigate the effect of AD-related genes on cholesterol pathways and turnover in microglia. This aim will explore how AD risk variants influence immune signaling in MDMi models via changes in cholesterol metabolism.
Methods: Microglia: Peripheral blood mononuclear cells (PBMCs) are isolated and microbead separation is used to further purify monocytes. These monocytes are cultured with a cytokine cocktail for 10-14 days to induce differentiation into MDMi.
Modulating cholesterol: Lentivirus-mediated shRNA knockdown is used to reduce expression of genes related to both cholesterol turnover and AD, like SPTLC1/2, ERLIN2, TREM2, CD33, and SCARB1 in MDMi. Small molecule drugs that inhibit cholesterol receptors are also used.
Functional assays: Cholesterol uptake is measured by flow cytometry and lipid droplets are stained using LipidTox. Gene expression is measured using Fluidigm.

Results: Blocking cholesterol internalization pathways suppresses cytokine expression (IL-1B, TNFa). We also found that reducing expression of the HDL receptor gene SCARB1 leads to reduced TREM2 and APOE expression, and reductions in cytokine and complement genes like C1QA/B/C, TLR8 and CTSS, involved in immune function.
Conclusions: Alterations in cholesterol and sphingolipid metabolism could contribute to the neuroimmune phenotypes characteristic of AD by altering cytokine signaling in MDMi.

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P0125 / #2311

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

PURINERGIC RECEPTOR P2Y12 IS A KEY REGULATOR OF BEHAVIOR AND MICROGLIA FUNCTION IN THE ZEBRAFISH

Francesco Locatelli, Sofia Wüstenhagen, Yasmin Abdul Jabbar, Camilla Chuang, Sarra Zenagui, Hajir Hayyawi, Yusuf Kaan Poyraz, Adrian Ekehorn Gimdal, Petronella Kettunen
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Aims: Microglia are the resident immune cells of the brain. During the past years, research has provided a better understanding of these cells and their importance in brain development and diseases. However, basic mechanisms underlying their function remain unclear. The purinergic receptor P2Y12 is expressed by microglia and has been proposed to be involved in both neuroinflammation and modulation of behaviors. In this study, we used a newly developed *p2y12* CRISPR zebrafish line to better understand the role of P2y12 in various brain functions.
Methods: To examine how knockout of *p2y12* affects behavior, we performed behavioral testing in larvae and adults. Moreover, to explore the role of P2y12 in microglia function, we crossed the *p2y12* mutants with transgenic ApoE:GFP fish marking microglia, enabling us to follow these cells using real-time imaging.
Results: Our experiments show that P2y12 is crucial for regulating behaviors in both young and adult animals, including locomotion, anxiety, social behavior and aggression. Our data indicate that the behavioral effects could be caused by a dysregulation of neuronal excitation mediated by microglial P2y12. Moreover, lack of P2y12 impairs the phagocytic properties of the microglia, including the uptake of amyloid-beta.
Conclusions: Taken together, our findings suggest that P2y12 is critical for CNS functions throughout life, including both behavioral regulation, as well as cellular functions of microglia.

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P0128 / #470

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

MICROGLIA-SPECIFIC EFFECTS OF THE PROTECTIVE PLCG2-P522R VARIANT IN ALZHEIMER'S DISEASE MODEL MICE

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Aims: A coding variant in *PLCG2* gene (PLCγ2-P522R) protects against Alzheimer's disease (AD) and promotes healthy aging. Previous studies suggest that the PLCγ2-P522R exerts beneficial effects by augmenting TREM2 and TLR-mediated functions in microglia. Thus, the focus was set on resolving PLCγ2-P522R-driven microglia-specific mechanisms in the molecular, cellular, and behavioral processes involved in AD.
Methods: Homozygous PLCγ2-P522R knock-in mice were crossbred with AD model mice (APdE9). Mice underwent microglia-PET at the age of 7 and 13 months. Thirteen-month-old mice were tested for learning and memory, after which brain tissue and isolated microglia were utilized for histological and biochemical analyses. Cultured primary microglia were used for studying the functional characteristics relevant for AD.
Results: At the age of 13 months, female, but not male PLCγ2 mice weighted less than wildtypes (WT) and showed increased innate fear and avoidance responses, which was further accentuated with APdE9 genotype. PLCγ2*x*APdE9 female mice had less insoluble amyloid-beta in the cortex than the APdE9 mice. PET data and histological staining of the brain are under analysis to evaluate changes in beta-amyloid plaque composition in relation to microglia activation. In cultured microglia, reduced accumulation of large lipid droplets (LD) was observed in PLCγ2 as compared to WT cells upon treatment with myelin and lipopolysaccharide. In comparison to WT, increased expression of genes promoting LD lipolysis was found in the acutely isolated microglia from 13-month-old PLCγ2 mice.
Conclusions: These findings suggest a sex-specific phenotype in PLCγ2-P522R mice. Forthcoming studies will underline whether more efficient lipid metabolism in PLCγ2-P522R microglia is related to enhanced immune functions and/or reduced Aβ pathology. Ultimately, these findings are expected to pinpoint microglia-specific protective pathways, which have potential to facilitate the design of novel therapeutic strategies for AD.

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P0129 / #1501

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

DAP12 LOSS-OF-FUNCTION IN MICROGLIAL PROCESSES RELEVANT FOR ALZHEIMER'S DISEASE

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Aims: TREM2-DAP12 signaling is a central microglial pathway regulating functions such as phagocytosis, inflammatory response and lipid metabolism. Rare genetic variants in *TREM2* and *TYROBP* (encoding DAP12) have been shown to increase the risk of Alzheimer's disease, highlighting their role in neurodegenerative disease. In this study, mechanisms of DAP12 loss-of-function (LOF) are studied in BV2 *Tyrobp* knock-out (KO) microglial cell lines, with specific focus on lipid metabolism and lysosomal function.
Methods: Stable BV2 *Tyrobp*-KO cell lines were generated using an all-in-one CRISPR/Cas9-based lentiviral vector. Phagocytosis of pHrodo-labeled zymosan and myelin were investigated using IncuCyte live-cell imaging system. Alterations in lipid metabolism will be studied using fluorescent lipid dyes and by quantifying levels of relevant proteins (such as Apoe, Plin2 and Abca1) by Western blot after myelin and lipopolysaccharide treatments. Similarly, lysosomal function will be studied using a pH-sensitive fluorescent lysosomal dye and by quantifying levels of lysosomal enzymes. Secreted inflammatory mediators will be measured from conditioned medium using ELISA assays.
Results: Biallelic *Tyrobp* gene editing was confirmed by Sanger sequencing, and lack of DAP12 protein expression was validated with Western blot. Two *Tyrobp*-KO lines were selected for further analyses. *Tyrobp*-KO cell lines presented major alterations in phagocytic activity, indicated by increased uptake of zymosan and reduced uptake of myelin compared to the control lines. Ongoing experiments will reveal whether the observed alterations extend to lysosomal processing and formation of intracellular lipid droplets and membrane lipid rafts.
Conclusions: Studying DAP12 LOF in BV2 *Tyrobp*-KO cell lines allows detailed assessment of cellular processes affected by abolished TREM2-DAP12 signaling. The results from this study will shed light into the mechanisms of neurodegeneration related to microglial dysfunction and aid in finding potential targets for future treatment strategies.

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P0130 / #1586

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

DOPAMINE-INFLAMMATION CONNECTIVITY AS MAIN ACTORS OF ALZHEIMER'S DISEASE.

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Aims: Background: In AD the atrophy of the hippocampus and the accumulation of extracellular amyloid plaques and intracellular neurofibrillary Tau tangles do not appear sufficiently early with respect to the loss of cognitive abilities and therefore do not allow therapeutic anticipation. The dopaminergic (DA) system, which is interconnected with the hippocampus, has been shown to be modified in AD. In addition, central deposits of Ab in senile plaques are surrounded by dystrophic neurites, activated microglia, and reactive astrocytes. Previous studies have shown that Ab is neurotoxic through microglial activation and the consequent production of toxic and inflammatory mediators, such as nitric oxide, cytokines, and reactive oxygen species, are likely involved in neuronal loss. Objectives: First, to test the hypothesis that DA dysfunctions appear early at the cellular level and during discrete stages of the pathology and that such alterations can be visualized by functional brain imaging of the DA system; second, to evaluate the link between neuroinflammation with dopamine activity.
Methods: Methods: PET imaging with [^{18}F]Fallypride at baseline and following DA neuron stimulation was performed on 15 healthy volunteers, 15 patients with subjective cognitive decline, 15 patients with mild cognitive impairment (MCI), and 15 AD patients to characterize DA dysfunction. PET imaging with [^{18}F]PBR111 was conducted one week after on the same subject. This radioligand is recently available in Geneva for the microglia. A standardized neuropsychological testing battery was applied by the same neuropsychologist to stratify patients into the MCI and AD groups. We measured central and peripheral inflammation.
Results: are being analyzed and will presented
Conclusions: This original study will analyze the links between inflammation, dopamine dysfunction, and cognitive deficits related to the continuum of clinical expression of AD.

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P0131 / #2619

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

ASTROGLIA AND NEURODEGENERATION: TOWARDS THE NORADRENERGIC HYPOTHESIS OF ALZHEIMER'S DISEASE

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Aims: We focus into astrocytes, neuroglial cells sharing metabolic properties with cancer cells. In Alzheimer's Disease (AD) the main noradrenergic nucleus (*Locus coeruleus*-LC) disintegrates, a defining factor of neurodegenerative disease progression[1]. LC axons project to most parts of the brain where they release noradrenaline, which stimulates astrocytes, homeostasis providing cells, enriched with adrenergic receptors[2]. Deficits in the LC lead to reduced levels of noradrenaline in the brain, which impairs the morphology, second messenger plasticity, vesicle-based signaling and aerobic glycolysis in astrocytes[3-8]. In support of a key role of astrocytes in homeostasis of neural networks, one may consider that astrocytes are important targets of established drugs including fingolimod and ketamine[9, 10], possibly also of new ones that affect neurodegeneration and play a role in the pathophysiology of AD.
Methods: Cultures and *Gdi1* KO mice were used[3, 6, 11], morphology, cytosolic levels of cAMP, D-glucose and L-lactate, vesicle mobility and fusion were monitored as described[3, 8]
Results: Adrenergic-stimulation induces cAMP-dependent arborization of astrocytes[7], regulates aerobic glycolysis and L-lactate production, which exits astrocytes, acts as fuel and/or signal. Extracellular L-lactate also acts in a positive feed-back manner on astrocytes to further enhance L-lactate production (metabolic excitability) via a novel, not yet identified L-lactate receptor[8], likely contributing more widely to neurological diseases[6].
Conclusions: The demise of LC leads to impaired function of homeostasis providing astrocytes, thus contributing to the pathophysiology of AD. Targeting mechanisms that regulate astrocytes may attenuate or even revert the progress of AD[12]. [1]Wilson-et-al, *Neurology*, 2013,**80:**1202. [2]Aoki, *J.Neurosci*, 1992,**12:**781. [3]Pirnat-et-al, *Glia*, 2021,DOI:10.1002/glia.24076. [4]Bozic-et-al, *Cell.Mol.Life.Sci*, 2020,**77:**3245. [5]Dolanc-et-al, *Cells*, 2022,**11**. [6]D'Adamo-et-al, *Metabolism*, 2021**116:**154463. [7]Vardjan-et-al, *Glia*, 2014,**62:**5669. [8]Vardjan-et-al, *Front.Mol.Neurosci*, 2018,**11**. [9]Trkov-Bobnar-et-al, *Mol.Neurobiol*, 2019,**56:**5971. [10]Lasic-et-al, *Sci.Rep*, 2019,**9:**10957. [11]Schwartz&Wilson, *Glia*, 1992,**5:**75. [12]Leanza-et-al, *Front.Mol.Neurosci.*, 2018,**11:**254.

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P0132 / #561

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

ASTROGLIAL POLARIZATION TO ANALYSE NEUROPROTECTIVE ACTIVITY OF VARIOUS COMPOUNDS.

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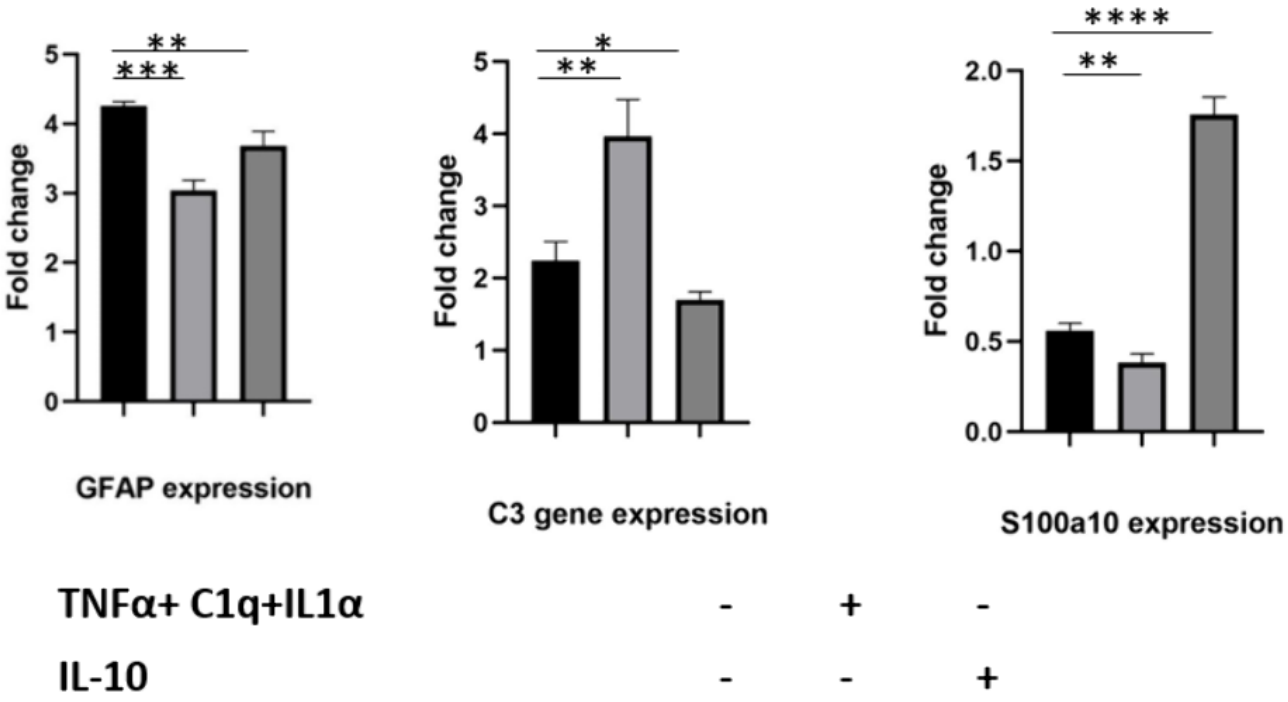
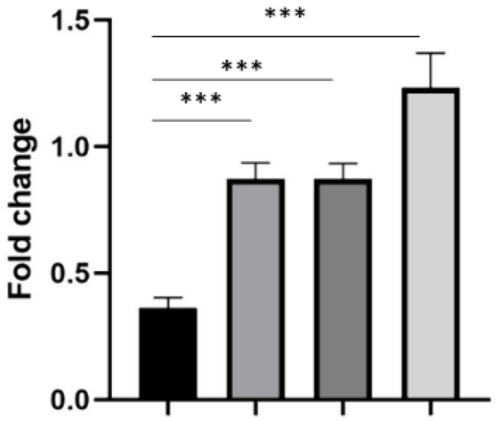
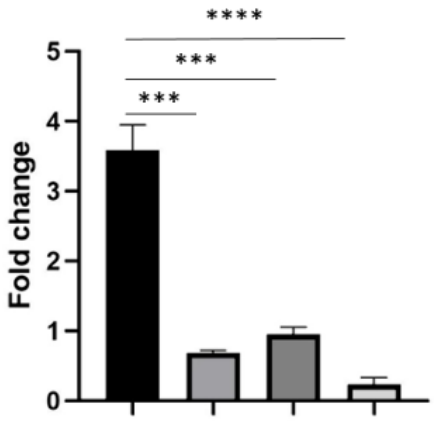
Aims: 1. To establish an astroglial polarized cell using U87Mg 2. To study the neuroprotective activity of vasicine on polarized cells
Methods: 1. Quantitative PCR 2. Western blotting 3. Immunocytochemistry
Results: The treatment of cells with pro-inflammatory cytokines converts naive astrocytes into activated astrocytes (A1) which in the presence of vasicine is transformed into the A2 phenotype. For phase contrast images, cells were first washed with 1X PBS and then images were taken at 10X, 20X, and 40X. Figure 1A shows cells with smaller extensions while Figure 1B shows elongated extensions, marker of differentiation. On comparison of Day 3 and Day 5 of retinoic acid treatment, day 3 treatment was found to have more profound changes in morphology.The differentiated cells treated with cocktail and IL-10 were analysed, and further change in expression of GFAP, C3 and S100a10 was obtained. In Figure 3, the expression of C3 (marker of A1) is increased with cocktail and S100A10 (marker of A2) is increased with Il-10. Thus, the final concentration of these cytokines is selected for further experimentation.Treatment with Vasicine and IL-10 showed significant reduction in the expression of C3 and GFAP indicating reduction in the reactive astrogliosis whereas the expression of S100A10 was enhanced with the treatment indicating the A2 phenotype progression.Immunocytochemistry of polarized cells indicates that the extensions were reduced in the presence of vasicine and cells started to shrink. Although the overall expression of GFAP seems to be enhanced with vasicine treatment.





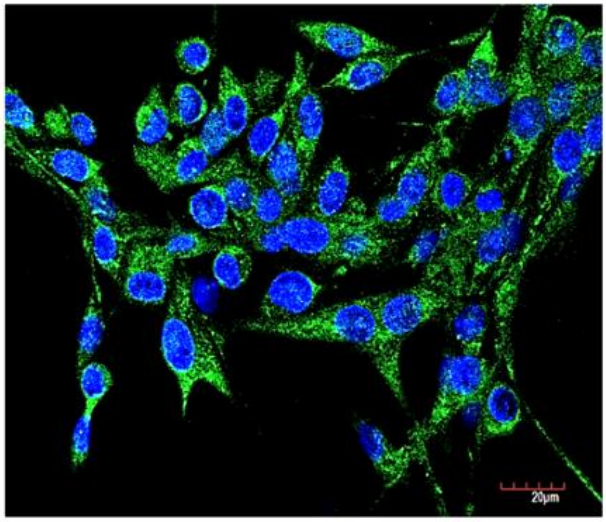
S100a10 expression

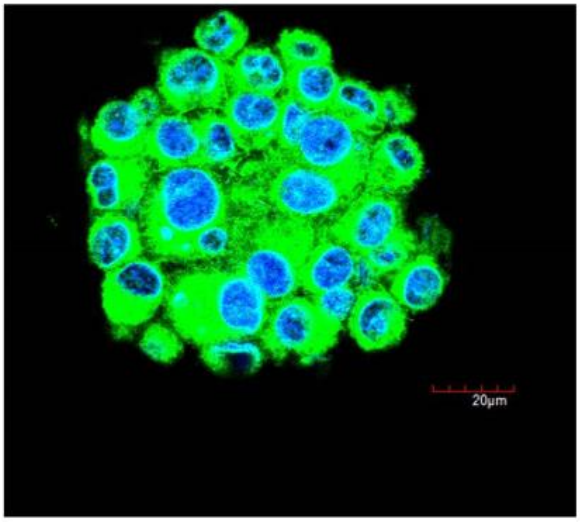
TNFα+ C1q+IL1α	-	+	+	+
Vasicine	-	-	+	+
IL-10	-	-	-	+



GFAP expression

TNFα+ C1q+IL1α	-	+	+	+
Vasicine	-	-	+	+
IL-10	-	-	-	+





Conclusions: The establishment of polarized astrocytes was successfully established and further exploration of the neuroprotective activity of vasicine was also achieved. Although individual treatment with vasicine does not provide a strong indication of neuroprotection, its cumulative action with IL-10 does show significant effects.

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P0133 / #1470

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

HUMAN PLURIPOTENT STEM CELL-DERIVED NEURAL PRECURSORS AND ASTROCYTES AS A PLATFORM TO MODEL ALZHEIMER´S DISEASE

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Aims: Alzheimer's disease (AD) is characterized by presenting a complex pathology, not fully resolved yet. This fact, together with the lack of reliable models, has impeded the development of effective therapies. Recently, several studies have shown that functional glial cell defects have a key role in the pathology of AD. However, this glial dysfunction, currently, cannot be correctly modeled using the available animal models, so we hypothesized that cells derived from Alzheimer's patients can serve as a better platform for studying the disease. In this sense, human pluripotent stem cells (hPSC) allow the generation of different types of neural cells, which can be used for disease modeling, identification of new targets and drugs development.

Methods: We have a collection of hiPSCs derived from patients with sporadic forms of AD stratified based on APOE genotype. We have differentiated these cells towards neural cells and mature them to neurons or astrocytes using a serum-free approach, to assess intrinsic differences between those derived from AD patients or healthy controls.

Results: We have implemented a serum-free approach and generated neural precursors and astrocytes from all the lines tested. We observe differences at the phenotypic level and a reduced capacity to differentiate towards neural lineage in those lines derived from APOE4 carriers.

Conclusions: Our preliminary data suggest intrinsic differences in the neural differentiation capacity between cell lines derived from APOE4 or APOE3 carrier subjects. Further experiments would contribute to elucidate novel pathogenic pathways associated with neurodegeneration and susceptible of therapeutic modulation, likely contributing to the development of new effective drugs against AD. Supported by ISCiii & FEDER funds: PI21/00915(AG) and PI21/00914(JV); by Junta de Andalucia & Programa Operativo FEDER 2014-2020: PY18-RT-2233(AG) and US-1262734(JV); Consejeria de Salud: PI-0276-2018(JAGL) and SNGJ4-11(LCP).

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P0134 / #1736

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

A TRANSLATIONAL APPROACH TO CHARACTERIZE THE ROLE OF NORADRENALINE IN ASTROCYTE RESPONSES IN ALZHEIMER'S DISEASE.

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Aims: Alzheimer's disease (AD) is the most common age-related neurodegenerative disease characterized by a progressive and irreversible cognitive decline. The early degeneration of the locus coeruleus (LC) in AD leads to a progressive depletion of noradrenaline (NA) in brain areas to which the LC projects such as the hippocampus, amygdala, and prefrontal cortex. NA is a potent modulator of microglia and astrocyte activities and is essential for memory processes. How its dysregulation disrupts glial cell functions and responses in AD needs to be further evaluated. This study aims to (1) characterize the modulatory effect of NA on phenotypic changes and responses of astrocytes in a physiological context and under pathological conditions, (2) define astrocytic phenotypes in AD patient samples and their relationship to alterations of the noradrenergic system.
Methods: We analyzed RNAseq data and protein levels of primary mouse astrocytes exposed or not to NA before and after pro-inflammatory and oxidative stress challenges (TNFα, IL1β, IFNγ, Menadione). We then investigated the distribution of some markers for differentially expressed genes (DEGs), their expression in astrocytes and their relationship with Amyloid and Tau pathologies in AD samples with light and high-resolution confocal microscopy.
Results: Our RNAseq data showed a modification of astrocyte phenotypes and responses after 48h exposure with 100 mM of NA. Some DEGs were directly involved in oxidative stress responses. We established a set of astrocytic, noradrenergic and pathological markers and studied their distribution in hippocampal and cortical AD samples.
Conclusions: We provide a detailed transcriptomic characterization of the effect of NA on the phenotypes of primary mouse astrocytes. We defined a new set of markers to study astrocyte phenotypic alterations in human samples and further characterize their relationship to NA.

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P0135 / #1363

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

MODELLING OF GLIA-NEURON CROSSTALK IN VITRO TO FACILITATE DRUG DISCOVERY FOR ALZHEIMER'S DISEASE.

Sarah Jolly[1], Leela Phadke[1], Dawn Lau[1], Nozie Aghaizu[2], Shania Ibarra[1], Carmen Navarron Izquierdo[1], Lucy Granat[1], Lorenza Magno[1], Paul Whiting[1,2], Paul Fish[1]
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Aims: Neuroinflammation has been implicated in the pathogenesis of Alzheimer's disease and potential new therapeutic targets have been identified in microglia and astrocytes. New in vitro models modelling neuroglia interactions are therefore required to facilitate drug discovery by enabling target identification studies as well as drug screening.
Methods: We first developed assays amenable to pharmacological modulations in rodent coculture of neurons and astrocytes. We then developed an approach to generate a quantitative and reproducible primary rodent triculture system that is suitable for pharmacological studies. The protocol was optimised to generate tricultures containing neurons, astrocytes and microglia by culturing in a serum-free medium designed to support all three cell types and adding exogenous microglia to cocultures. Immunocytochemistry and multi-electrode array (MEA) recordings have been used to characterise the model and to test tool compounds.
Results: We showed that, while astrocytes increase neuronal activity, microglia in the triculture model suppress neuronal activity in a dose-dependent manner. Furthermore, increased neuronal activity in cocultures and suppressed neuronal activity in tricultures correlated with different density of dendritic spines and of the postsynaptic protein Homer1 along dendrites, indicative of a direct or indirect effect of astrocytes and microglia on synapse function. These models were then used to investigate the effect of tool compounds on neuronal activity.
Conclusions: In summary, our models provide robust and reliable tools for studying the role of glia-neuron crosstalk in the regulation of neuronal activity. They allow for pharmacological manipulation of the system in a high-throughput manner and have the potential to be used for disease modelling, drug screening and target validation.

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P0136 / #619

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

CROSSTALK BETWEEN HUMAN IPSC-DERIVED ASTROCYTES AND NEURONS IN A CELL CULTURE MODEL OF ALZHEIMER'S DISEASE

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Aims: The role of astrocytes in Alzheimer's disease has recently received much attention, due to their central function in brain homeostasis and synaptic function. Astrocytes can ingest large amounts of aggregated amyloid-beta (Aβ), but then store, rather than degrade, the ingested material. This incomplete degradation results in severe cellular stress, which could be of relevance for AD progression. By generating a co-culture system of human induced puripotent stem cell (hiPSC)-derived astrocytes and neurons, we aimed to investigate how inclusions of aggregated Aβ in astrocytes affect their homeostatic function and consequently influence nearby neurons in terms of cellular viability and synaptic activity.
Methods: For this purpose, hiPSC-derived astrocytes were exposed to sonicated Aβ42 fibrils and their impact on hiPSC-derived neurons was analyzed by performing neuron-astrocyte co-cultures as well as additions of conditioned media or extracellular vesicles to pure neuronal cultures. Cellular viability was assessed via TUNEL staining, while synaptic funtion was evaluated via electrophysiological recordings of neurons.
Results: In the co-culture setup, the presence of Aβ inclusions led to an elevated clearance of dead cells by the astrocytes, indicating increased glial reactivity. In contrast, conditioned media from control, but not from Aβ-exposed astrocytes, benefited the wellbeing of neuronal monocultures. Furthermore, electrophysiological recordings showed a significant decrease in the frequency of excitatory post synaptic currents in neurons co-cultured with Aβ-astrocytes compared to control astrocytes, while conditioned media from Aβ-exposed astrocytes had the opposite effect.
Conclusions: Taken together, our results demonstrate that inclusions of aggregated Aβ affect the reactivity state of astrocytes, as well as their ability to support neuronal function.

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P0137 / #464

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

TRANSCRIPTOMIC PROFILING OF CEREBRAL ORGANOIDS REVEALS DYSREGULATED GENES IN A SUBPOPULATION OF PSEN1-MUTANT ASTROCYTES IN REGULATING MITOCHONDRIA AND LYSOSOMAL PROCESSES

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Aims: Alzheimer's disease (AD) is the primary form of dementia with at least 50 million people suffering from it. Our understanding of AD pathophysiology is still rudimentary, due to the complexity of the brain and disease and limitations with animal models. Cerebral organoids (COs) are self-organizing and offer an unprecedented model with better structural and functional complexity resembling the human brain. Our work aims to model Presenilin1 (PS1)-L271V AD pathogenesis and study the effects of astrocytes on Aβ clearance using patient iPSCs-derived COs.
Methods: COs were differentiated from patient-derived iPSCs that harbour PS1-L271V mutation and their isogenic controls were corrected via CRISPR/Cas9. Subsequently, we conducted single-cell RNA sequencing (snRNAseq) on young mutant and corrected COs and observed transcriptomic differences in a population of astrocytes.
Results: We observed typical neurodevelopment patterning and spontaneous differentiation of astrocytes in COs with accumulation AD disease hallmarks such as Aβ aggregates and p-Tau in PS1-L271V COs which recapitulates AD progression. scRNAseq revealed three genes that were significantly upregulated in a population of astrocytes present in PS1-L271V COs: CTSF, CHCHD2 and SLC39A4. These genes are implicated in lysosomes, mitochondria and zinc transport processes respectively and have also been reported to be implicated in other diseases such as Parkinson's Disease. To our knowledge, PS1-L271V in AD and the role of these genes in astrocytes have not been studied extensively.
Conclusions: Studying these genes in the context of AD could help us unravel new mechanisms leading up to AD neuropathology and provide an opportunity to develop drugs to intervene in AD progression. Ultimately, unravelling deregulation of mitochondria and lysosomal processes in astrocytes and its effects on Aβ clearance will shed light on their involvement in AD progression.

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P0138 / #919

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

ASTROGLIAL REACTIVITY IN RESPONSE TO B-AMYLOIDOSIS IS ASSOCIATED WITH MITOCHONDRIAL PATHOLOGY IN THE HIPPOCAMPUS OF ALZHEIMER'S TRANSGENIC MICE

Elba López Oliva[1,2], Laura Trujillo Estrada[1,2], Elisabeth Sánchez Mejias[1,2], Marina Mejias Ortega[1,2], Juan José Fernández Valenzuela[1,2], Ángela Gómez Arboledas[1,2], Jose Carlos Davila[1,2], Francisco Javier Vitorica[2,3], Antonia Gutierrez[1,2]
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Aims: Alzheimer's diseaase (A)D is associated with early energy hypometabolism, synaptic and mitochondrial dysfunction, oxidative stress, inflammation, abnormal proteostasis and progressive neurodegeneration. During the pathogenic process, amyloid-beta and phospho-tau pathologies have a detrimental effect on neurons and glial cells, affecting neuronal stability, and compromising ATP production and energy metabolism. Though mitochondrial dysfunction is thought to be an early event in the pathogenesis of this AD, the vast majority of studies have focused on neurons, and little is known about the functional characteristics and dynamics of mitochondria in astrocytes. Here, we aim to analyze mitochondrial subcellular features of reactive astrocytes in APP/PS1 mice hippocampus in order to a better understanding of this pathology.
Methods: Mitochondrial features were observed by transmission electron microscopy and immunogold labeling. Image analysis was performed to assess morphological changes.
Results: Our results show mitochondrial structural alterations including mitochondrial cristae loss, broken double membrane structure and fragmentation. In addition, an increase in both number and size of mitochondria in this transgenic model compared to age-matched WT mice, was found.
Conclusions: Since mitochondrial morphology is directly related to mitochondrial fusion/fission, the ultrastructural pathology of astrocytic mitochondria in this amyloidogenic model suggests dynamics abnormalities in these organelles that might lead to astroglial functional deficits compromising neuronal survival. *Supported by ISCiii grants PI21-0915 (AG) and PI21-00914 (JV) co-financed by FEDER funds from European Union, by Junta de Andalucia grants P18-RT-2233 (AG) and US-1262734 (JV) co-financed by Programa Operativo FEDER 2014-2020, and by grant PPIT.UMA.B1-2021_32 (LTE).*

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P0139 / #540

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

ANALYZING THE METABOLIC FUNCTION OF DJ-1 IN ASTROCYTES TO DEFINE ITS ROLE IN THE PATHOGENESIS OF PARKINSON`S DISEASE (PD) AND GLIOBLASTOMA MULTIFORME (GBM)

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Aims: Here, we are comprehensively studying the function of DJ-1 in PD and GBM to better understand its role in neurodegeneration and cancer. Mutations in the PD-associated gene *PARK7* leading to loss of function of DJ-1 protein cause autosomal-recessive PD, whereas high levels of DJ-1 protein were found in different cancers like GBM.
Methods: To analyze the role of DJ-1 in the regulation of the metabolic switch of increased glycolysis in cancer and impaired metabolism in PD, stable isotope labeled glucose metabolite tracing was used. Metabolomics analysis was performed using human iPSC derived midbrain dopaminergic neurons, human iPSC derived astrocytes of two different isogenic pairs and DJ-1 overexpression and GBM cell lines (U87, U251 and LN229).
Results: In human iPSC derived midbrain dopaminergic neurons, glucose tracing showed a significantly increased glycolytic and TCA flux in the DJ-1 overexpression line and a decreased TCA flux in DJ-1 deficient neurons. Concordant with the increased TCA flux, we found significantly increased protein levels of pyruvate dehydrogenase in DJ-1 overexpressing neurons. In contrast, glucose tracing in astrocytes revealed that overexpression of wildtype DJ-1 increases the glycolytic and TCA flux. The loss of DJ-1 significantly reduced the glycolytic and TCA flux in astrocytes. The knockdown of DJ-1 reduces the glycolytic and TCA flux in GBM cells.
Conclusions: Our results show that the effect of DJ-1 on the metabolism in neurons, astrocytes and GBM cells is depending on its different protein levels. High levels of DJ-1 in GBM cells support, and low levels of DJ-1 in PD impair the metabolism. Based on the alterations in the glucose metabolism observed, we aim to identify the molecular target of DJ-1 that is responsible for these metabolic phenotypes in PD and GBM models.

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P0140 / #497

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

DIFFERENT GLIOVASCULAR ALTERATIONS IN THE FRONTAL CORTEX OF SPORADIC AND FAMILIAR ALZHEIMER'S DISEASE: PROTECTION BY APOE3 CHRISTCHURCH MUTATION.

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Aims: To characterize the frontal cortex histopathology and the gliovascular unit in terms of astrocytes distribution and morphology, and their association with blood vessels, in human brain samples of sporadic Alzheimer's disease (SAD) and familial Alzheimer's disease (FAD).
Methods: Human brain cortex samples from controls, SAD, FAD (E280A), and APOE Christchurch (E280A) were fixed in 4% PFA. Slices of 50 µm thick were cut in cryostat. Brain slices were labeled with antibodies against GFAP, GS, GLAST, and lectins, for confocal microscopy and 3D analysis using Fiji . Immunohistochemistry for Amyloid beta (Aβ) and p-tau was performed for brightfield whole slide imaging using a NanoZoomer-XR 193 tissue scanner for analysis using QuPath and Fiji.
Results: Amyloid load was higher in the FAD group, followed by SAD and CNT. APOEch had the highest amyloid load. p-tau levels followed a similar pattern except that APOEch had the lowest p-tau load as the CNT. GFAP+ astrocytes were more abundant in FAD, followed by SAD, while APOEch and CNT had the lowest amount of astrocytes. SAD astrocytes had shorter and fewer processes, while FAD astrocytes had thicker processes. Blood vessels of FAD were more covered by GFAP+ and GS+ processes, followed by SAD and CNT, while APOEch blood vessels coverage by GFAP was similar to SAD. The vascular diameter was smaller in SAD had more vascular gaps, and were highly covered by GLAST+.
Conclusions: The gliovascular unit is differentially altered in SAD, FAD and APOEch. SAD showed more vascular damage and degenerative astrocytes, while FAD vessels were similar to CNT, and astrocytes showed a hyperreactive pattern. The APOEch mutation appears to have a protective role, as the case had similar results to the CNT, despite the highest amount of Aβ.

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P0141 / #952

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

SINGLE-CELL TRANSCRIPTIONAL PATTERNS IMPAIRMENT IN AN ADULT NEUROGENESIS MODEL OF ALZHEIMER´S DISEASE

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Aims: Adult Hippocampal Neurogenesis (AHN) is the generation of functional, mature neurons throughout life. This process is important to maintain learning and memory, the main functions of the hippocampus, which is one of the first brain regions to be affected in Alzheimer's disease (AD). Amyloid β (Aβ) peptide deposition is one of the neuropathological hallmarks of AD. Here, we aim to gain insight into the molecular dynamics of adult neurogenesis at single-cell resolution using a human Neural Progenitor Cells (NPCs) based model in order to identify the molecular signature of Aβ protein deposition throughout this continuous biological process.
Methods: We performed single-cell RNA sequencing of human NPCs derived from XCL1 DCXpGFP, an induced Pluripotent Stem Cell (iPSC) line. For that purpose, NPCs were differentiated and harvested on Day 0, 7, 13, and 20. Aβ Protein Fragment 1-42 was added to the culture once a week. Viable cells were sorted on the basis of the negative expression of TOPRO-3.
Results: Unbiased clustering of cellular profiles identified 15 distinct types of cells and their molecular signatures. Two trajectories were specified for the neuronal and astrocyte lineage by pseudotime analysis. We characterized the human neurogenesis pathway comprising stem cells, intermediate progenitors, and immature and mature neurons. Aβ protein addition caused directional shifts in the differential expression patterns of key genes in the neurogenesis process. Functional analysis related these findings to neurogenesis regulation, nervous system development and axonogenesis, and annotated for AD after the fate specification stage. Additionally, a population of astrocytes originated from astroglia progenitors.
Conclusions: Our results recapitulate transcriptional patterns underlying human neurogenesis and show how Aβ protein deposition might affect the process.

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P0142 / #2453

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

FUNCTIONNAL CHARACTERIZATION OF HUMAN AND BRAIN-SPECIFIC LONG NON-CODING RNAS ASSOCIATED WITH NEURODEGENERATIVE DISEASES

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Aims: Long non-coding RNAs (lncRNAs) are important cellular regulators as they are involved in chromatin remodeling, transcription modulation and post-transcriptional regulation through a variety of chromatin-based mechanisms and interplay with other RNA species. Studies have reported the functional implications of lncRNAs in the developing and mature brain, and lncRNA deregulations have been associated with many neurodegenerative diseases. Some lncRNAs are evolutionary conserved, suggesting a critical role across diverse species. The goal was 1/ to identify lncRNAs that are human- and brain-specific, 2/ investigate whether the expression of these lncRNAs was critical for neuronal differentiation, and 3/ determine whether deregulations of their expression could be associated to neurodegenerative diseases.
Methods: The functional characterization of these lncRNAs was performed using neurons derived from human induced pluripotent stem cells and brain tissue of patients with neurodegenerative diseases.
Results: We performed a bioinformatic analysis on lncRNA expression in different tissues and organisms and identified 8 lncRNAs that are specifically expressed in humans and in a high abundance in brain tissue. Subsequent quantitative PCR analysis validated the expression of these lncRNAs in mature neurons and brain tissues. We demonstrated that that their expression is dynamically regulated during neuronal differentiation and that the knock-down of these lncRNAs strongly altered the neurite outgrowth and maturation of neurons. Finally, we showed that the expression of these lncRNAs is deregulated in brain tissue of patients with Alzheimer's and Huntington's disease.
Conclusions: We identified human and brain-specific lncRNAs whose expression is critical for neuronal maturation and deregulations associated with neurodegenerative diseases. Our next step is to identify the molecular mechanisms by which they are important contributors to the brain pathophysiology.

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P0143 / #2151

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

APOE4 MODULATES EMBRYONIC NEUROGENESIS DURING THE EARLY STAGES OF HUMAN BRAIN DEVELOPMENT

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Aims: Polymorphism in the apolipoprotein E (*APOE*) gene is a major genetic risk determinant of late-onset Alzheimer's disease (AD), however, the ApoE-driven molecular mechanism that leads to AD pathology is not well understood.While the *E2* allele of the *APOE* gene is associated with neuroprotection compared to the neutral *APOE3* allele, the *E4* allele confers a higher risk for developing AD. Interestingly, neonates, infants, and adolescents carrying *APOE4* manifest a reduction in brain volume, gray matter, and cortical thickness. However, whether ApoE alters neurogenesis from early developmental stages of the brain remains unknown.
Methods: Here, we generated human cerebral organoids from isogenic human-induced pluripotent stem cells expressing different human *APOE* alleles (*E2*, *E3*, and *E4*) to investigate alterations in neurogenesis. To validate these results, we also used a mouse model expressing the different human ApoE isoforms.
Results: Our results show that ApoE4 expression led to a significant decrease in the size of brain organoids from the early stages of development. More importantly, Apoe4 organoids exhibited a significant reduction in the thickness of the ventricular zone, together with increased neurogenic division and premature neurogenesis, which decrease the neuronal progenitor pool. At later time points during development, organoids expressing ApoE4 also showed significantly fewer neurons and increased glia compared to ApoE2 organoids. Similarly, mice expressing human ApoE4 exhibited fewer neurons in relation to ApoE2.
Conclusions: Together, our findings suggest that ApoE4 causes early neuronal changes, an effect that may contribute to the development of AD pathology in later stages.

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P0144 / #963

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

ROLE OF ALZHEIMER'S DISEASE-ASSOCIATED ENDOCYTOSIS RISK FACTORS IN REGULATING CELL CYCLE EVENTS IN NEURONAL CELLS

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Aims: Late-onset Alzheimer's disease (LOAD) is the most common neurodegenerative disorder characterized by the formation of extracellular amyloid-β (Aβ) plaques and cytoplasmic neurofibrillary tangles (NFTs). Although much has been learnt about Aβ plaques and NFTs, we lack a complete understanding of the cellular pathways that contribute to apoptosis of cells in brain of LOAD patients. Endocytosis is strongly implicated in the pathogenesis of LOAD. Genome-wide association studies (GWAS) have identified several endocytosis-related LOAD-linked risk gene loci, including BIN1, PICALM and lately AP2A1. These genes encode adaptor proteins with the function in clathrin-mediated endocytosis (CME). How precisely CME contributes to the pathogenesis of LOAD is still under debate.
Methods: Here we describe that that CME components non-canonically regulate brain function and are required for cell cycle progression in neural progenitor cells. We show that adaptor protein complex- 2 (AP-2) functions in NPCs to maintain centrosome integrity and that NPCs deficient for AP-2 reveal defects in centrosome formation and p53-dependent G1/S phase cell cycle arrest.
Results: This function of AP-2 in regulating NPC proliferative capacity is independent of clathrin and requires its association with components of γ-TURC. We find that AP-2 stabilizes protein levels of γ-TuRC components and regulates the centrosome at the level of MT nucleation. AP-2-dependent γ-TuRC assembly at the centrosome prevents premature NPC differentiation. More importantly, we find that the levels of the AP-2 complex and γ-TuRC complex components are decreased in the cortex of 18 month-old TgF344-AD rats.
Conclusions: Taken together, our data identify a novel non-canonical function of the endocytic adaptor AP-2 in the regulation of proliferative capacity of NPC and set directions for the identification of novel therapeutic strategies for the treatment of LOAD with AP-2 complex dysfunction.

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P0145 / #300

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

MECHANISM OF CR1 INVOLVEMENT IN ALZHEIMER'S DISEASE

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Aims: Considering the close relationship between *CR1* and AD susceptibility, it is particularly important to reveal the relationship between *CR1* and AD pathology.
Methods: First, our study verified the relationship between the single nucleotide polymorphism (SNP) of *CR1* gene and the disease susceptibility of Chinese AD patients. Then we used ADNI database to analyze the influence of *CR1* gene polymorphism on the cerebrospinal fluid (CSF) proteins of AD patients. Finally, we used P301S transgenic mice to explore the mechanism of *CR1* involved in the tau pathology of AD.
Results: Our study first showed that rs6656401 genotype distribution was significant, suggesting that the A allele of rs6656401 was a risk allele for AD. Eight SNPs of *CR1* can regulate the levels of T-tau and p-tau in the CSF of AD patients. In this study, we also found that P301S mice, a mouse model which was widely used to study tau pathology, had significantly elevated Crry protein expression in the hippocampus and cortex compared with wild-type mice. Compared with wild-type mice, P301S mice showed higher levels of phosphorylated Tau proteins. After inhibiting the expression of Crry, phosphorylated Tau proteins were significantly reduced. Crying downregulation can reduce neuronal apoptosis and save cognitive impairment. Crying downregulation also altered the levels of neuroinflammatory cytokines interleukin-1β, tumor necrosis factor-α, interleukin-6, and complement components complement 3 and complement component 3b.
Conclusions: *CR1* gene is closely related to AD, which may become one of the targets for the treatment of AD in the future.

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P0146 / #1203

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

SMALL VESSEL DISEASE IS ASSOCIATED WITH TAU BURDEN AMONG MIDDLE-AGED ADULTS

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Aims: Amyloid-β plaques are associated with the spread of neurofibrillary tau tangles, leading to neurodegeneration and Alzheimer's disease (AD) dementia. Small vessel disease may contribute to tau phosphorylation in an amyloid-independent manner. We performed unsupervised voxel-based analyses to identify the spatial pattern of association between greater small vessel disease and greater tau burden.
Methods: Participants from the Offspring Study of Racial Disparities in Alzheimer's Disease and the Northern Manhattan Study of Metabolism and Mind (n=177; 63±5yrs; 67% women; 73/18/9% Latinx(L)/Non-Latinx Black(NLB)/Non-Latinx White(NLW)) underwent T2 FLAIR MRI for global and lobar white matter hyperintensity (WMH) segmentation and MK6240 PET for voxelwise tau SUVR. Regression models at every voxel tested associations between tau burden and global or regional WMH, across and within racial/ethnic groups (used as a social construct, not a genetic variable).
Results: Greater global WMH, mostly attributable to increased volume in the parietal lobe, was associated with greater tau in the frontal, temporal, and parietal lobes, and the thalamus. WMH volume was greatest in NLB participants (3.6±3.6 cm^3; $F(2,169)=3.1$, $p=0.05$) compared to L (2.6±3.5 cm^3) and NLW (2.6±3.0 cm^3) participants
(Fig1).

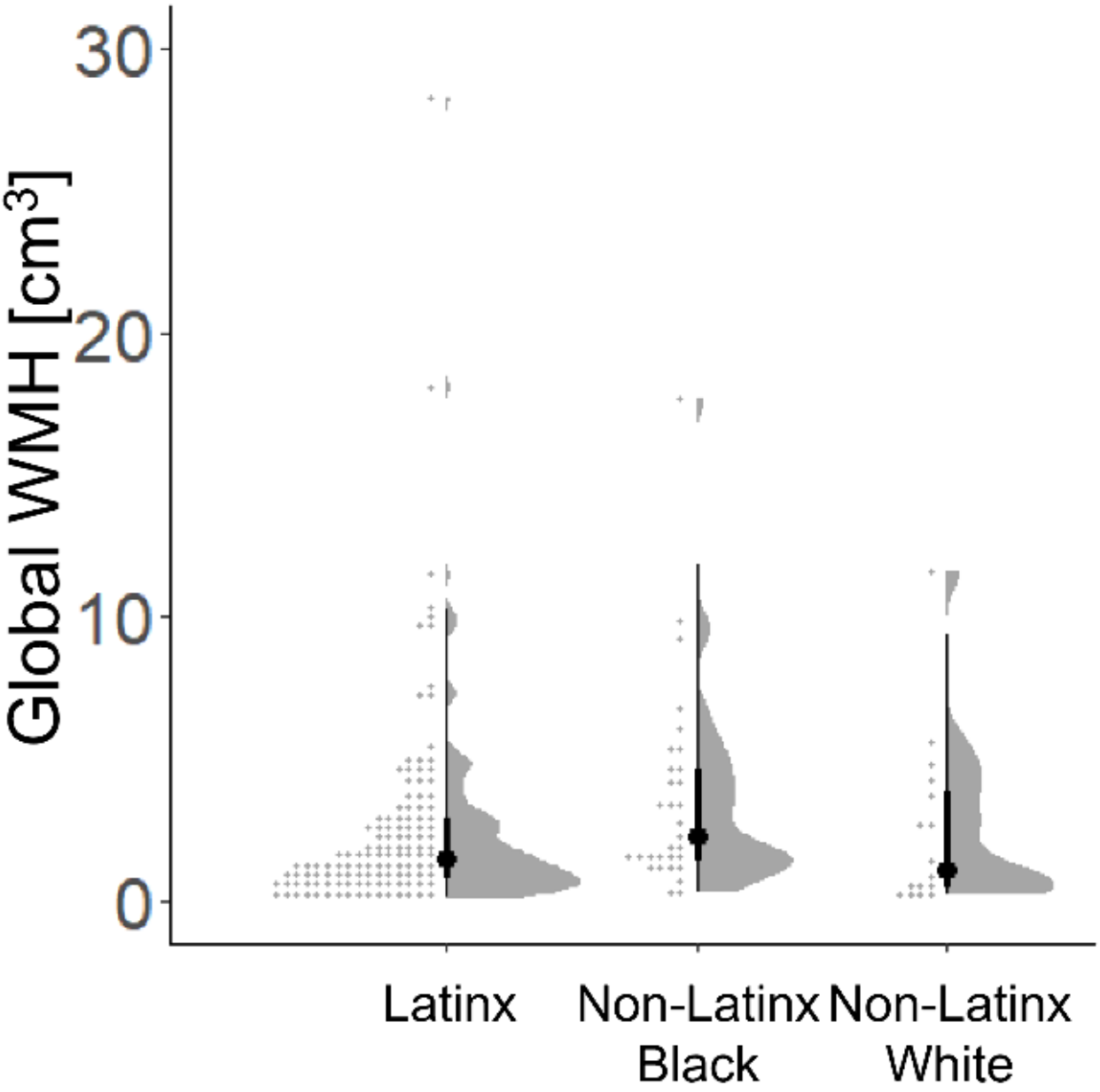

Figure 1. Plot demonstrating highest median value in Non-Latinx Black participants, and highest values in Latinx and Non-Latinx Black participants.

Within L participants, greater global WMH, driven by the parietal lobe, was associated with greater tau in the frontal and temporal lobes, and the thalamus. Within NLB participants, greater global WMH, driven by the frontal lobe, was associated with tau in the temporal and parietal lobes. There were no associations within the NLW group. There were no associations in off-target regions (e.g., meninges).

Conclusions: The contribution of small vessel disease to late Braak stage tau burden, and ultimately AD risk, was more pronounced in minoritized racial and ethnic groups with greater WMH, likely due to structural barriers to optimal vascular brain aging.

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P0147 / #562

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

TRANSCRIPTOMIC CHANGES IN ASTROCYTES AND FIBROBLASTS FROM AN APP KNOCK-IN AD MOUSE MODEL（APPNLGF）

Hao Li[1], Katrine Bjørnholm[1], Helena Karlström[1], Christer Betsholtz[2], Michael Vanlandewijck[2], Per Nilsson[1]
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Aims: Alzheimer disease (AD) exhibits aberrant protein aggregation in the brain, but our understanding of the vascular response to these aggregates is limited [1]. Amyloid Precursor Protein (*App*) knock-in mice (*App*^{NLGF}) recapitulate several aspects of AD including amyloid beta (Aβ) plaque formation, neuroinflammation and synaptic loss. We investigated the potential vasculature impairment in this mouse model by performing CD31 panning to isolate the vasculature recovering several main vascular components.
Methods: The pool of perivascular fibroblasts (FB) and astrocytes were limited. For the specific isolation of astrocytes, established microbeads-based purifications will be used. However, no such isolation procedures are established for FB cells. Thus, we have crossed *App* knock-in mice with reporter mice [2] that specifically express eGFP in the FB cells (driven by the promoter for platelet-derived growth factor alpha receptor (*Pdgfra*)) [3]. Dissected brains were homogenized followed by single cell FACS into a Smart-seq3 compatible lysis buffer. RNA was reverse transcribed to cDNA, fragmented by the Tn5 transposase and finally sequenced on an Illumina NextSeq2000. Cluster analysis, gene expression comparisons and pathway analysis are ongoing.
Results: Based on these results, validation of target genes will be performed to find the molecular questions that drive brain vascular dysfunction (ischemic damage [4], oxidative stress [5], cytokines [6], inflammasome, etc.)
Conclusions: By single cell RNA sequencing, we will use immunohistochemical staining and develop RNA-scope probes to characterize the corresponding mRNA distribution and compare the data with protein/mRNA distribution in brain sections from control and AD patient brains to determine the molecular underpinnings of vasculature changes in AD to discover possible biomarkers and drug targets.

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P0148 / #2072

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

UTILIZING THE WSB GENETIC CONTEXT TO TRACK ALZHEIMER'S DISEASE-ASSOCIATED VASCULAR DEFICITS, PLAQUE DEPOSITION, AND NEURODEGENERATION IN THE BRAIN AND RETINA

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Aims: Cerebral amyloid angiopathy (CAA) co-occurs with cognitive impairment and neurodegeneration in Alzheimer's disease (AD) patients. CAA is absent in commonly used AD models. We showed, unlike C57BL/6J (B6), wild-derived WSB/EiJ (WSB) mice transgenic for *APP/PS1* robustly developed CAA. To further evaluate vasculopathies in WSB mice, we utilized a human-relevant amyloid driver (humanized Aβ with Swedish, Austrian, and Arctic mutations; *hAPP^{SAA}*) and investigated CAA, vascular abnormalities, and neurodegeneration. We are also assessing the retina as a viable biomarker for these AD pathologies.
Methods: Male and female WSB.*hAPP^{SAA}* brains were histologically assessed for parenchymal plaque deposition, CAA, and neurodegeneration at 4, 5, 6, and 10 months. Cognitive function was evaluated at 8 months using the Novel Spatial Recognition Y-maze. Retinas are being imaged longitudinally from 4-12 months for amyloid (via curcumin), structure and function (ocular coherence tomography and pattern-electroretinography), and vascular integrity (fluorescein angiography). Data are compared to B6.*hAPP^{SAA}*, which lack cortical CAA at these ages.
Results: Sex differences were observed in WSB.*hAPP^{SAA}* mice for onset of CAA, parenchymal plaque deposition, and neurodegeneration. Female CAA and parenchymal plaque deposition began at 4 months, which became increasingly severe from 5-10 months. Cortical neurons became apoptotic (cCASP3+) by 5 months, and NeuN+ neurons were lost by 10 months. Male WSB.*hAPP^{SAA}* mice developed CAA and parenchymal plaques at 6 months but did not have neurodegeneration at the ages tested. Female, but not male WSB.*hAPP^{SAA}* mice exhibited cognitive impairment at 8 months. Retinas had no obvious baseline neurodegeneration or vasculopathies and will be continually assessed with age.
Conclusions: WSB.*hAPP^{SAA}* mice develop human-relevant AD pathologies, suggesting their use as an improved preclinical model. Ongoing work is utilizing *in vivo* retinal examination to detect early vascular deficits and neurodegeneration in AD.

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P0149 / #974

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

AGING OF THE VASCULAR NICHE IN ALZHEIMER'S DISEASE - ASSOCIATION WITH STRING VESSELS

Heike Mrowetz[1,2], Kathrin Kniewallner[1,2], Michael Unger[1,2], Diana Bessa De Sousa[1,2], Ludwig Aigner[1,2,3]
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Aims: Around 60-90% of Alzheimer's disease (AD) patients show cerebrovascular pathological alterations linked to neurodegeneration, including vascular Aβ accumulation, fragmented blood vessels, changes in blood vessel diameter and thickness of the vascular basement membrane of capillaries. Cerebrovascular dysfunction is also linked to a compromised blood-brain barrier (BBB) structure and function. However, the molecular and cellular changes leading to BBB dysfunction remain largely unexplored. Here, we aim to characterize vascular and cellular changes occurring at the neurovascular unit in a mouse model of AD and aged mice.
Methods: In a quantitative immunohistochemical approach, we used collagen IV and PDGF receptor beta staining to assess vessel density, volume and fragmentation, as well as pericyte number and pericyte coverage of blood vessel, in brain sections from 3-, 10- and 12-months old in APP-PS1 mice and wild type (WT) littermates.
Results: We observed a decrease in vessel density and vessel volume as well as an increase vessel fragmentation with aging. In aged APP-PS1 mice, these vascular alterations were more pronounced than in aged WT mice. We also observed an increase in string vessels (i.e., avascular basement membrane strands, remnants of capillaries) in APP-PS1 mice already at pre-plaque stages. Pericyte numbers were highly decreased in aged APP-PS1 and WT mice.
Conclusions: Age-related cellular and structural changes of neurovascular unit appear earlier and are more pronounced in AD transgenic mice, potentially contributing to the disease progression.

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P0150 / #990

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

TRANSCRIPTOMIC DISSECTION OF IMPAIRED ANGIOGENESIS AND BLOOD BRAIN BARRIER FUNCTION IN AD

Stergios Tsartsalis[1,2], Hannah Sleven[3], Nurun Fancy[4], Frank Wessely[5], Nanet Willumsen[4], Michal Rokicki[5], Vicky Chau[4], Eseoghene Ifie[6], Combiz Khozoie[4], Olaf Ansorge[6], David Owen[2], Caleb Webber[5], Johanna Jackson[4], Zameel Cader[3], Paul Matthews[4]
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Aims: Brain perfusion and blood brain barrier (BBB) integrity are reduced in Alzheimer's disease (AD). We hypothesized that dysfunction of pathways regulating the structure and function of the BBB endothelial cells (EC), pericytes (PC) and fibroblasts (FB) is related directly to the pathological protein load.
Methods: We performed single nucleus RNA sequencing (snRNAseq) of vascular cells isolated from *post mortem* samples from AD patients and controls. We developed a meta-analytic approach to integrate these data with related publicly available datasets. First, we explored vascular cell-type enrichment for the expression of genes associated with genetic risk for AD. We then performed a differential gene expression (DGE) analysis using two approaches: a categorical comparison of AD vs controls and a regression of transcriptomic alterations to either regional total beta-amyloid (Aβ) or neurofibrillary tangle (NFT) burden.
Results: EC are enriched for expression of genes related to AD genetic risk. Among them, *PICALM* was downregulated in AD and *CTGF* positively correlates to Aβ in EC. EC transcriptional signatures also identified mechanisms for impaired Aβ clearance and increased apoptosis and interferon signalling genes were upregulated in the EC, as well as in PC. In the AD vs control comparison, an imbalance of angiogenic signalling, with an enhanced pro-angiogenic response driven by *HIF1A* and *ANGPT2* and a downregulation of the effectors of this response, notably including the angiopoietin receptor, *TEK,* and associated growth factor pathways, were observed in association with downregulation of extracellular matrix genes in FB.
Conclusions: Transcriptional signatures of brain vascular cells suggest a potentially causal role for EC in AD. They identify early vascular mechanisms of disease include impaired angiogenesis, reduced Aβ clearance and impaired integrity of the microvascular extracellular matrix composition.

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P0151 / #2651

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

LPS-INDUCED INFLAMMATION OF BLOOD BRAIN BARRIER IS REDUCED BY SODIUM NITROPRUSSIDE

Manuel Campos-Toimil[1], Nuria Seoane[1], Aitor Picos[1], Amalia Dolga[2], Martina Schmidt[2], Dolores Viña[1]
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Aims: Enhanced inflammatory response and release of proinflammatory cytokines are often associated with the pathogenesis of different neurodegenerative disorders, such as Alzheimer's disease (AD), multiple sclerosis (MS) or Parkinson's disease (PD). It has been described that neuroinflammation compromises blood-brain barrier (BBB) integrity, the highly selective barrier that stabilizes the brain microenvironment, and may lead to oxidative stress, amyloid-beta accumulation and neuronal loss. Therefore, the maintenance of its integrity is crucial to prevent neurodegeneration.
Methods: Nitric oxide (NO) is vasoactive molecule that plays a central role in vascular homeostasis, regulating endothelium vasomotor tone. In addition, NO also presents anti-inflammatory effects and reduces reactive oxygen species (ROS) production. In this study, the potential protective effects of sodium nitroprusside (SNP), a NO donor, on lipopolysaccharide (LPS)-challenged bEnd.3 cells were evaluated.
Results: Our preliminary results suggest that 24-hour inflammatory stress decreases cell viability and increases the cell index and ROS production. Under these conditions, SNP shows a protective effect by decreasing the cell index as well as ROS levels. However, LPS-induced inflammation does not affect barrier integrity and mitochondrial superoxide production.
Conclusions: More studies need to be carried out to further elucidate the mechanism behind the protective effect that NO shows against inflammation.

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P0152 / #980

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

CEREBROSPINAL PDGFRB IS A MARKER OF NEUROVASCULAR DYSFUNCTION RELATED TO NEUROINFLAMMATION BUT NOT ALZHEIMER'S DISEASE

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Aims: Pericytes are part of the neurovascular unit (NVU), an anatomical and functional complex that includes neurons, glial cells and vascular cells. Blood-brain barrier (BBB) injury causes release of platelet-derived growth factor receptor β (PDGFRβ) from pericytes in cerebrospinal fluid (CSF). BBB damage is present in aging and Alzheimer's disease (AD), however it is still unclear how CSF PDGFRβ reflects these processes. The aim of this study was to determine whether CSF PDGFRβ is associated with AD pathological changes, age, BBB integrity and neuroinflammation as measured by glial markers.
Methods: We measured PDGFRβ in the CSF of 771 cognitively unimpaired (CU), mild cognitive impairment (MCI) and dementia subjects from the Swedish BioFINDER-2 study. Linear regression analysis (adjusted for age, sex, diagnosis and ventricular volume) was used to assess associations to Aβ-PET and tau-PET pathology, *APOE* ε4 genotype, MRI measurements of cortical thickness, white matter lesions (WML), cerebral blood flow (CBF) and CSF concentrations of neuroinflammatory markers related to astrocytic activation (i.e. YKL-40 and GFAP). Sequential mediation analysis was performed to study the relationship between age, BBB dysfunction (measured by CSF/plasma albumin ratio, QAlb) and neuroinflammation.
Results: Higher CSF PDGFRb concentrations were related to older age, BBB permeability (QAlb) and increased CSF YKL-40 and GFAP ($p<0.001$). The effect of age on QAlb was partly mediated by pericyte damage (PDGFRb, 16.6% of total effect) and neuroinflammation (16.6-33% of total effect). However, PDGFRb showed no associations with *APOE* e4 genotype, Aβ and tau PET imaging or MRI measures of brain atrophy, CBF and white matter lesions ($p>0.05$).
Conclusions: Pericyte damage seems to play a role in age-related BBB disruption together with neuroinflammation, but PDGFRβ is not related to Alzheimer-related pathological changes.

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P0154 / #388

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

A DEFECTIVE CEREBROVASCULAR INSULIN RECEPTOR IN ALZHEIMER NEUROPATHOLOGY

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Aims: Alzheimer's disease (AD) is an age-related disorder, sharing risk factors with metabolic diseases. Recent evidence indicates that the AD brain displays a lower response to insulin. However, as a mainly circulating hormone insulin must first interact with the blood-brain barrier (BBB) through its receptor (INSR) before having an impact on brain function.
Methods: We used microvessel-enriched brain samples from individual classified as Controls, with mild-cognitive impairment (MCI) or AD and from 3xTg-AD mice from different ages. In mice, microvessels extraction was combined with in situ cerebral perfusion to assess INSR activation in response to insulin.
Results: We first showed that INSR is concentrated within the cerebral vasculature in both human and mouse. Lower levels INSRα-B (long isoform of the extracellular α chain) were observed in microvessels from AD individuals and 3xTg-AD mice, while other subunits (INSRα-A, INSRβ and pro-INSR) were unchanged in both microvessel and parenchymal fractions. Of note, INSRα-B was not detected in parenchymal fraction. INSRα-B was inversely correlated with Aβ plaques in the cerebral cortex and β-site APP cleaving enzyme 1 (BACE1) in microvessels. In addition, positive associations between INSRα-B and cognitive scores, insulin-degrading-enzyme (IDE), neprilysin or ABCB1 were observed. The resulting higher cerebrovascular INSRα-A/B ratio is postulated to underlie brain insulin resistance. In the mouse, cerebral perfusion of insulin induced the phosphorylation of the intracellular β-chain INSR in microvessels from controls but not 3xTg-AD 18-month-old mice.
Conclusions: Overall, the present data in postmortem AD brains and in an animal model of AD neuropathology indicate that defects in the insulin receptor located at the BBB may contribute to brain insulin resistance in AD.

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P0155 / #2701

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

INSULIN SIGNALLING AND INSULIN RESISTANCE IN ALZHEIMER'S DISEASE.

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Aims: Increasing evidence links insulin resistance to the Alzheimer's disease (AD) development. Hence, our aim is to use a multidisciplinary approach to unravel the contribution of insulin signalling and insulin resistance in AD development.
Methods: A primary care-based cohort (pcb-cohort), set up in the laboratory was analysed for the incidence of diabetes mellitus (DM). In parallel a bioinformatic analysis exploring the synaptic crosstalk between insulin signalling and AD, focusing on phosphorylation related events was implemented. Correlations were tested experimentally, using in vitro insulin resistance and AD mimicking models.
Results: Evidence from the pcb-cohort showed a tendency for patients with DM to perform poorly in cognitive tests. Two major AD genetic risk factors were also assessed (APOE and BIN1) in function of DM. While APOE2 allele showed protective characteristics against DM, APOE4 allele showed no correlation. However, BIN1 rs744373 G+ showed an increased risk for developing DM, which was already reported to be an AD risk factor. The bioinformatic analysis unravelled 6 kinases (LRRK2, GSK3B, AKT1, EGFR, MAPK1, and FYN) that emerged as potential links between insulin signalling and AD, of which, two (FYN and GSK3B) were chosen to be further explored. To finalize, using insulin resistant and AD in vitro models here developed, the role of these two kinases in APP metabolism and Aβ peptide production as well as tau hyperphosphorylation were assessed.
Conclusions: Insulin signalling and insulin resistance clearly play a role in AD development, specifically in APP metabolism and Tau phosphorylation.

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P0156 / #885

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

INVESTIGATING THE DISTINCT NEURONAL AND GLIAL ROLES OF THE AD RISK GENE WWOX IN DROSOPHILA MELANOGASTER

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Aims: Many risk genes have been identified that may mediate an individual's risk of developing Alzheimer's Disease (AD). Understanding the roles of these genes in neuronal and glial functions, and how this relates to molecular and behavioural changes, will further our understanding pathological mechanisms. In this study we wished to decipher the neuronal vs. glial role of the ubiquitously expressed AD risk gene WW-containing oxidoreductase (WWOX).
Methods: Using variations of the GAL4-UAS system in *Drosophila melanogaster*, we ablated, reduced, and overexpressed the highly conserved *Drosophila* homolog of WWOX in neurones and/or glia and assessed the impact on survival, negative geotaxis, sleep, electrophysiology, seizures and transcriptomics.
Results: Here we show that homozygous knockout significantly shortened lifespan, whereas glial knockdown had no effect. Interestingly, overexpression of glial Wwox was marginally protective. Negative geotaxis, a read out of overall CNS function, was decreased after knockout whereas glial knockdown alone had no effect. Furthermore, both glial and neuronal knockdown increased sleep duration. Although phenotypes were witnessed after neuronal and glial knockdown, our data suggest that neuronal Wwox may be the stronger driver of disease associated changes. Consistently, electroretinograms revealed that knockdown of Wwox led to a decrease in laminar neurone hyperpolarisation and homozygous knockouts were more susceptible to seizures. Transcriptomic analysis identified alterations in metabolism and ECM receptor interactions after neuronal knockdown however performing knockdown in conjunction with AB42 dysregulated pyruvate and retinol metabolism. Overexpression of Wwox altered fatty acid biosynthesis and metabolism whereas overexpression with AB42 altered pathways including fatty acid oxidation, glycolysis, peroxisome function and the pentose phosphate pathway.
Conclusions: In conclusion, decreased neuronal Wwox in *Drosophila* resulted in increased sleep and reduced hyperpolarisation. Transcriptomics revealed large variations in metabolism that could reveal potential therapeutic targets.

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P0157 / #1503

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

EARLY-LIFE METABOLIC DYSFUNCTION IMPAIRS COGNITION AND MITOCHONDRIAL FUNCTION IN MICE

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Aims: This study aimed to evaluate the relationship between peripheral metabolic and bioenergetic changes induced by a two-hit protocol and their impact on cognitive function in juvenile mice.
Methods: To this purpose, 3-week-old male C57BL/6 mice received a high-fat diet (HFD) or control diet (CD) for 7 weeks, associated with 2 low doses of streptozotocin (STZ, 40mg/Kg each) or vehicle. In spite of the absence of obesity and changes in lipid profile, HFD+STZ induced impaired glucose metabolism.
Results: The two-hit protocol impaired recognition and spatial memories in juvenile mice, without inducing a depressive-like behavior. Increased immunoreactivity for GFAP and a trend towards a decrease in NeuN staining were verified in the hippocampus of HFD+STZ mice. The treatment caused a bioenergetic impairment in the hippocampus, characterized by a decrease in both O_2 consumption related to ATP production and in the maximum respiratory capacity. The thermogenic capacity of brown adipose tissue was impaired by the two-hit protocol, here verified through the absence of a decrease in O_2 consumption after uncoupled protein-1 inhibition and an increase in the reserve respiratory capacity. Impaired mitochondrial function was also observed in the liver of HFD+STZ juvenile mice, while no changes were verified in O_2 consumption in the heart of mice.
Conclusions: These results indicate that exposure to HFD + low doses of STZ early in life has a detrimental impact on the bioenergetic and mitochondrial function of tissues with metabolic and thermogenic activities, which is likely related to hippocampal metabolic changes and cognitive impairment.

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P0158 / #1873

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

CORRELATION OF INSULIN AND BETA AMYLOID IN THE SERUM OF PATIENTS WITH PREMATURE OVARIAN FAILURE

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Aims: Women are at greater risk than men for developing Alzheimer's disease during their lifetime. The aim of our study is to determine the relationship between insulin and beta amyloid in the serum of patients suffering from premature ovarian failure.
Methods: In the serum of affected patients, insulin and beta amyloid were determined using the Elisa technique.
Results: The results of our study conducted on 78 patients with POF and 75 controls showed that there is a positive correlation between insulin and beta amyloid levels in the serum.
Conclusions: From this we can conclude that insulin can be a target for testing therapy in patients and opens a new avenue.

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P0159 / #1305

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

SEX-DEPENDENT DIFFERENCES IN GLUCOSE-METABOLIC DYSFUNCTION IN ALZHEIMER'S DISEASE

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Aims: Females have increased susceptibility to Alzheimer's disease in clinical and pathological process, compared to male. The authors studied the sex-dependent differences during pathogenesis of Alzheimer's disease and suggest the mechanism of increased risk for female.
Methods: PiB-PET imaging, 18F fluorodeoxyglucose-PET (FDG-PET) imaging, magnetic resonance imaging (MRI) data from participants Measurement of plasma biomarkers of Aβs levels Transcriptome analysis and functional network modeling Statistical analysis
Results: We suggest sex-dependent metabolic dysregulations in the brains of Alzheimer's disease (AD) patients through analysis of cross-sectional and longitudinal study. For this analysis, we utilized the results of cohort 1 (South Korean, n = 181) with Pittsburgh compound B-positron emission tomography (PET), fluorodeoxyglucose PET, magnetic resonance imaging, and blood biomarkers quantification at baseline and two-year follow-up studies. Transcriptome analysis using data from cohort 2 (European, n= 78) was performed to verify the sex differences in AD-related metabolic changes. In our study, imaging biomarkers represented stable correlation with AD progression in females, however not in males. Females showed brain metabolic dysfunction during longitudinal study, and the plasma beta-amyloid 42/40 ratio represented as biomarker for brain metabolism in females, but not in male. Moreover, our transcriptome analysis supported this finding through transcriptomic and metabolic differences in the brains of AD patients between sexes.
Conclusions: This study suggests female-specific metabolic dysfunctions in the brains of AD and their association with plasma Aβ42/40 level. Our longitudinal and transcriptome analyses of brains and blood samples of AD patients revealed differences in human brain transcriptomic and metabolic changes associated with AD between the females and males.

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P0160 / #1651

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

THE PATHWAY TO DEMENTIA: RESULTS FROM THE PROSPECTIVE POPULATION STUDY OF WOMEN IN GOTHENBURG (PPSWG) 1968 – 2003

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Aims: Previous results from PPSWG showed a U-shaped association between fasting serum insulin and incident dementia[a]. We now aim to determine the time-ordering between metabolic risk factors for dementia up to 35 years before diagnosis or end of follow-up (EOF) distinguishing between dementia with and without type-2 diabetes (T2D) comorbidity.
Methods: Dementia diagnoses were based on information from psychiatric examinations and close informant interviews, hospital discharge register, inpatient and outpatient departments, and general practitioners' offices. Baseline risk factors included body mass index (BMI) and fasting values of blood glucose and serum insulin. Cubic-spline regression was used to model the dependence of risk factors on time to dementia diagnosis/EOF.
Results: Among 1220 women aged 38-60 and free of T2D/dementia at baseline 143 developed dementia until 2003 (22 with T2D). Mean biomarkers were stable over 35 years in women without T2D or dementia (reference). Similar to reference, mean BMI in women with incident dementia but no T2D was stable around 23 kg/m^2 and started to decrease 10 years before dementia diagnosis. Mean insulin values were lower than reference 35 years before diagnosis, but similar later on. At all times, BMI and insulin were higher in women with incident T2D but no dementia compared to reference, while glucose started to rise 10 years before EOF. Women with both T2D and dementia showed a rapid increase of BMI 30 years before dementia, and a steep decrease from 20 years before dementia diagnosis, while insulin followed the linear increase observed in T2D without dementia.
Conclusions: Conclusion: The time course of metabolic markers differs between dementia with and without T2D. Work in progress includes HOMA estimates for insulin resistance and dementia updates until 2020. [a]Mehlig et al., Neurology 91(5):e427-e435 (2018)

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P0161 / #2488

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

CAN METFORMIN USE REDUCE AMYLOID BETA DEPOSITION IN ELDERLY INDIVIDUALS WITH DIABETES?

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Aims: There is a shred of growing evidence demonstrating that diabetic patients are at higher risk of developing Alzheimer's disease compared to the general population. The previous investigation showed the protective effect of metformin for delaying dementia in diabetic patients. However, there are limited data on the effect of metformin on Aβ deposition. This study aims to investigate the effect of metformin on Aβ deposition in non-demented diabetic individuals.
Methods: We entered 198 non-demented diabetic subjects including 101 mild cognitive impairment (MCI), and 97 cognitively healthy individuals from Alzheimer's disease Neuroimaging Initiative (ADNI) which were then categorized as metformin users and non-users. We used the ANCOVA model for measuring the association between metformin use and hippocampal and cortical volumes.
Results: AIn total 96 individuals were stratified as metformin users. Results of the univariate model indicate that metformin users had a lower overall Aβ deposition (p=0.022) in the baseline. Moreover, after two years the difference in Aβ deposition remained between groups (p=0.007).
Conclusions: Our findings showed the protective effects of metformin on Aβ deposition in non-demented elderly individuals with diabetes. Comparing the groups show strong enough results regarding the lower Aβ deposition in metformin users.

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P0162 / #651

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

THE HUMAN RECOMBINANT FIBROBLAST GROWTH FACTOR 21 (RHFGF21) AS A THERAPEUTIC TOOL IN AD

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Aims: Alzheimer's disease is an incurable form of dementia that shares risk factors with metabolic diseases. The recombinant human FGF21 (rhFGF21) is a hormone that is being tested for the treatment of diabetes. We aimed to evaluate the effect of rhFGF21 administration (1 mg/kg/day, 4 weeks) on metabolic, cognitive, and neuropathological markers of Alzheimer's disease (AD) in the 3xTg-AD mouse model.
Methods: We used the triple transgenic mouse model of AD (3xTg-AD), which develops tau and beta-amyloid pathologies over time. To induce an obese phenotype, mice were fed a High-Fat (35% w/w) compared to a control (5% w/w) diet starting at 6 months. Then, rhFGF21 (1 mg/kg/day, osmotic minipump) or vehicle was administered from 15 to 16 months of age. After the third week of treatment, glucose, insulin tolerance, and cognitive tests were performed. Mice were ultimately euthanized for post-mortem protein analysis.
Results: (1) Administration of rhFGF21 with osmotic pumps for one month led to blood levels averaging 154 ng/ml (~8 nM) and resulted in weight loss, decreased fasting glucose, leptin, and insulin as well as improved insulin resistance and glucose response in NonTg and 3xTg-AD mice. (2) rhFGF21 increased locomotion and improved anxiety in all mice but attenuated HFD-induced memory deficits only in 3xTg-AD mice. (3) rhFGF21 did not alter tau phosphorylation but reduced soluble beta-amyloid 42/40 ratio in the hippocampus of 3xTgAD females. (4) rhFGF21 activated the FGFR1 receptor in the liver with limited effect in brain regions.
Conclusions: Beside robust regulation of metabolism, the effects on cognitive endpoints observed here suggest that rhFGF21 can also present a therapeutic potential for AD. Whether its impact on the brain is direct or indirect through the periphery remains to be determined.

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P0163 / #1119

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

GENETIC DETERMINANTS OF HUMAN METABOLITES IN CSF AND BRAIN LINK METABOLITES TO 15 BRAIN-RELATED TRAITS AND DISEASES

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Aims: Brain metabolism perturbation in dementia is poorly understood. Existing metabolite quantitative trait loci (MQTL) were found using tissues other than cerebrospinal fluid (CSF) (except for Panyard, et al 2021) and brain, which is not ideal for studying neurological disorders (ND). We expanded the knowledge on ND using a large-scale brain and CSF study by integrating MQTL with metabolome-wide association study (MWAS), colocalization, and mendelian randomization (MR).
Methods: We performed M-GWAS to identify MQTL, and performed MWAS, mendelian randomization, and colocalization to identify metabolites contributing to 29 brain-related traits. We analyzed 440 metabolites in 2311 CSF samples and 962 metabolites in 1016 Brain samples (WU, ROSMAP, MAYO). FUSION was used for MWAS, Coloc.abf was used for colocalization, and Two-sample MR was used for MR.
Results: The CSF study identified 220 independent signals within 191 associations for 144 metabolites at 101 loci. Of those, 113 associations and 24 loci were novel. The brain study found 35 associations at 27 loci. Through MWAS, we identified 75 associations (17 pairs colocalized) between 47 metabolites and 15 traits. MR identified 101 causal metabolites for traits. Importantly, galactosylglycerol was not only strongly associated (colocalized) but also causal to Parkinson Disease (PD). In addition, succinylcarnitine and adenine were found both associated and causal to Alzheimer Disease (AD). Other strongly associated (colocalized) and causal relationships includes for example cognitive performance and metabolites 6-oxopiperidine-2-carboxylate, 3-hydroxyisobutyrate and argininosuccinate.
Conclusions: The large-scale CSF and brain MQTL study not only identified potential tissue specific MQTLs, but also provided insights to disease etiology, including AD and PD. Importantly, 7 strongly associated and causal relationships warrant further mechanistic exploration.

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P0165 / #1443

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

UTILIZING ΔFOSB ACTIVITY TO LOCALIZE NEURONAL HYPEREXCITABILITY IN APP/PS1 MOUSE MODELING ALZHEIMER'S DISEASE

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Aims: Objectives: In overnight video-EEG recordings, 30-40 % of patients with Alzheimer's disease (AD) show epileptiform discharges during sleep. These discharges are usually asymptomatic; however, follow-up studies have shown that they strongly correlate with accelerated cognitive decline. The focus of the epileptiform discharges and seizures remains unclear, which makes it difficult to find their connection to pathological processes at the cellular level. We have previously documented sleep-related epileptiform discharges in the cerebral cortex and hippocampus of amyloid plaque producing transgenic APP/PS1 mice. This study aims to localize the hyperexcitability at the network level and determine the onset age of epileptiform discharges in regard to the onset of amyloid plaque pathology.
Methods: Methods: This study searched for the epileptic focus by immunohistochemical staining of brain slices from transgenic APP/PS1 mice and their wild-type littermates with ΔFosB at 6 (pre-plaque) and 12 weeks (presence of plaques) of age. ΔFosB is a biomarker of mean neuronal activity over the last 1–3 weeks. Additionally, double staining with ΔFosB and W02 (anti-Aβ) was utilized to study the possible connection of ΔFosB-positive cells with Aβ -plaques and intracellular Aβ.
Results: Results: Our preliminary data revealed that APP/PS1 mice showed increased ΔFosB signal compared to their wt littermates in the dentate gyrus at 12 weeks of age but not yet at 6 weeks. We are extending these studies to include all brain areas directly connected to the hippocampus.
Conclusions: Conclusions: Dentate gyrus is at least one region of origin of the epileptiform discharges seen in APP/PS1 mice. Results obtained from this study may help to locate the epileptic focus in AD patients.

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P0166 / #1931

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

MODELLING THE BASAL GANGLIA FOR WORKING MEMORY TASKS IN HEALTHY CONTROL AND PARKINSON'S DISEASE CONDITIONS

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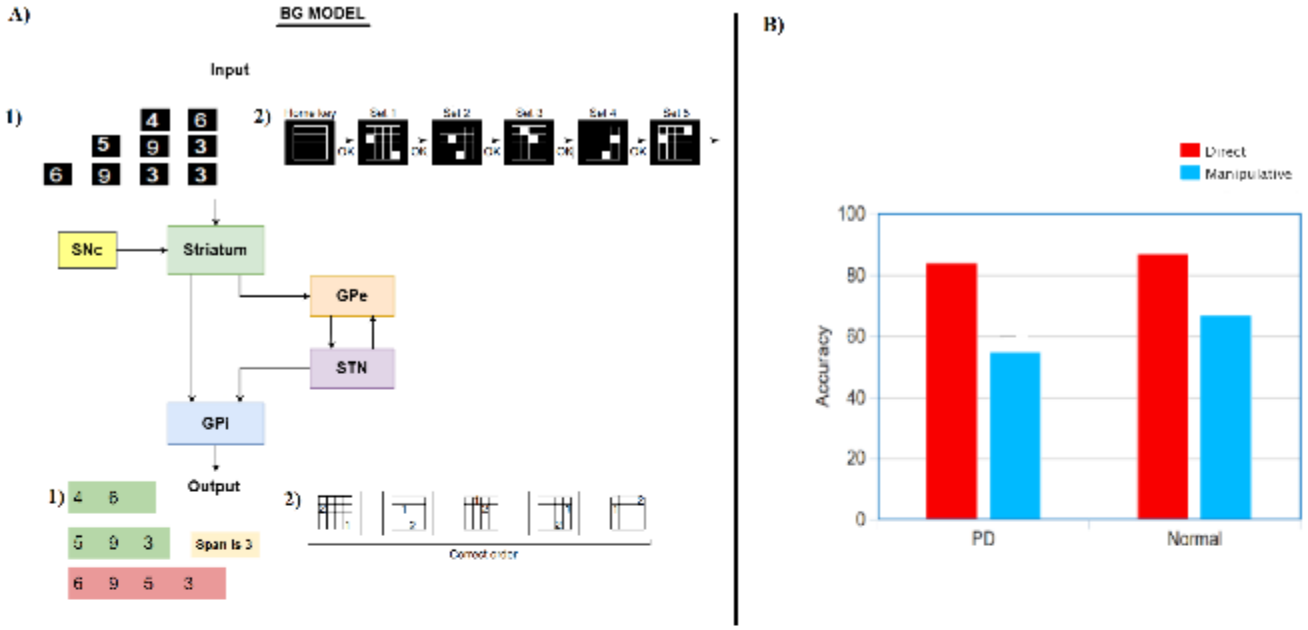
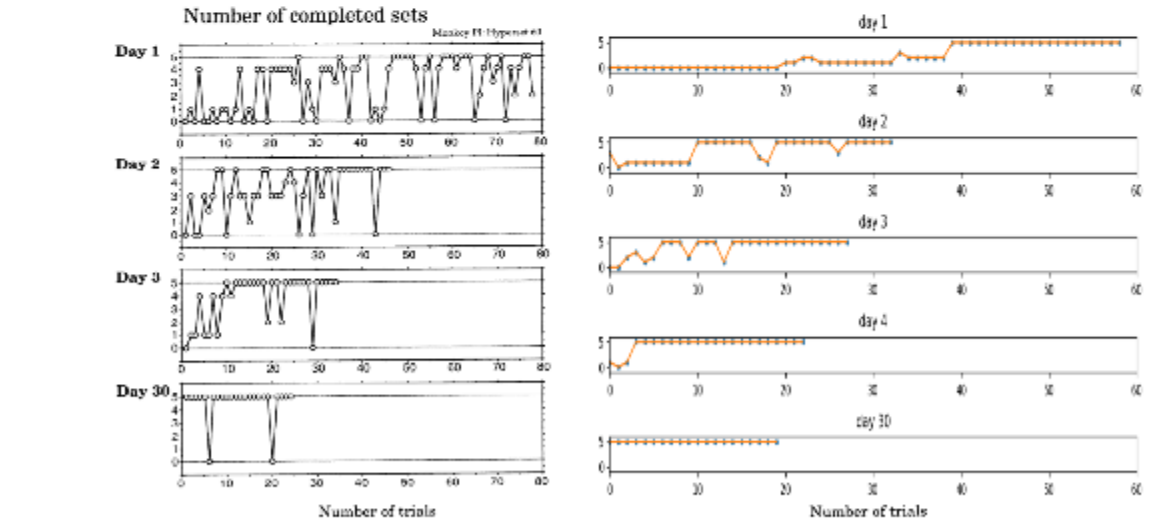
Aims: Basal Ganglia (BG) circuit, in addition to its familiar contributions to motor function, has also a major role in Working Memory (WM) functions. Loss of dopaminergic cells in the Substantia Nigra pars compacta (SNc), a BG nucleus, in Parkinson's Disease (PD) conditions affects the WM capacity of the patients.
Methods: A special class of striatal neurons that exhibit UP/DOWN states are thought to form the cellular basis for WM in the BG. Since BG circuit has often been described as a Reinforcement Learning engine, in the current model, the striatum serving as the critic, is trained by Q-learning, with the Sub-Thalamic Nucleus – Globus Pallidus externa (STN-GPe) loop by virtue of its complex dynamics performs exploration, dopamine release from SNc is the TD error, Globus Pallidus internus (GPi) performs action selection and training is done by Q-learning (Chakravarthy and Balasubramani 2014).
Results: In this work we present a model of the BG circuit and apply it to two classic WM tasks: Sequential 2xN button pressing task (Hikosaka et.al.1995) and Verbal WM tasks (Gilbert et. al. 2005). In the first task, we describe how our BG model can learn the sequential 2xN button pressing task and compare the learning patterns with experimental data. In the second task, we show that our BG model can closely replicate the performance of PD patients in span tests (manipulative and updating).





A) Model Block Diagram of Cortico- Basal Ganglia circuitry depicting 2xN and digit spanning tasks. B) Performance Results of Digit spanning and manipulation tasks. Starting with two digits the complexity is incrementally increased by adding one digit each on two successful attempts until failure to reproduce atleast two successful recalls out of six trials. The manipulation task involves arranging digits in ascending order and is selective to PD. C) Performance Results of 2xN task for a particular hyperset. The learning pattern of 2xN involves correctly predicting 20 sequences (Each sequence constitutes 5 sets(one hyperset).

Conclusions: Our Model closely replicated the experimental results for sequential 2xN tasks. For digit spanning tasks we couldn't observe any significant difference with respect to the accuracy of Normal and PD patients whereas in case of manipulative task a reduction in accuracy is observed in case of PD patients that is inline with the experimental results.

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P0167 / #1349

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

EFFECT OF SLEEP-RELATED EPILEPTIC SPIKING ON MEMORY CONSOLIDATION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) and epilepsy share multiple common pathological hallmarks, and they are risk factors for each other in older age. Clinical studies have discovered faster cognitive decline in AD patients with sleep-time epileptic spiking compared to AD patients without epileptic events. The systems consolidation theory suggests that memories are transferred from temporary buffer memory in the hippocampus to long-term storage in the cortex during sleep, which requires synchronization of hippocampal, cortical and thalamo-cortical oscillations. We set out to investigate whether epileptic activity during sleep perturbs this memory transfer.
Methods: We trained APP/PS1 transgenic (n=5) and wild-type (n=7) male mice at 3.5 months of age to perform the Barnes circular platform test. The mice were then implanted with cortical and hippocampal EEG electrodes. Each mouse underwent weekly test session consisting of training a new escape hole location (4 trials), 3 h video-EEG during sleep, and 4 trials of memory testing. The mice received anti-seizure drug levetiracetam or vehicle on alternate sessions to test whether elimination of epileptic spiking improved post-sleep test performance.
Results: The preliminary results suggest that regardless of the genotype, all mice learned the new hole location during the 4 acquisition trials and showed memory retention after the sleep session. The selected dose of levetiracetam drastically reduced but not eliminated sleep-related spiking. Analysis on the correlation between the sleep-related spiking and memory on a session-by-session basis is underway.
Conclusions: The data to be presented will shed light on the contribution of sleep-related epileptiform spiking on systems memory consolidation.

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P0168 / #1303

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

ABERRATIONS IN NATURALISTIC RISKY DECISION-MAKING AND CORTICOLIMBIC CODING IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: While much basic research on animal models of Alzheimer's disease (AD) has focused on neuropathological markers and loss of memory functions, there is sparse knowledge as to how AD adversely impacts neural activities involved in risky decision-making. Here, we investigated how the presence of amyloid pathology affects foraging decision performance and corticolimbic circuit activity in a mouse model of AD.
Methods: Five familial AD (5XFAD) mice (4-8 mos old) were tested in a naturalistic 'approach food-avoid predator' paradigm (Kim et al., 2016). 5XFAD and wild-type (WT) mice implanted with tetrode arrays in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC; i.e., the CA1 subregion) ipsilaterally underwent nest habituation, baseline foraging, and predator testing in a T-maze with two different pellets in each arm (grain-based vs. a chocolate-flavored). Tetrodes were gradually advanced towards their target structures, and neural activities were recorded during the predator testing session, which consisted of successive pre-predator, predator, and post-predator stages. During the predator trials, each time the animal approached the preferred pellet, the predator (a puppet eagle on wheels) surged forward via a linear actuator.
Results: In response to the predator, the WT mice switched their foraging choice from the preferred to non-preferred pellets. In contrast, the 5XFAD mice continued to choose their preferred pellets, indicating an inability to adjust their foraging behavior as a function of danger. When compared to the WT mice, the 5XFAD mice had less mPFC-dHPC spike synchrony and dCA1 sharp wave ripples (SWRs) during the predator session and the post-predator session, respectively.
Conclusions: These findings suggest that risky decision-making performance deficits found in AD mice might be due to abnormal interregional neuronal interactions between the dHPC and mPFC.

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P0169 / #2275

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

AMYLOID-B AND PHOSPHORYLATED-TAU ACCUMULATION IN RETROSPLENIAL CORTEX OF YOUNG ALZHEIMER'S MODEL: IMPACT ON NETWORK ACTIVITY

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Aims: Our aim in the present study was to evaluate molecular and functional alterations in the retrosplenial cortex (RSC) of very young Alzheimer's transgenic mice (3xTg-AD). The RSC is a cortical area that functions as a key component of the core network of brain regions involved in cognitive functions such as episodic memory, navigation, and planning.
Methods: Electrophysiology: Local field potentials were recorded using borosilicate electrode (2-6 MΩ). Integrated theta-band power was calculated in 5 s binds over a period of 2-10 min and the mean spectrum was taken as the grand mean of each animal. **Immunohistochemistry**: For immunofluorescence, antibodies: pS396 and BAM10 were used. The brain areas were visualized using an epifluorescence microscope (Axioplan2, Zeiss).
Results: Our results show significant accumulation of intracellular amyloid-β (Aβ) and hyperphosphorylated tau (pTau) in principal neurons from 1-month-old 3xTg-AD mice, which correlates with GSK3β activation and tau phosphorylation at serine 396. Coincidently, oscillatory activity from the RSC is altered in the young 3xTg-AD mice. Specifically, we found that theta frequency is significantly higher in the transgenic animals.
Conclusions: Despite the wide consensus that Aβ deposition in a variety of AD transgenic mice, including 3xTg-AD, is detected after several months of age, this study shows the first evidence of intracellular Aβ accumulation in pyramidal cells as early as 30 days of age, which does not seem to be related to any cognitive compromise. Thus, early Aβ and pTau accumulation was correlated with altered oscillatory activity from the RSC. In sum, our results indicate that very early accumulation of intracellular Aβ may impact the excitability of the RSC network, possibly due to changes in pTau throughout GSK3β activation.

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P0170 / #1593

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

SEX-SPECIFIC HIPPOCAMPAL GABAERGIC INTERNEURONS AND THEIR ROLE IN GAMMA OSCILLATION IMPAIRMENT IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Aims: Our objective is to elucidate the sex-specific impairment affecting the hippocampal oscillatory network during amyloidogenic progression in an Alzheimer's disease (AD) model.
Methods: We used a knock-in AD mouse model (App^{NL-G-F}) to characterize parvalbumin-positive GABAergic interneurons (GI), which are the neuronal population responsible for gamma oscillation's onset, in male and female wild-type and App^{NL-G-F} mice. Single-cell patch clamp recordings were performed in ex vivo hippocampal slices; simultaneously, the patched cell was filled with a cellular tracer for immunofluorescence identification (neurobiotin). Immunofluorescence was performed on these hippocampal slices to confirm the expression of parvalbumin (PV) and proteins related to gamma oscillatory activity (GluRA1 and GABAR1alpha) on neurobiotin-marked GI. The presence and distribution of proteins on the GI were assessed with a confocal microscope, together with the morphology of the neuron and its synaptic spines.
Results: We have previous evidence from our lab that the hippocampal network responsible for gamma oscillations differs between males and females. Therefore, we wondered if the amyloidogenic progression typical of AD would affect males and females differently. This project generated the opportunity to match functionality, molecular features, and morphology of a single GI. We characterized the synaptic changes that may lead to the gamma oscillation impairment detected in our App^{NL-G-F} model and how they differ between males and females. We found that amyloidogenic progression affects the hippocampal GI differently in males and females. In males, amyloidosis changes the time between consequent action potentials of the GI, while in females, it affects the depolarizing phase of the action potential.
Conclusions: Neurons from male and female samples are affected differently by the amyloidogenic progression. This finding suggests that there are sex-specific vulnerabilities that lead to cognition-relevant gamma oscillation impairment in the hippocampus.

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P0171 / #1055

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

SMALL RNAS, SHORT BUT MIGHTY: THE UNKNOWN PLAYERS IN AD PATHOBIOLOGY

Aleksandra Beric[1,2], Patricia Baldrich[3], Carlos Cruchaga[1,2], Laura Ibanez[1,2]
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Aims: MicroRNAs (miRNAs) are known to be involved in Alzheimer's disease (AD), but little is known about the other classes of small RNAs (sRNAs). We performed the first comprehensive study of sRNAs in AD brains.
Methods: After RNA extraction with a Maxwell RSC instrument, we generated sRNA libraries using the RealSeq®-AC sRNA kit version 2. Libraries were aligned to the reference genome and known small RNAs using Bowtie2. After stringent quality control we performed differential expression analyses using DESeq2. We integrated the sRNA data with RNA-seq data from the same samples to test whether any of the dysregulated sRNAs significantly correlate with known AD-genes.
Results: We identified four miRNAs (eg. miR-3614-3p and miR-6126) and eleven Piwi-interacting RNAs (piRNAs) (eg. piR-1880415 and piR-3746502) that are significantly dysregulated in AD brains. We found significant positive correlation between miR-6126 and miR-3614-3p, miR-6126 and two piRNAs, as well as relationships among several piRNAs. Further, we identified dysregulated sRNAs that significantly correlate with AD genes such as *APP*, *PSEN1*, and *PSEN2*. For example, piR-3746502 negatively correlates to over ten AD-genes, but associates with *MS4A4A* and *TREM2* in the opposite direction of other AD genes, consistent with biological knowledge.
Conclusions: Our findings emphasize the importance of non-coding RNAs in the pathobiology of AD. We showed that sRNAs beyond miRNAs contribute to AD and that large-scale studies of sRNAs in brain are crucial to understand the pathways involved in AD pathogenesis. Here, we described that several sRNAs seem to be regulating known AD genes, with associations in the expected direction.

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P0172 / #572

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

DIFFERENTIAL CHANGES IN CIRCULAR RNAS DOWNSTREAM OF CHRONIC LYSOSOMAL DYSFUNCTION IN AN ALZHEIMER'S DISEASE MOUSE MODEL

Skarleth Cardenas Romero[1], Abdallah Eteleeb[2], Niko-Petteri Nykänen[2], Kevin Kevin O'Dell[2], Marie Nunez[2], Oscar Harari[2], John Cirrito[2], Mark Sands[2], Bruno Benitez[1]
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Aims: Evidence from neuropathological and genetic studies suggests that endolysosomal dysfunction contributes to Alzheimer's disease (AD). Circular RNAs (circRNAs) are a novel category of non-coding RNAs that are highly expressed in the nervous system and enriched in synapses. The most well-established role of circRNAs is in microRNA (miRNA) sequestration. Clinical and pathological associations exist between significant differences in circRNAs levels in the brain of controls and AD patients. CircRNAs regulate the endolysosomal pathway. However, the role circRNAs downstream of chronic lysosomal dysfunction (CLD) and AD is poorly understood. Here, we aimed to test whether CLD affects circRNAs levels impacting the amyloid (Aβ) generation/accumulation in the 5xFAD mice.
Methods: Five groups of transgenic mice [5xFAD, PPT1$^{+/-}$, 5xFAD:PPT1$^{+/-}$ (P5X), Naglu$^{+/-}$, 5xFAD:Naglu$^{+/-}$ (N5X)] were used to assess the circRNA expression profile in the brain cortex by bulk RNA sequencing. The insoluble Aβ-40 and Aβ-42 were quantified by ELISA in the hippocampal fraction. The Aβ plaque load was quantified in coronal brain sections using immunohistochemistry.
Results: The P5X and N5X mice exhibit increased hippocampal amyloid plaque load, Aβ-40, and Aβ-42 insoluble levels in the hippocampus and reduced lifespan compared to 5xFAD mice. The levels of circAdam10, circPan3, circMbtd1, circ4930402H24Rik, circSt6gal2, and circCdc14b were reduced, while circZranb1 and circMyo9a were increased in P5X and N5X compared with 5xFAD. *In silico* analyses show amyloidogenic-related microRNAs exhibit circRNAs binding sites. miR-361-3p has binding sites for circZranb1 and circADAM10. It has been demonstrated that miR-361-3p traps and inhibits BACE1 function and Aβ production. CircPan3 regulates the autophagy-related miR-421. Experimental evidence shows that overexpression of circPan3 suppresses autophagy through a miR-421/Pink1 pathway.
Conclusions: CLD-induced differential changes in circRNAs levels could contribute to AD by affecting APP processing machinery or regulating autophagy.

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P0173 / #2369

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

AUTOPHAGY IMPAIRMENT AND MITOCHONDRIA DEFECTS IN TNFR1 MEDIATED NEURONAL CELL DEATH

Chih Hung Lo[1], Jialiu Zeng[1,2], Richard Reynolds[1,3], Anna Barron[1]
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Aims: Tumor necrosis factor receptor 1 (TNFR1) signaling contributes to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD). Recently, it has been shown that TNFR1 signaling regulates autophagic function which plays a key role in mediating neuronal cell death. Autophagy is a homeostatic mechanism involved in the disposal of damaged organelles and toxic protein aggregates. However, the exact mechanism of how TNFR1 induced autophagic dysfunction leads to neuronal death remains unclear. Our goal is to examine the changes in metabolic gene profile due to TNFR1 induced autophagy dysfunction to identify the underlying mechanisms causing neuronal death.
Methods: We investigate metabolic gene profiles changes associated with TNFR1 induced autophagy dysfunction in SH-SY5Y neuronal cells and human iPSC derived primary neurons using gene profilers related to mitochondria and autophagy functions as well as cell death pathways. Additionally, we examine the effect of TNFR1 induced autophagy dysfunction in mitochondria functions and mitophagy.
Results: We show that TNFR1 activation results in a downregulation of genes associated with mitochondria and autophagy functions and an upregulation of genes in cell death pathways. Furthermore, we illustrate that there is an increase in mitochondrial reactive oxygen species and a decrease in mitochondria membrane potential indicative of mitochondria dysfunction, together with the presence of mitophagy defects in neurons with TNFR1 activation. We are currently conducting in vivo studies to confirm these observations using the APP knock-in mouse model.
Conclusions: In summary, metabolic dysfunction, in particular mitochondria functional defects, may contribute to TNFR1 induced neuronal death. This opens avenues for new therapeutic directions to target autophagy dysfunction, in addition to the existing efforts in developing receptor-specific inhibitors that target TNFR1 signaling.

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P0175 / #2523

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

ROLES OF AMYLOID-BETA, A PATHOGENIC PROTEIN OF ALZHEIMER'S DEMENTIA IN SARCOPENIA DEVELOPMENT

Sujin Kim, Sohee Moon, Bon-Sang Gu, Keren Mantik, Nattha Suwanprakorn, Chan-Young So, Ju-Hee Kang
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Aims: Alzheimer's disease(AD) and sarcopenia are important disorders that impair the quality of elderly life. The majority of AD is accompanied with sarcopenia, and recognizing the intricacies of both diseases' pathophysiology is critical for prevention and therapy. It has been reported that Aβ has detrimental effect on glucose metabolism in peripheral tissue, however the probable involvement of Aβ in skeletal muscle dysfunction remains to be elucidated. Accordingly, in this study, the effect of Aβ on sarcopenia was evaluated, and we were to elucidate the mechanism of Aβ-induced sarcopenia.
Methods: We measured the Aβ42 concentration in the skeletal muscle of senescence-accelerated mice SAMP8 and SAMR1 at 32wks of age to evaluate whether Aβ42 is upregulated in aged muscle. Differentiating C2C12 myoblasts and fully differentiated myotubes were treated with Aβ-oligomer(Aβo) for evaluating the effects of Aβo on differentiation and myotube dysfunction, respectively. We evaluated the effects by measuring protein levels of myogenic factor, signaling pathway contributing muscle atrophy and mitochondrial function.
Results: The level of Aβ42 was significantly higher in the muscle tissue of SAMP8 than in SAMR1 control. Aβo-treated muscle cell resulted in a reduction in the levels of myogenic transcriptional factors. SA-β-gal stain revealed the cellular senescence of Aβo-treated myoblasts. Specifically, Aβo-treated muscle cells showed the significant pathogenic changes including mitochondrial dysfunction, apoptosis, and cellular senescence, which are common mechanisms of AD and sarcopenia.
Conclusions: Our results suggested that sarcopenia might be accelerated by an increase in the levels of Aβ42 in skeletal muscle as the AD develops. Detrimental changes of advancing sarcopenia may result in a "vicious cycle" in which AD occurs more rapidly in sarcopenic patients, and *vice versa*. We are currently further characterizing the molecular mechanisms of Aβ-mediated acceleration of sarcopenia.

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P0176 / #2471

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

EFFECT OF DIABETES ON COGNITIVE DYSFUNCTION FOR OVERALL MORTALITY

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Aims: Cognitive dysfunction continue to be globally a pubilc health burden in the general population. As the world population ages, there are renewed efforts to understand newer, effective treatment. In this research, we demonstrate the effect of diabetes on the impact of cognitive dysfuntion.
Methods: In the National Health and Nutrition Survey, we used population-based cohort study of 1999-2002 National Health and Nutrition Examination Surveys with mortality data obtained through 2015. Adults aged 20 years or older with diabetes were assessed for cognitive skills using Digit Symbol Substitution Test (DSST) and if they were considered obese. Outcomes of all-cause mortality were evaluated using Cox regression.
Results: We had a mean follow-up of 9.4 years. Percent of deaths from low cognitive function among the population (N=1,759) was high. For all-cause mortality, the overall unadjusted hazard ratio (HR) of low cognitive dysfunction had a hazard ratio of 2.25 (95% confidence interval [CI], 1.94-2.62, p = 0.001). Adjusted HR was elevated, 1.81 (CI 1.16-2.84, p = 0.01), among individuals with diabetes and low cognitive function but closer to 1.81 (CI 1.16-2.84, p = 0.011) among individuals without diabetes with low cognitive function, after controlling for medical (myocardial infrarction, congestive heart failure, myocardial infarctions and hypertension) and demographic risk factors (age and gender).
Conclusions: Our research shows that cognitive dysfunction leads to overall mortality, especially indivduals with obestiy. This effect is further accentualed ith added effect of diabetes. Diabetes and cognitive dysfunction can lead to more increased mortality. Individuals are more likely to have higher mortality from cognitive dysfunction with diabetes than those individuals without diabetes if the individual has obesity. Our research shows that low cognitive function leads to higher mortality, especially in the presence of obesity.

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P0177 / #1105

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

A STUDY ON THE EFFECTS OF CYP46A1 UPREGULATION IN THE APP KNOCK-IN MOUSE MODEL

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Aims: To determine whether enhanced cholesterol turnover via CYP46A1 upregulation modulates aspects of Alzheimer's disease (AD) pathology such as amyloid beta deposition, neuroinflammation, and cognition, we have generated a novel mouse model by crossing transgenic CYP46A1 mice (CYP46 Tg) with $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ knock-in mice (CYP46 Tg x $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$).
Methods: Aging cohorts of male and female wild-type, $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$, and CYP46 Tg x $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice have undergone a behavior battery assessing locomotion, anxiety-like behavior, spatial working, and recognition memory. Tissue was collected post-mortem; immunohistochemical analyses of the brain tissue were carried out to quantify markers of microglia (Iba1), astrocytes (GFAP), and amyloid-beta (Aβ) deposits in the cortex and the hippocampus. Brain and serum cholesterol and oxysterols levels were measured by mass spectrometry in the brain and the serum.
Results: We observed alterations in anxiety-related behavior in male $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice in the elevated plus maze and the open field. Similar behavior was detected in the CYP46 Tg x $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ group. On the contrary, female mice of the same age did not exhibit alterations in the emotional domain. At six months of age, cognitive deficits assessed through the Y-maze, novel object recognition, and fear conditioning tests were not clearly present in mice with $APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$genotype, and a significant effect of CYP46A1 overexpression has not been remarked.
Conclusions: These results suggest sex-mediated effects in the onset of behavioral changes in the APP knock-in mice with prospects of benefits of CYP46A1 upregulation. Further experiments in older cohorts will unravel how the aging determinant affects cholesterol signaling in AD pathology.

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P0178 / #1334

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

LYSOSOMAL DYSFUNCTION CONTRIBUTES TO AGE-DEPENDENT SYNAPSE LOSS

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Aims: Background: The etiology of late-onset Alzheimer's disease is likely multifactorial, with aging being the most significant risk factor and genetic predisposition likely accelerating the disease onset. We established that endocytosis increases in aged neurons, potentiating beta-amyloid, which only partially contributes to synapse decline. We are investigating amyloid-independent mechanisms of synapse decline with aging. Since lysosomes are a cellular aging target and relevant for synapses, we hypothesized that aging lysosomes might drive synapses dysfunctional. **Objectives:** We are investigating lysosome dysfunction in aged neurons and whether it contributes to synapse loss.
Methods: We analyzed wild-type primary mouse cortical neurons matured or aged in culture using a sensitive cell biological and neurobiological approach to characterize lysosomes in mature and aged neurons and in the aged brain.
Results: Lysosomes are abundant in dendrites showing degradative activity distally in mature neurons. In aged neurons, endolysosome anterograde movement increases, likely leading to distal lysosome accumulation. Lysosomal degradation is reduced in aged neurons due to deacidification despite accumulating the lysosomal hydrolase, cathepsin D. Increasing the acidification of aged lysosomes reverted synaptic decline. In contrast, lysosome alkalinization mimicked age-dependent synapse decline.
Conclusions: We identify the deacidification of distal lysosomes as a neuronal mechanism of age-dependent synapse loss. Our findings suggest that future therapeutic strategies to address lysosomal defects might be able to delay AD onset.

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P0179 / #2361

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

MAGNETOENCEPHALOGRAPHY DETECTS CHANGE IN PRECUNEUS OF MILD COGNITIVE IMPAIRMENT PATIENTS.

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Aims: In our dementia clinic, we often see normal aging cases and mild cognitive impairment (MCI) as well as dementia patients. For initial exam, we perform MRI, SPECT, neuropsychiatric examination and Magnetoencephalography (MEG). We analyzed those data to determine the difference between normal aging and MCI.
Methods: We examined retrospectively 44 patients selected from our clinic. Twenty-four patients were diagnosed normal aging and 20 were MCI. Each patient performed MRI, SPECT, MEG and neuropsychiatric examination. Between normal aging group and MCI group, we analyzed with two sample t-test. Age variation were corrected with covariate of no-interest.
Results: In MCI group, MEG detected decrease of beta-wave in left precuneus.
Conclusions: This result suggest that MEG finding implies demyelination in precuneus of MCI patients, since beta-wave is related to myelination.

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P0180 / #1650

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

TOWARD THE REMEDIES FOR EARLY DETECTION, DIAGNOSTICS AND THERAPEUTICS OF ALZHEIMER'S DISEASE

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Aims: The primary goal of this investigation is to demonstrate the therapeutic capabilities of F-SLOH to intervene/mitigate multiple neuropathological changes of AD in prophylactic treatment of mouse models.
Methods: In the present study, the multiple therapeutic beneficial aspects of F-SLOH have been experimentally demonstrated in both 5XFAD and 3XTg-AD mouse models. We have shown that the F-SLOH reduced the levels of Aβ oligomers, Aβ plaques, phosphorylated Tau aggregates, as well as APP and its metabolites in AD mouse models.
Results: F-SLOH treatment also mitigated microgliosis and reduced the reactive glial cells and astrocytes, thus alleviating neuroinflammation in 5XFAD and 3XTg-AD mice. Furthermore, F-SLOH ameliorated synaptic dysfunction and cognitive impairment in 5XFAD and 3XTg-AD mice mitigating the disease progression of AD. The significant decrease in Tau aggregates and insoluble Aβ aggregate formation after F-SLOH treatment was attributed to the promotion of autophagy and lysosomal biogenesis, involving the activation of TFEB, which resulted in mitigation of Aβ pathogenesis in both 5XFAD and 3XTg-AD mouse models. Our results unambiguously demonstrated the remarkable and multiple etiology-targeting capabilities of theranostic F-SLOH.
Conclusions: In conclusion, F-SLOH can abrogate multiple neuropathological abnormalities in AD mouse models, and hold outstanding therapeutic potential for prophylactic and treatment applications of AD.

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P0181 / #522

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

EXPOSURE TO HIGH 27-HYDROXYCHOLESTEROL LEVELS DURING PREGNANCY ALTERS MITOCHONDRIAL FUNCTION IN EMBRYONIC STAGES AND INDUCES COGNITIVE DECLINE IN AGED MICE

Maria Latorre Leal[1], Luana Naia[1], Raul Loera-Valencia[1], Patricia Rodriguez-Rodriguez[1], Serena Giannelli[2], Francesca Eroli[1], Lynn Alaeddine[1], Angel Cedazo-Minguez[1], Maria Ankarcrona[1], Paula Merino-Serrais[1], Silvia Maioli[1]
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Aims: Maintenance of lipid homeostasis during pregnancy is essential for normal neurodevelopment in embryonic stages. Several studies show that alterations during the perinatal period determine the susceptibility to pathological conditions later in life, such as Alzheimer's Disease (AD). Hypercholesterolemia and the disbalance of cholesterol homeostasis in the brain are risk factors for developing AD. Moreover, AD patients report high levels of an oxidized metabolite of cholesterol known as 27-hydroxycholesterol (27OH) in both CSF and the brain. In this study, we aim to understand whether high maternal levels of 27OH in mice affect the neurodegeneration and cognitive decline of the offspring during ageing.
Methods: Our research was conducted in transgenic CYP27A1 overexpressing mice (Cyp27Tg), wild-type littermates (WTlm), whose mothers were transgenic Cyp27Tg and wild-type mice whose mothers were wild type. We performed our experiments at the embryonic stages (E19) and adulthood. 6- and 18-month-old mice underwent behavioural memory tasks. Transcriptomic, molecular and bioenergetic studies were performed in E19 embryos and adult brains from all groups of mice.
Results: We observed aged WTlm mice have similar cognitive deficits to Cyp27 Tg animals. Microarray data display common changes in senescence and metabolic-related signallings in WTlm and Cyp27 Tg mice. WTlm and Cyp27 Tg isolated mitochondria from embryos indicate a deficiency in mitochondrial function in the brain that supports our transcriptomic data.
Conclusions: Here we show that high maternal 27OH levels negatively affect neurodevelopment and mitochondrial function in mice at the embryonic stage, leading to cognitive decline during ageing. A deeper understanding of the biological mechanisms by which disturbances at the neurodevelopment stage affect the neurodegenerative process later in life can lead to new preventive and therapeutic approaches for AD and other neurodegenerative disorders.

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P0182 / #387

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

THE ENTERIC NERVOUS SYSTEM DURING AGING AND ALZHEIMER'S DISEASE

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Aims: The study aims to unravel how the enteric nervous system (ENS) changes during aging and diseased aging as in Alzheimer's disease (AD). Moreover, we aim at understanding how these changes affect the gut, its function, and its interaction with the aging brain.
Methods: The longitudinal muscle/myenteric plexus (LMMP) derived from 8-month-old 5xFAD and wild-type mice was collected for whole transcriptome analysis. Colonic organoids from 3- and 10-month-old senescence-accelerated (SAMP8) mice and control (SAMR1) mice were established, and their growth properties were compared.
Results: A preliminary transcriptomic data analysis revealed genes differentially expressed between 5xFAD and wild-type mice that are associated with AD in GWAS, AD progression in the CNS, and circadian rhythm in a sex-dependent manner. Particularly among these genes, downregulation of *Fkbp5*—encoding FK506 binding protein 5, *Fbln5*—encoding Fibulin-5, and *Per2*—encoding Period circadian regulator 2 are notable. Additionally, the colonic organoid forming efficiency was significantly decreased with age in male and female SAMP8 mice, while a similar decrease was observed only in the male SAMR1 mice. Interestingly, a reduction in efficiency of colonic organoid formation was remarkably observed in the aged male SAMP8 mice compared to SAMR1 while it was not significant in the aged female SAMP8 mice compared to SAMR1.
Conclusions: Our study provides evidence of a shared characteristic between the ENS and CNS in a disease model and an age-related decline in gut function. Next step is to investigate how the aged ENS mechanistically affects the CNS or CNS disease development.

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P0183 / #1551

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

METACOGNITION AND SUBJECTIVE COGNITIVE DECLINE IN A MEMORY CLINIC POPULATION

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Aims: Subjective Cognitive Decline (SCD) is an at-risk condition of cognitive decline and dementia. Indeed, around 15% of SCD individuals progress to dementia. Cognitive complaints may represent the expression of metacognitive processes of memory function. This leads to hypothesize that the metacognitive judgements of cognitive performance may be more useful than actual performance to distinguish progressors from non-progressors. The aim of this study is to investigate different aspects of metacognition in a memory clinic population.
Methods: 45 patients with SCD, mild cognitive impairment and controls were recruited from the Geneva Memory Center. A questionnaire on cognitive complaints (cognitive change index,CCI), and the performance of a word pair learning task requiring:(i) judgments of the subject's global performance before word-pair recall (prediction);(ii) judgements of the subject's global performance after word-pair recall (postdiction) have been collected. The accuracy of the global judgments of learning (JOLs) was computed as the difference between the prediction and the actual performance (JOL-pre) and between the postdiction and the actual performance (JOL-post). Spearman correlations were calculated between: (i) CCI and JOL-pre;(ii) CCI and anxiety and depression;(iii) JOL-pre and JOL-post. The JOL-pre differences by APOE ε4 carriership were tested using a Kruskal-Wallis test.
Results: We have found that individuals who underestimate their memory performance (JOL-pre) are those reporting more cognitive complaints (r=-0.36;p=0.018), and higher anxiety and depression (r=0.51;p=<0.001). Individuals APOEε4 non-carriers tend to underestimate their performances (JOL-pre: carriers 0.9±2.5 vs carrier -0.7±1.5) compared to APOEε4 carriers.
Conclusions: The results suggest that the complaints of individuals underestimating their performance may reflect subtle psychological dysfunction (i.e. depression, neuroticism) rather than dementia risk, and might benefit from metacognitive training. Further analysis to study the cognitive decline over time by metacognitive status (under-estimators vs over-estimators) are planned.

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POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

THE TAXONOMY OF SUBJECTIVE COGNITIVE DECLINE, A PROPOSAL FROM THE GENEVA MEMORY CLINIC COHORT

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Aims: Subjective Cognitive Decline (SCD), namely subjective cognitive complaints without objective cognitive impairment, is an at-risk condition of dementia and cognitive decline. However, most of these patients will not develop neurodegenerative disorders but they may suffer from minor psychiatric conditions, neurological, and/or somatic comorbidities. The aim of the present study is to provide a clinical taxonomy of SCD by isolating clinically homogenous SCD subgroups with specific cognitive trajectories.
Methods: 55 SCD individuals were selected from the Geneva Memory Clinic cohort. Based on clinical reports, they were classified in three, clinically pre-defined, subgroups: those with subtle psychiatric conditions (Psy), those with physical comorbidity (Som) and those with no apparent cause (NAC). Baseline demographics, clinical, cognitive and biomarkers differences among the SCD subgroups were assessed. Longitudinal cognitive changes by baseline SCD subgroup were estimated using a linear mixed model.
Results: Out of 56, 48% were female, mean age was 69 years. 16 Som, 18 Psy and 21 NAC. We observed higher percentage of APOEe4 carriers in NAC (53% vs 14% of Som, 0% of Psy;p=0.023), and lower level of plasma $A\beta_{42}$ in NAC (6.8±1.0) compared to Som (8.4±1.1, p=0.031). Som were older (74 yrs vs 67 yrs psychiatric;p=0.011), they had greater value of medial temporal lobe atrophy scale (p=0.005) and worse episodic memory performances (p=0.032). We observed a slightly steeper cognitive decline in NAC compared to the other groups yet not statistically significant (NAC β=-0.48, Som β=-0.24 vs Psy β=-0.28; p=0.268).
Conclusions: Higher proportion of APOE e4 carriers and lower plasma $A\beta_{42}$ in the NAC group are suggestive of a higher risk of developing AD dementia signifying that high-risk profile can be identified applying the proposed taxonomy. This taxonomy should be validated on an independent cohort.

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P0185 / #813

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

THE ACCUMULATION OF DYSFUNCTIONAL MITOCHONDRIA DURING ACCELERATED SENESCENCE AND ITS INVOLVEMENT IN ALZHEIMER'S DISEASE

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Aims: Although aging is the leading risk factor for Alzheimer's disease (AD), the exact mechanisms through which aging becomes pathogenic and triggers neurodegeneration have not yet been identified. Recent evidence suggests that AD is tightly correlated with the appearance of senescent cells, and that mitochondrial dysfunction is an event occurring during senescence and AD. Our goal was to explore if a reduced removal of dysfunctional mitochondria during aging is a key contributor of amyloid pathology and neurodegeneration in AD.
Methods: Since telomere shortening is a known trigger of cellular senescence, the Terc-/- mouse model of accelerated senescence was used. Primary cultures and brain tissue samples were evaluated for mitochondrial function/content and mitophagy alterations. Then, we explored the relationship between amyloid pathology and mitochondrial dysfunction by crossing the Terc-/- mice with an amyloid-related AD mouse model (5xFAD) and exploring mitophagy alterations and amyloid-β (Aβ) accumulation in disease-vulnerable regions.
Results: We evidenced the presence of mitochondrial dysfunction and accumulation in senescent neurons, along with a down-regulation of the mitophagy modulator BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3). Additionally, we observed that senescence induces intraneuronal Aβ accumulation in specific brain regions (e.g., the subiculum) of an AD mouse model and we suggest that mitochondrial dysfunction and altered mitophagy might lead to Aβ accumulation.
Conclusions: Our results indicate that dysfunctional mitochondria might accumulate during aging due to mitophagy impairment and contribute to AD neuropathology by triggering amyloid pathology.

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P0186 / #269

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

AGE-RELATED TAU-PET DOWNSTREAM EFFECTS EXTEND BEYOND THE MEDIAL TEMPORAL LOBE IN NORMAL AGING

Anika Wuestefeld[1], Alexa Pichet Binette[1], Nicola Spotorno[1], David Berron[1,2], Danielle Van Westen[3,4], Trevor Glenn[5], Erik Stomrud[6,7], Niklas Mattsson-Carlgren[8,9,10], Olof Strandberg[6], Ruben Smith[6,8], Sebastian Palmqvist[6,7], Lisa Barnes[11], Konstantinos Arfanakis[12], David Bennett[11], Julie Schneider[12], Laura Wisse[3], Oskar Hansson[6,7]
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Aims: Age-related amyloid-beta (Aβ) independent tau pathology may be present outside the medial temporal lobe (MTL; Kaufman et al., ActaNeuropathol, 2018). In cognitively unimpaired adults and low-Aβ subgroups, we examine (1) in vivo and ex vivo tau deposition in regions typically involved earlier/later in Alzheimer's disease and (2) downstream effects on neurodegeneration and cognition.
Methods: We included cognitively unimpaired adults from two cohorts (in vivo BioFINDER-2, n=537, age: 40-92; ex vivo: ROSMAP/MARS/ClinicalCore, n=638, age: 64-108). In vivo MTL volumes (subiculum (SUB), cornu ammonis 1) and thickness (entorhinal cortex (ERC), Brodmann area (BA35)) were obtained using Automated Segmentation for Hippocampal Subfields packages. Thickness of early/late neocortical AD-regions was determined using FreeSurfer. Regional tau-PET ([^{18}F]RO948) and global/regional Aβ-PET ([^{18}F]flutemetamol) standardized uptake value ratios were calculated. Ex vivo immunohistochemistry determined Aβ and tangle burden. Global cognition estimates were obtained.
Results: Older age was associated with higher tau-PET uptake in frontal/parietal/temporal regions, also when adjusting for Aβ-PET, in the full and low-Aβ groups (Fig. 1). These results were validated in the ex vivo cohort. Regional tau-PET was, independently of Aβ-PET, negatively associated with temporal/parietal thickness/volume (Fig. 2). ERC/BA35 tau-PET partially mediated age-structure associations in the MTL (SUB/BA35; Fig. 2) and the age-cognition association (Fig. 3).

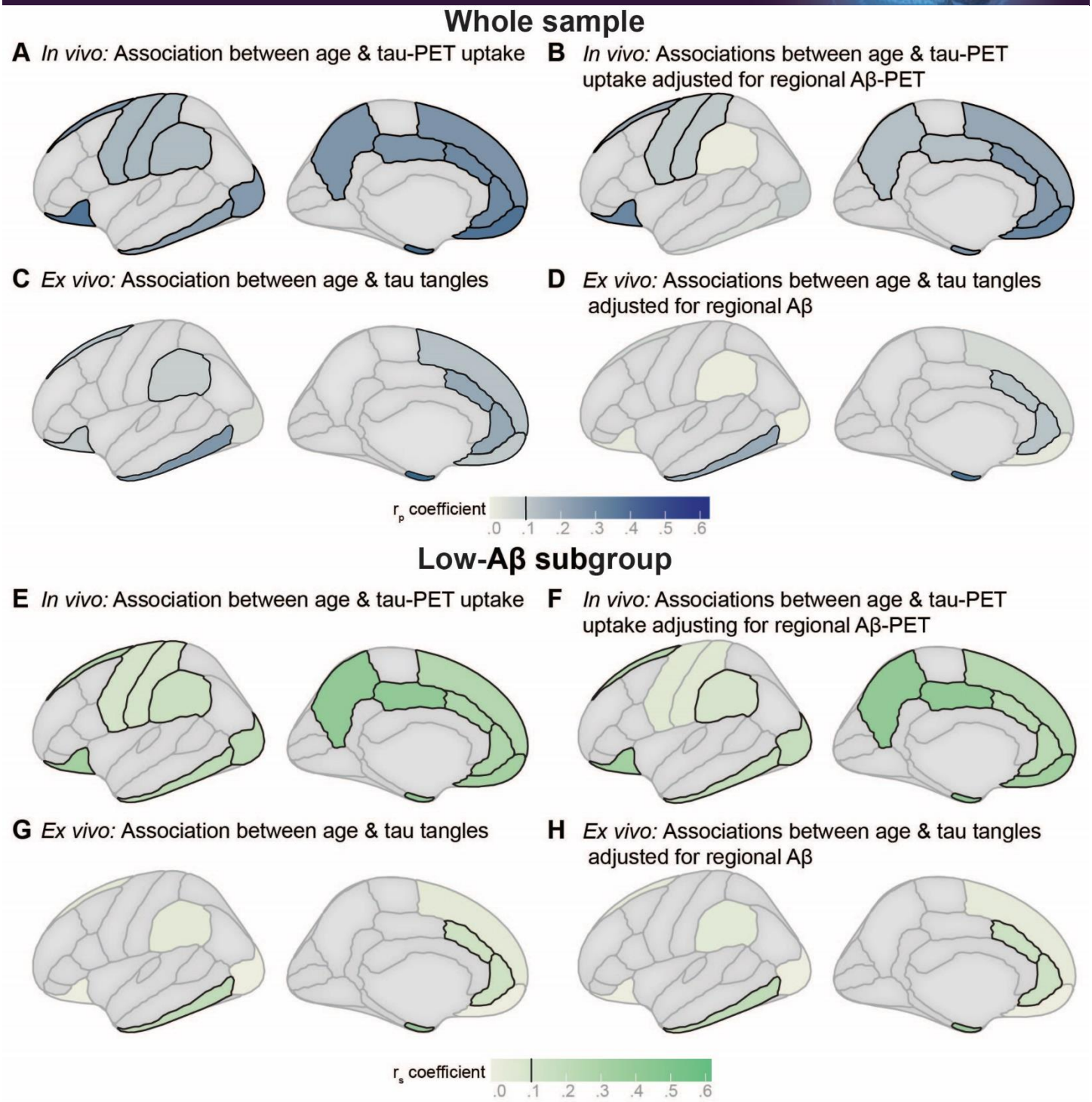


Fig 1. Association between age and regional tau-PET [18F]RO948 uptake (in vivo) or regional tau tangles (ex vivo) in the whole samples and low-Aβ subgroups.
A: Increasing age is associated with increased regional tau-PET [18F]RO948 uptake in medial temporal, parietal, and frontal regions. B: Aβ-PET independent associations between age and regional tau-PET in regions from A. Pearson partial correlation coefficients >.10 are p_{FDR}<.05 and have a black border. C: Increasing age is associated with increased regional tau tangles in medial temporal, parietal, and frontal regions. D: Aβ-PET independent associations between age and regional tau tangles in temporal and frontal regions. Spearman rank correlations coefficients >.10 are p_{FDR}<.05. E-H: same associations as in A-D but in the low-Aβ subgroups. In vivo Aβ-status based on Aβ-PET or CSF Aβ42/40 if PET not available (n=413). Ex vivo Aβ-status based on on semiquantitative estimates of neuritic plaque density as recommended by the Consortium to Establish a Registry for Alzheimer's Disease (n=318). All

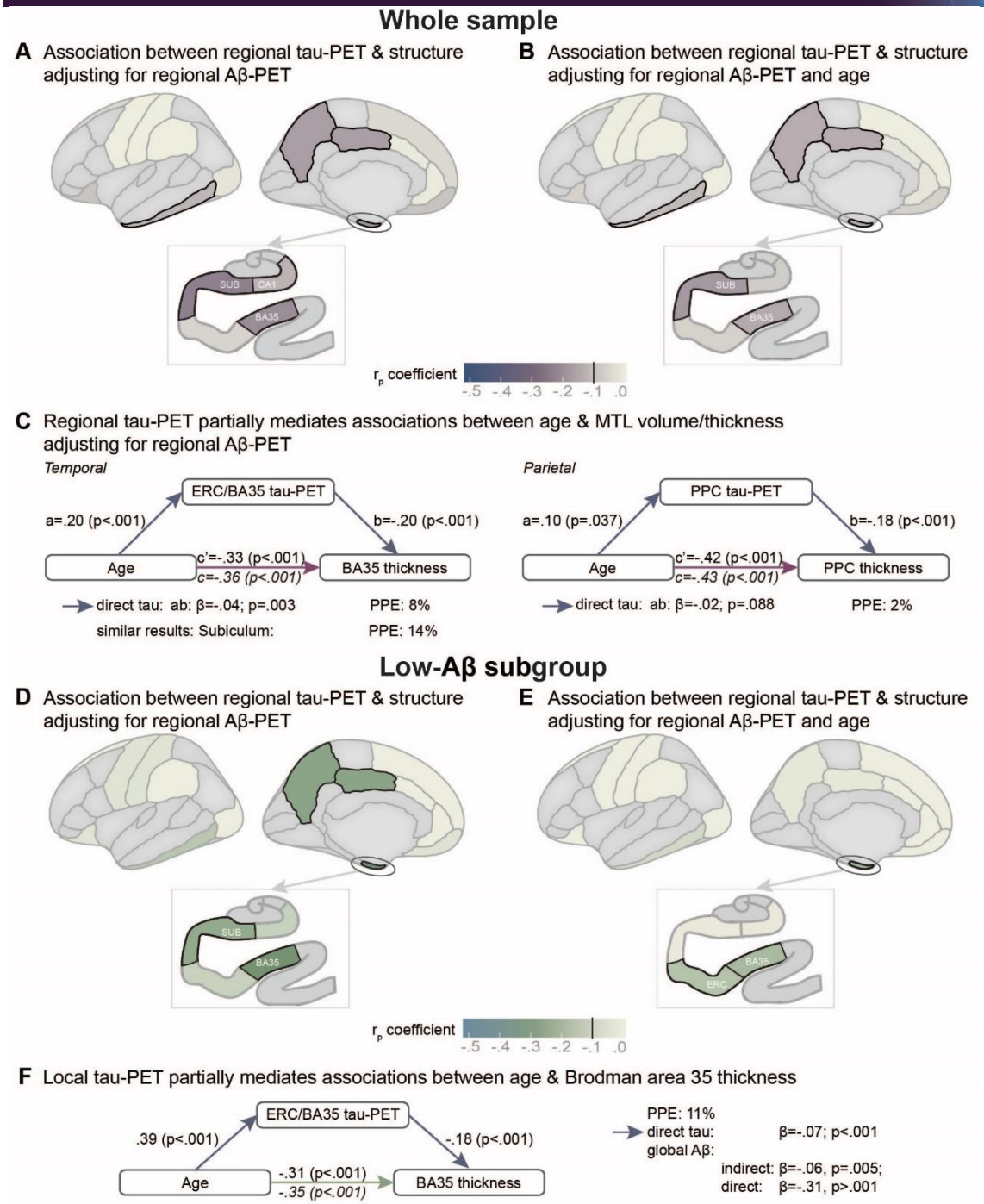
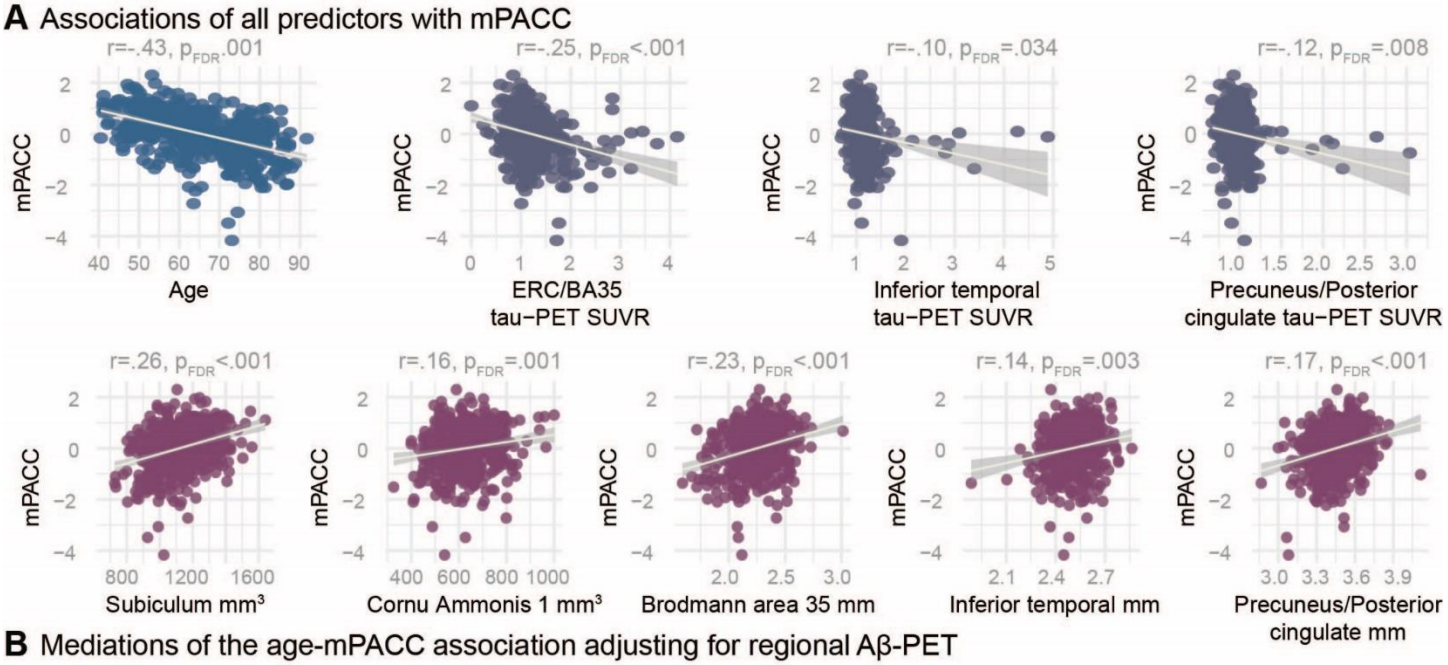


Fig 2. Age and regional [18F]RO948-PET uptake associations with regional volume/thickness in the in vivo whole sample and low-Aβ subgroup.

A: Increasing regional tau-PET deposition associated with decreased thickness/volume in medial temporal and parietal regions. B: Increasing regional tau-PET deposition associated with decreased thickness/volume in medial temporal and parietal regions.C: There is an Aβ-independent effect of regional tau-PET on the age-structure associations in the whole group for MTL and at trend level parietal regions (blue paths). The direct effect is reported below the arrow (italic) going from age to structure. D: In the low-Aβ subgroup, increasing regional tau-PET deposition associated with decreased thickness/ volume in medial temporal and parietal regions. E: In the low-Aβ subgroup, increasing regional tau-PET deposition associated with decreased thickness/volume in medial temporal and parietal regions. F: In the low- Aβ subgroup, there is an Aβ-independent effect of regional tau-PET on the age-structure associations in the whole group for BA35. All models include sex as a covariate. Models including tau-PET are adjusted for age-independent putamen tau-PET uptake. Using global Aβ-PET shows similar results. Pearson partial correlation coefficients >.10 are p_{FDR}<.05 and have a dark border. Dark grey regions were not investigated. Abbreviations: BA=Brodmann area; CA1=Cornu Ammonis 1; ERC= entorhinal cortex; MTL=medial temporal lobe; PPC=precuneus/posterior cingulate cortex; PPE= proportion of variance explained by the mediator; SUB=subiculum



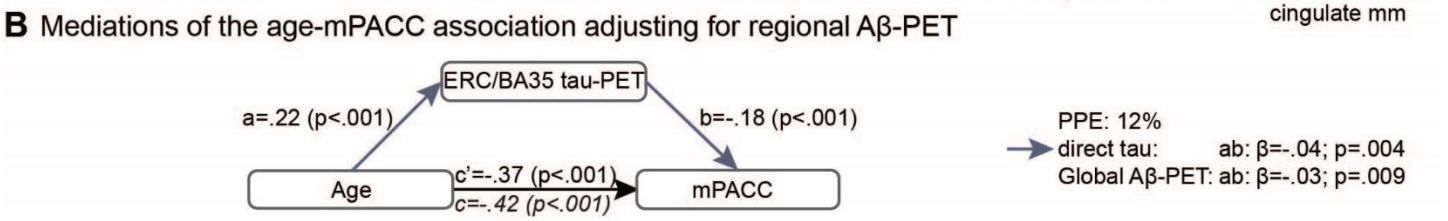


Fig 3. Age, regional tau-PET, and regional volume/thickness associations with cognition in the in vivo whole sample.

A: Increasing tau-PET, age, and lower volumes/thickness in selected regions are associated with reduced global cognition. Associations are adjusted for sex and education and off-target binding variable if tau-PET is the main predictor. B: There is an Aβ-independent mediating effect of ERC/BA35 tau-PET on age-mPACC association in the whole group (blue path). The direct effects are reported below the arrow (italic) going from age to mPACC. Models adjusted for age, sex, regional Aβ-PET. Models adjusted for age, sex, regional Aβ-PET. Abbreviations: Aβ=beta-amyloid; BA=Brodmann area; ERC=entorhinal cortex; PPE=proportion of variance explained by the mediator(s).

Conclusions: We show widespread age-related Aβ-independent tau-PET uptake. This is associated with atrophy in the MTL and the precuneus/posterior cingulate, while MTL tau-PET mediates age-structure and age-cognition associations. This potentially provides in vivo support for Primary Age-related Tauopathy downstream effects and supports the idea of anti-tau interventions for age-related neurodegeneration and cognitive decline.

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POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

RACIAL DIFFERENCES IN PREDICTING CONCURRENT AND LONGITUDINAL COGNITIVE OUTCOMES BY CSF BIOMARKERS OF ALZHEIMER DISEASE AMONG COGNITIVELY NORMAL INDIVIDUALS

Chengjie Xiong[1], James Lah[2], Cecelia Manzanares[2], Allan Levey[2], David Wolk[3], Leslie Shaw[3], Suzanne Schindler[4], Rachel Henson[4], Anne Fagan[4], Jason Hassenstab[4], Tammie Benzinger[5], Quoc Bui[1], Folasade Agboola[1], Elizabeth Grant[1], Julia Gray[4], John Morris[5,6]
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Aims: To examine racial differences in predicting concurrent and longitudinal cognition by CSF biomarkers from 110 cognitively normal(CN) Black/African Americans and 801 White participants, and to estimate the sample size of Blacks and Whites necessary for a future secondary prevention trial of AD.
Methods: CSF samples were centrally processed for Aβ42, Aβ40, total tau(t-tau), tau phosphorylated at 181(p-tau181), and NfL. We analyzed the association of each biomarker with baseline and longitudinal cognition by implementing random intercept and slope models with fixed intercept (concurrent cognition) and slope (rate of change) as functions of biomarker and race.
Results: CN Blacks had a higher level of Aβ42/40, lower level of t-tau, p-tau181, and NfL, but similar level of Aβ42. All biomarkers were correlated with concurrent cognition in Whites but not Blacks, with a significant difference for Aβ42/40. At baseline, lower cognitive performance was observed for Blacks. Regardless of race, biomarker positive participants had a faster cognitive decline than negative participants, and the rate of decline did not differ by race among positive individuals. Assuming a race-stratified randomization in a future 1:1 secondary prevention trial with semi-annual cognitive assessments over 2 years, a total of 2886 Aβ42/40 positive participants (289 Blacks vs. 2597 Whites=1:9) and 3550 p-tau181 positive participants (355 Blacks vs. 3195 Whites) provides 80% power to detect a 50% reduction on the rate of cognitive decline between the active and placebo arm. The sample sizes reduce to 1386 and 1704, respectively, if Black enrollment is increased to 25%.
Conclusions: Cross-sectional differences in CSF biomarkers and their association with concurrent and future cognition among CN Black and White individuals have consequences to the design and analysis of future secondary prevention trials of AD.

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P0188 / #454

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

EVALUATING THE EFFICACY OF SODIUM OLIGOMANNATE (GV-971) IN AMYLOID-DEPOSITING MICE

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Aims: Sodium oligomannate (GV-971), an algae-derived oligosaccharide, was found in a previous study in mice to alter gut microbiome composition and amino acid metabolism reducing peripheral inflammation. GV-971 was shown to reduce amyloid-b (Ab) plaque pathology and improve memory, identifying the gut microbiome as a potential therapeutic target of this molecule (Wang X et al. Cell Research, 29:787-803). It is not yet known whether the timing of treatment or sex play a major role in the effects of GV-971.
Methods: To examine this, Ab depositing mice were gavaged with GV-971 or vehicle from 2-4 (pre-plaque development) or 7-9 months (advanced Aβ plaque pathology) of age. Metagenomics analysis was conducted using 16s sequencing on fecal DNA. Microscopy and fluidigm chip qPCR were utilized to investigate GV-971 effect on pathology and neuroinflammation.
Results: Treatment with GV-971 modified gut microbiota composition. Specifically, GV-971 increased species with probiotic functions such as *Bifidobacterium* and *Parabacterodies* and reduced bacteria correlated to dysbiosis such as *Clostridium, Alistipes,* and *Oscillibscter.* Early intervention with GV-971 showed no effect on plaque burden nor neuroinflammation. Interestingly, delayed GV-971 treatment reduced Ab plaques, specifically targeting the plaque halo, in male but not in female mice. GV-971 significantly reduced Iba-1, Clec7a, and Hexb expression, known markers of disease-associated microglia, and reduced CD11b, IL-1β, and GFAP, suggesting a reduction in microglial and astrocyte reactivity.
Conclusions: Our data indicates that GV-971 functions in a time and sex dependent manner in amyloid depositing mice. The data also suggests that the effects of GV-971 on Aβ pathology and glial reactivity are via its effect on the gut microbiome. Taken together with other data, this further suggests that microbiome is a target worth further exploring for treatment of AD.

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P0189 / #1411

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

SHORT-TERM ANTIBIOTIC TREATMENT AND REGULAR ADMINISTRATION OF ACID SUPPRESSANT (PROTON PUMP INHIBITOR) REDUCE CEREBRAL AND INTESTINAL AMYLOID AB42 LOAD

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Aims: Microbiota depletion with antibiotic treatment (ABT) is associated with a reduction of cerebral amyloid in AD mice. Interestingly, amyloid can also deposit in the gut, within proximity to vasculature, nerves, and nerve plexuses. Additionally, acid suppressant drug such as proton pump inhibitors (PPI) have been shown to modify the gut microbiota. Here we tested the hypothesis that ABT+PPI modulate the gut microbiota and amyloid load in the gut and in the brain.
Methods: Sixty female, two-year old 3xTgAD mice (APP^{SWE}/$PS1^{M146V}$/ Tau^{P301L}) were divided in 2 groups and received: (1) 2-weeks of ABT to deplete the microbiota followed by recurrent PPI administration (5days/weeks) simultaneously with fecal microbiota transplantation (FMT) once a week for 2 months or (2) FMT only at same frequency. The FMTs consisted in water or bacteria isolated from litter mate mice or from 1 young and 1 cognitively unimpaired elderly donors.
Results: We observed that ABT-PPI treatment reduced the soluble and insoluble form of Ab42 in the hippocampus (ANOVA $p<0.05$) and, interestingly, also in the colon (ANOVA $p<0.05$), independently of the microbiota transplanted. No difference was observed in the levels of Ab40. 16SrRNA sequencing of the cecum indicates a strong effect of the treatment in disturbing the bacterial population both in alpha (Kruskal-Wallis, FDR corrected $p<0.001$) and beta-diversity (PERMANOVA $p=0.001$, 999permutations, bray-curtis distance).
Conclusions: The short ABT intervention and the 2 months delay before sample collection suggests that the driver of the effect observed is the PPI administration. The link between the amyloid in the gut and in the brain remain a black box and more research is needed to rule out that the Ab42 detection in the gut is not due to circulating amyloid from blood.

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P0190 / #2059

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

ELEVATED TLR2 AND AFFERENT SENSORY SIGNALS ASSOCIATED WITH LUMINAL BACTERIAL AMYLOID-CURLI IN THE GUT OF AD MICE WITH CENTRAL AB PATHOLOGY

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Aims: Background: Substantial evidence from recent research suggests an influential and underappreciated force in Alzheimer's disease (AD) pathogenesis: the pathological signals originate from outside the brain. Pathogenic bacteria produce amyloid-like proteins "curli" that form biofilms and show functional similarities to human amyloid-β (Aβ). These proteins may contribute to neurological disease progression via signaling cascade from the gut to the brain. **Objective:** We propose that curli causes neuroendocrine activation from the gut to brain that promotes central Aβ pathology.
Methods: Methods: PGP9.5 and TLR2 levels in response to curli in the lumen of Tg2576 AD mice were analyzed by immunohistochemical and qRT-PCR analysis. Western blot and human 3D in vitro enteroids culture systems were also used. 16S rRNA gene sequencing was used to investigate bacterial dysbiosis.
Results: Results: We found significant increase in bacterial-amyloid curli with elevated TLR2 at the mRNA level in the pre- and symptomatic Tg-AD gut compared to littermate WT controls. This data associates with increased gram-positive bacterial colonization in the ileum of the symptomatic AD mice. We found fundamental evidence for vagus nerve activation in response to bacterial curli. Neuroendocrine marker PGP9.5 was significantly elevated in the gut epithelium of symptomatic AD mice, and this was colocalized with increased TLR2 expression. Enteroids, 3D-human ileal mini-gut monolayer in vitro model system also revealed increase levels of TLR2 upon stimulation with purified bacterial curli fibrils.
Conclusions: Conclusion: These findings reveal the importance of pathological changes within the gut-vagus-brain signaling in response to luminal bacterial amyloid that might play a vital role in central Aβ pathogenesis seen in the AD brain.

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P0191 / #1498

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

NEUROPROTECTIVE EFFECT OF SYNBIOTICS AGAINST CHEMOTHERAPY INDUCED GUT- DYSBIOSIS AND COGNITIVE DYSFUNCTION

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Aims: To evaluate the neuroprotective effect of synbiotics (probiotic mixtures + vanillic acid) against Chemotherapy induced Gut–dysbiosis and cognitive dysfunction
Methods: Male Swiss albino mice(n=24) weighing 25-30 g were randomly allocated to 4 groups Groups –I is DMSO treated, Group II is DMSO + 5-FU treated (5-FU `450 mg/kg, ip single dose). Group – III is Synbiotic mixture SM-1 treated (*Lactobacillus acidophilus, Lactobacillus rhamnosus , Lactobacillus paracasei , Bifidobacterium lactis* containing 1× 10^{9} CFU in the proportion of 1: 1 :1: 1: + Vanillic acid 50 mg/kg P.O) was administered 1 hour before – 5- FU 450 mg/kg .ip . Group –IV is Synbiotic mixture -2 SM-2 treated (*Lactobacillus acidophilus , Lactobacillus rhamnosus, Bifidobacterium longum , Bifidobacterium bifidum ,* and *Saccharomyces boulardii* containg 1 × 10^{9} CFU in the proportion of 1: 1: 1: 1: 1 + VA) .Finally after last day of treatment various biochemical and behavioral investigations were carried out in order to investigate the neuroprotective effect of synbiotic treatment on 5-FU induced cognitive dysfunction.
Results: 5-FU treatment induced Intestinal mucositis, weight loss, and morphological alterations in the ileum and hippocampal regions of treated animals. 5-FU treatment altered the antioxidants like GSH, SOD, increased lipid peroxidation (MDA levels), MPO, and also significantly increased AChE levels in the brain indicating the cognitive impairment.SM -2 treatment group when compared to SM-1 showed significant protective effect by attenuating all the biochemical and behavioral alterations induced by 5-FU treatment in mice.
Conclusions: SM-2 showed protective effects against 5-FU-mediated oxidative stress and neuro-inflammation, which is responsible for neurodegeneration. Synbiotics used in this study helped to rebuild the intestinal microbiome thus preventing the memory loss in mice with gut dysbiosis by modulating Gut-Brain axis.

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P0192 / #2402

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

NITRATE-REDUCING ORAL BACTERIA ASSOCIATE WITH MRI BRAIN VOLUMES IN COGNITIVELY NORMAL SUBJECTS

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Aims: ***Background:*** Periodontal-associated bacteria have been implicated in Alzheimer's disease (AD) pathology. Recent studies have shown that health-associated bacteria including nitrate-reducing bacteria may have health benefits. However, no studies investigated the relationship between nitrate-reducing oral bacteria and AD pathology. ***Objectives:*** We tested the hypothesis that subgingival bacteria with nitrate-reducing capabilities would associate with biomarkers of neural preservation.
Methods: ***Methods:*** MRI derived brain volumes and cortical thickness were used as biomarkers of neurodegeneration. Subgingival bacterial composition was assessed using 16S rRNA sequencing. MRI images were acquired on a 1.5T GE Signa Imager scanner. The main outcome was an MRI composite volume of AD vulnerable regions (hippocampus, entorhinal, amygdala, middle temporal, inferior temporal, and temporal pole. In addition, average gray matter thickness from 5 ROIs was also calculated: entorhinal, inferiorparietal, middle temporal, inferiorparietal, and fusiform gyrus. Nitrate-reducing bacteria were defined as the sum of subgingival bacteria at genus level with evidence of nitrate reducing capabilities (carrying genes for nitrate reductase: NapA and NarG): *Haemophilus* and *Aggregatibacter.* Multivariate linear regression analyses were carried out to determine the association between sum of abundance of *Haemophilus* and *Aggregatibacter* bacteria and MRI brain volumes and thickness. Rank transformations were done for bacteria.
Results: ***Results:*** 49 cognitively normal subjects with mean age 69 (SD=8) were examined. Subjects were highly educated, relatively healthy and 57% were ApoE non-carriers. Regression analyses showed age-adjusted association between rank sum *of Haemophilus* and *Aggregatibacter* abundance and MRI composite brain volume (partial r=0.39, p=0.006) and gray matter thickness (partial r=0.27, p=0.06).
Conclusions: ***Conclusion:*** These results suggest that nitrate-reducing oral bacteria may contribute to brain health by preventing neurodegeneration. Further studies of the bacterial contribution to enterosalivary NO3-NO2-NO pathways and their relationship to AD pathology are warranted.

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P0193 / #1544

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

PORPHYROMONAS GINGIVALIS INFECTION IN DOWN SYNDROME AND A MARMOSET MODEL AND ITS POSSIBLE ROLE IN NEURODEGENERATION

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Aims: Individuals with Down Syndrome (DS) have a high susceptibility to infections, and they have a high risk of developing early Alzheimer's disease (AD)-like dementia. Recently, a strong correlation has been found between periodontitis and AD. *Phorphyromonas gingivalis* (P. gingivalis), a key periodontal pathogenic bacterium, and its major virulent factors called gingipains, have been found in AD brains. Aggressive periodontitis is common in DS people and *P. gingivalis* is highly prevalent in patients over 5 years old. As young adults with DS show an unique and exacerbated neuroinflammatory profile before developing dementia, a brain bacterial colonization could initiate a vicious cycle of deleterious inflammation that could result in early and chronic neurodegeneration. The main goal of this work is determine whether *P. gingivalis* infection is related to neuronal degeneration in DS and in a non-human primate model (common marmoset).
Methods: Post-mortem DS and marmoset samples (at different ages) were analyzed by immunofluorescence and biochemistry techniques
Results: We identified *P. gingivalis* and its gingipains in DS tissue at different ages. We observed a correlation between the presence of *P. gingivalis* and beta-amyloid accumulation, with neurons from young DS individuals showing perinuclear gingipain accumulation and nuclear condensation. High levels of neurodegeneration and glial cell reactivity were detected in individuals over 40 years. Infected cells were also observed in control individuals but at a lower level when compared with DS individuals. We also observed natural *P. gingivalis* infection in marmosets at different ages with high glial reactivity in aged animals, mirroring some of the pathology detected in older DS samples.
Conclusions: These results suggest that *P. gingivalis* brain infection could alter neuronal and glial cell function and contribute to neuronal death in DS individual and non-human primates.

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P0194 / #977

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

ENTERIC GLIA ADOPT AN ACTIVATED PRO-INFLAMMATORY STATE IN RESPONSE TO HUMAN AND BACTERIAL AMYLOIDS

Peter Verstraelen[1], Samuel Van Remoortel[1], Nouchin De Loose[1], Rosanne Verboven[1], Gerardo Garcia-Diaz Barriga[1], Anne Christmann[2], Manuela Gries[2], Cagla Tukel[3], Sales Ibiza Martinez[1], Karl-Herbert Schafer[2], Jean-Pierre Timmermans[1], Winnok De Vos[1]
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Aims: Mounting evidence suggests a role for the microbiome-gut-brain axis in amyloid-associated neurodegeneration. Given the diagnostic and therapeutic potential at an early disease stage, we aimed to acquire insight into the pathogenic changes induced by amyloids in the gastro-intestinal tract and its enteric nervous system.
Methods: To examine the early response to amyloids of human and bacterial origin, we challenged primary murine myenteric networks with $A\beta_{1-42}$ (vs a scrambled version of $A\beta_{1-42}$) and curli (vs culture medium), respectively, and performed shotgun RNA sequencing. We used *in vitro* neurosphere-derived cultures and *in vivo* amyloid injections into the colon wall to further scrutinize amyloid-induced pathogenic pathways.
Results: Both amyloid types induced a transcriptional signature of DNA damage and cell cycle dysregulation. We found that enteric glia and smooth muscle cells were the most responsive cell types, showing increased proliferation, γH2AX burden and SOD2 levels after amyloid challenge. Consistent with this activated state, we identified a pro-inflammatory hub in the transcriptional profile of amyloid-stimulated myenteric networks. Enteric glia were the principal source of the associated cytokines, and *in vivo*, this was accompanied by an influx of immune cells.
Conclusions: Together, these results shed new light on the intrinsic vulnerability of ENS cells to both amyloid species and position enteric glial cell activation as an early driver of neurodegenerative disease progression.

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P0195 / #1863

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

THE GUT MICROBIOME AND ALZHEIMER'S DISEASE: TIMING OF COLONIZATION INFLUENCES AMYLOID PATHOLOGY IN GNOTOBIOTIC APPPS1 MURINE MODEL

Katie Zarbock[1,2], Kendra Hanslik[3], Tyler Ulland[3], Federico Rey[1], Barbara Bendlin[4]
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Aims: Disturbances along the microbiota-gut-brain axis have been associated with neurodegenerative disorders, including Alzheimer's disease (AD). Germ-free (GF) and gnotobiotic mice are critical tools for establishing causal connections between the gut microbiome and AD. Early work in this area showed that GF APPPS1 mice have decreased amyloid-β plaque (Aβ) pathology as compared to SPF conventionally-raised (ConvR) APPPS1 mice, and that colonizing GF APPPS1 mice leads to greater Aβ peptide accumulation. However, optimized experimental approaches for colonizing GF APPPS1 mice to reproduce ConvR levels of Aβ plaque pathology do not exist. We sought to understand how timing of colonization influences AD pathology.
Methods: Male and female GF APPPS1 mice received a conventional mouse microbiome at birth or 6 weeks of age. The later were colonized via 2-week co-housing of GF APPPS1 mice with sex-matched ConvR wild type B6 mice. Pups born from these conventionalized mice were naturally colonized at birth. Mice were sacrificed after 6 months (n=6-9/group). Brains were analyzed for plaques, microglia, and astrocytes, and fecal samples were analyzed by 16S rRNA gene sequencing.
Results: Male mice colonized at birth had significantly lower cortical plaque counts as compared to male counterparts colonized at 6 weeks. Examined under high-power, plaques in males differed in count but not in size, intensity, or sphericity. Total and per plaque microglial and astrocyte counts in males did not differ between groups, but number of astrocytes correlated with plaque count. 16S rRNA gene analysis revealed no significant difference in communities between groups.
Conclusions: Timing of colonization influences Aβ plaque pathology, which is strongly correlated with the number astrocytes. These results suggest that perinatal microbial exposures shape AD progression. Furthermore, this work has important implications for design of gnotobiotic AD studies.

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P0196 / #2577

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

DEAD BOX HELICASE 24 AS A NOVEL PRESYMPTOMATIC REGULATOR OF ALZHEIMER DISEASE PATHOLOGY

Michael Axenhus, Per Nilsson, Bengt Winblad, Lars Tjernberg, Sophia Schedin Weiss
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Aims: Alzheimer disease (AD) pathology is characterized by extracellular amyloid plaques composed of fibrillar Aβ and intracellular aggregates composed of hyperphosphorylated tau. The pathology starts to develop several years before clinical signs can be observed and a multitude of proteins and pathways are affected during the AD continuum. Our aim was to identify and characterize novel proteins that are altered during the AD continuum.
Methods: We used an unbiased ^{18}O labelling proteomics approach to analyze protein levels in hippocampal and cortical brain regions from five AD and five age-matched control cases. The most significantly altered protein (DEAD box Helicase 24, DDX24) was characterized by immunohistochemistry of human brain and at various disease stages of the *App*$^{NL-F}$ knock-in AD mouse model. siRNA treatment of cortical neurons was used to determine how DDX24 relates to the amyloid precursor protein (APP) and whether DDX24 expression affects neuronal morphology. Finally, the effect of Aβ on DDX24 expression was evaluated.
Results: Immunohistochemistry of human brain confirmed the increased levels of DDX24 observed by quantitative proteomics and indicated an altered subcellular distribution of DDX24 in pyramidal neurons in AD brain. Immunohistochemical studies in *App*$^{NL-F/NL-F}$ mice showed that the increase of DDX24 starts before the onset of amyloid pathology and memory impairment. siRNA targeting of DDX24 in primary neurons decreased both APP and Aβ. High concentrations of Aβ42 lowered DDX24 levels in primary neurons.
Conclusions: We have identified DDX24 as a protein with potential regulatory function in AD.

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P0197 / #2658

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

ABETA AND TAU LEVELS IN PLASMA NEURON-DERIVED EXTRACELLULAR VESICLES (NDEV) IN ALZHEIMER'S DISEASE: DIAGNOSTIC AND THERAPEUTIC VALUE

Anton Alvarez[1], Charisse Winstom[2], James Barlow[2], Floyd Sarsoza[2], Irene Alvarez[1], Manuel Aleixandre[3], Carlos Linares[4], Manuel Garcia-Fantini[5], Birgit Kastberger[6], Stefan Winter[6], Robert Rissman[2]
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Aims: We investigated the associations of six plasma neuronal-derived extracellular vesicles (NDEV) markers with Alzheimer disease (AD) severity, cognition and functioning, and changes in these biomarkers after Cerebrolysin®, donepezil and combination therapy in AD
Methods: Plasma NDEV levels of Aß$_{42}$, total tau, P-T181-tau, P-S393-tau, neurogranin, and REST were determined in: 1) 116 mild to advanced AD patients and in 20 control subjects; 2) 110 AD patients treated with Cerebrolysin®, donepezil, or combination therapy in a randomized clinical trial (RCT). Samples for NDEV determinations were obtained at baseline in the NDEV study and at baseline and study endpoint in the RCT. Cognition and functioning were assessed at the same time points.
Results: NDEV levels of Aß$_{42}$, total tau, P-T181-tau, and P-S393-tau were higher and those of neurogranin and REST were lower in mild-to-moderate AD than in controls ($p<0.05$ to $p<0.001$). NDEV total tau, neurogranin, and REST increased with AD severity ($p<0.05$ to $p<0.001$). NDEV Aß$_{42}$ and P-T181-tau correlated negatively with serum BDNF ($p<0.05$), and total-tau levels were associated to plasma TNF-α ($p<0.01$) and cognitive impairment ($p<0.05$). Combination therapy reduced NDEV Aß$_{42}$ with respect to monotherapies ($p<0.05$); and NDEV total tau, P-T181-tau, and P-S396-tau were decreased in Cerebrolysin-treated patients compared to those on donepezil monotherapy ($p<0.05$).
Conclusions: The present results demonstrate the utility of NDEV determinations of pathologic and synaptic proteins as effective AD biomarkers, as markers of AD severity, and as potential tools for monitoring the effects of anti-AD drugs

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P0198 / #2766

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

THE ALZHEIMER'S DISEASE-RELATED GENETIC RISK FACTORS ALTERATION DURING ENDOTOXIN-EVOKED SYSTEMIC INFLAMMATION; THE ROLE OF BET PROTEINS

Marta Matuszewska, Magdalena Cieślik, Grzegorz Czapski
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Aims: Our aim was to analyze if LPS-evoked systemic inflammation affects the expression of AD-GRF genes in the hippocampus. Moreover, we studied the role of bromodomain and extraterminal domain (BET) proteins, the readers of acetylation code, in controlling the expression of AD-GRF genes.
Methods: In our studies, we used a mouse model of systemic inflammation. In these conditions, we analyzed the level of mRNA up to 12 h after administration of LPS. Furthermore, the role of BET proteins was investigated *in vitro* in microglial BV2 cells using JQ1, as a pan-inhibitor of the BET family.
Results: Our studies demonstrated that systemic administration of LPS altered hippocampal expression of many inflammation-related genes, including *Il1b*, *Il6*, *Tnf*, and several AD-GRF genes, e.g. *Cd33*, *Clu*, *Bin1*. *In vitro* analysis using microglial BV2 cells demonstrated that BET proteins are involved in controlling the expression of many LPS-activated genes.
Conclusions: Our data indicated that LPS-evoked systemic inflammation altered gene expression patterns in the hippocampus, at least in part via a mechanism controlled by BET proteins. The contribution of LPS-sensitive AD-GRF genes to the pathomechanism of AD requires further studies, but our results suggest that Gram-negative bacteria and LPS may be an important factor affecting AD.

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P0199 / #1080

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

POST-MORTEM EVIDENCE FOR PSYCHOTROPIC MEDICATION-AUGMENTED AMYLOID-B PATHOLOGY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Aims: Major depressive disorder (MDD) is linked with a 2-fold higher risk of developing Alzheimer's disease (AD), although the mechanisms behind this association are unclear and are confounded by psychotropic drug use. We, therefore, aimed to investigate AD-related changes and the mechanisms behind these changes in post-mortem MDD brains without symptoms of dementia and their matched controls, taking in consideration their history of psychotropic medication.
Methods: Aβ levels and mRNA and protein expression of amyloidogenic processing components of the amyloid precursor protein (APP) were investigated in post-mortem prefrontal cortex tissue of suicide victims with MDD diagnoses, including 13 drug-free cases and 13 with previous history of psychotropic medication use (serological screening: antidepressants, antipsychotics, benzodiazepines), and 26 age and sex matched non-neurological controls . Gene expression levels were measured using Nanostring nCounter and confirmed via quantitative qPCRs. Protein levels were measured using immunohistochemistry, western blotting and ELISAs.
Results: Immunohistochemical staining for Aβ was carried out in cortical sections of a small group of MDD patients and their matched controls, showing that some MDD patients presented moderate diffuse Aβ deposition. ELISA analysis revealed an upregulation of Aβ42 levels (12.62%) in brain homogenates of MDD patients with serologically detected psychotropic medications compared with matched controls, without changes in the MDD drug-free group. These effects were concomitant with increased expression of secretases involved in the amyloidogenic processing of APP in patients with psychotropic drug use. The results were also supported by Nanostring transcriptional profiling, suggesting dysregulated APP processing in MDD, exacerbated by psychotropic medication use.
Conclusions: Psychotropic medications used to treat the symptoms of MDD might increase Aβ deposition. The results highlight the need for further investigations into the effect of these drugs on AD pathology and risk.

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P0200 / #614

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

THE ROLE OF YRNAS AND YRNA FRAGMENTATION IN THE DEVELOPMENT AND PROGRESSION OF ALZHEIMER'S DISEASE (AD)

Ingrid Lovise Augestad, Ingrun Alseth
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Aims: Despite intense research efforts over the past decades, the exact causes underlying AD is unknown and there is still no effective treatment or cure. In order to develop AD therapies, we need reliable and non-invasive biomarkers for diagnosis and disease progression. Therefore, it is crucial to investigate underlying pathophysiological mechanisms. The role of exosomes, a subgroup of extracellular vesicles, has recently gained a lot of attention for their potential as diagnostic biomarkers. Most cells in the body release exosomes, which are important for maintaining cell homeostasis and in cell-to-cell communication. We are interested in cytoplasmic (y) RNA, that are found enriched in exosomes. The fact that yRNAs are found in higher levels in exosomes suggest a highly selective packaging process. Previous work from our group has shown that yRNA bind to the human ribonuclease Endonuclease V (EndoV) and that deletion of EndoV in mice leads to milder disease in three different disease models.
Methods: Blood plasma will be collected from wildtype, AD mice (5XFAD), EndoV-/- and 5XFAD/EndoV-/- mice at different timepoints before (1-month- old) and during (2.5-, 4.5- and 9-month-old) the progression of AD. Exosomes will be isolated using size exclusion chromatography columns and exosomal yRNA levels and fragmentation will be analyzed with RT-qPCR. Neuronal and glial markers will be used to analyze brain tissue for neurodegeneration and inflammation.
Results: Our main hypothesis is that AD has a specific exosomal yRNA profile that can be used as biomarker. Further, we hypothesize that EndoV is instrumental for exosomal packaging of yRNAs and is involved in regulating inflammation.
Conclusions: We expect to generate new knowledge about AD and to our knowledge this is the first time yRNAs and EndoV in AD will be studied.

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P0201 / #2423

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

SYMPATHOEXCITATION IN ALZHEIMER'S DISEASE: POTENTIAL ROLE IN THE MAINTENANCE OF AUTONOMIC FAILURE

Rodrigo Del Rio[1], Camilo Toledo[1], Claudia Melipillan[1], Angelica Rios-Gallardo[1], Karla Schwarz[1], Nibaldo Inestrosa[2]
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Aims: Objective: Besides the well-known cognitive alterations present in Alzheimer's disease (AD), patients also displayed cardiovascular disorders. Importantly, cardiovascular dysfunction has been closely linked to increase morbidity and mortality in AD. Despite no comprehensive studies have previously addressed autonomic function in patients with AD. Accordingly, we first characterized autonomic function in AD patients and then, using experimental AD mice, we determined the level of neural activity in autonomic control areas at the central nervous system.
Methods: Methods: 16 subjects (8 AD and 8 age-matched controls) were enrolled to record sympathetic nervous system (SNS) activity and cardiac autonomic function. In addition, autonomic function was study in experimental AD (APP/PS1 double transgenic mice). At the end of mice experiments, brains were harvested and micropunches from autonomic control areas (NTS, PVN, LC, RVLM) were obtained to determine the level of neuronal activation using ΔFosB immunoblot.
Results: Results: Compared to age-matched healthy subjects, patients with AD showed larger increases in neural sympathetic discharges during autonomic testing. In addition, cardiac autonomic function was markedly impaired in AD patients. Indeed, heart rate variability analysis in AD patients showed a shift in spectral components towards a more sympathetic influence. Remarkably, we found that autonomic function impairment in the APP/PS1 mice resembles what we found in AD patients. Indeed, compared to wild-type mice (WT), APP/PS1 mice displayed a higher heart rate response (~55%) to systemic administration of a beta-blocker. Finally, we found that APP/PS1 mice showed neuronal hyperactivation in brain autonomic control centers.
Conclusions: Conclusions: Our results show for the first time that AD patients display both systemic and cardiac sympathoexcitation and that experimental AD mice exhibit overt signs of neuronal hyperactivation in critical brain areas associated with autonomic regulation.

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P0203 / #2388

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

AMYLOID BETA-BINDING PROTEINS IN PATHOGENIC BACTERIA

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Aims: Human Aβ is highly conserved among the whole animal kingdom as nearly 60-70% of vertebrates express Aβ identical to human Aβ. Several studies have shown that Aβ protects against microbial infections in animal models. At the same time, recent studies have shown that a toxin, gingipain, from *Porphyromonas gingivalis* bacterium is neurotoxic *in vivo* and *in vitro.* The levels of this toxin in AD brains correlates with tau pathology and could thereby be associated with AD. This indicates that although Aβ can efficiently trap microbes, some pathogenic bacteria may evade this defense system and express virulence factors that induce neuroinflammation. The aim of this study was to analyze whether pathogenic microbes harbor molecules to avoid Aβ capture and trigger inflammation in the central nervous system (CNS).
Methods: We screened 15 microbial molecules from different pathogens that are known to infect the CNS (*Streptococcus pneumonia, Streptococcus agalactiae, Streptococcus pyogenes, Staphylococcus aureus, Borrelia burgdorferii*) for Aβ1-42 binding using ELISA and microscale thermophoresis (MST).
Results: We discovered five microbial molecules from three different bacteria that bound Aβ1-42. Some of these virulence factors (PLY, Efb, LukS) are released in fluid phase and known to interact with the immune system.
Conclusions: These data indicate that binding of Aβ by microbial molecules may be an important immune evasion mechanism that triggers Aβ oligomerization and neuroinflammation that are known to contribute to AD pathogenesis. Our further studies aim to find out whether these molecules could increase bacterial survival and induce Aβ oligomerization away from the microbe.

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P0204 / #989

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

AXONAL INJURY OF HIPPOCAMPAL NEURONS INITIATES AMYLOIDOGENIC DISEASE CASCADES IN 3D COLLAGEN CULTURES.

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Aims: Traumatic brain injury (TBI) and Alzheimer's disease (AD) share common and complex pathological features, including the deposition of amyloid beta plaques. In AD, these deposits have previously been linked to neurodegeneration - yet they are a poor predictor of disease development. Instead, AB deposition in AD may be an epiphenomenon of an earlier pathology, such as axonal degeneration. Here, we utilise models of axonal injury as a time-point zero of disease initiation to study events preceding and contributing to AD progression.
Methods: Hippocampal cells from wild-type and APP NL-F embryos were grown in 3D collagen cultures to DIV7 prior to a focal or diffuse injury. Cells were probed for the amyloidogenic pathway at either 24-or-96 h post-injury using immunohistochemistry, live FRET imaging and Western blot. Hippocampal cells were further co-cultured with astrocytes to validate the injury model and elucidate whether the addition of astrocytes mitigates the amyloidogenic pathway post-injury.
Results: In 3D collagen hippocampal cultures, the amyloidogenic pathway was successfully initiated post-injury at several processing steps. We further observed that in co-cultures post-injury, astrocytes demonstrated a reactive phenotype that was increasingly hypertrophic with proximity to the injury site. Finally, we show here that cells taken from APP NL-F embryos show a clear progression towards amyloid beta deposition post-injury in our experimental platform.
Conclusions: The data shown here establish axonal damage as a potential initiator of the amyloidogenic pathway in a 3D culture platform after injury. These experiments further position plaque deposition as a consequence – rather than a cause - of earlier pathological events in AD and neurodegenerative conditions.

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P0205 / #530

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

POTENTIAL ROLES OF INFILTRATING IMMUNE CELLS IN OLFACTORY DYSFUNCTION IN ALZHEIMER'S DISEASE MOUSE MODEL

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Aims: Olfactory dysfunction, among other sensory impairments implicated in clinical tests, is also an apparent and early symptom of Alzheimer's disease (AD) which appears in approximately 90 percent of the patients. However, olfactory dysfunction is often unnoticed by patients and clinicians compared to auditory or visual changes. Despite the increasing interest in olfactory dysfunction as an early and non-invasive diagnostic tool, the underlying mechanism of the impairments in olfactory function in the disease is poorly understood. In this study, we aimed to investigate the underlying mechanism for olfactory function and whether increased infiltration of immune cells in the olfactory epithelium of AD model may play an important role on olfactory dysfunction and may affect the progression of AD.
Methods: To confirm the functional olfactory impairment, behavior tests examining olfactory function (food pellet and odorant preference tests) were performed in 5xFAD AD mouse model. Simultaneously, a hippocampus-dependent spatial memory (Y-maze) test was performed to confirm the progression of olfactory deficits and memory impairment. In addition, we observed pathological changes found in the olfactory system by employing immunofluorescence staining and confocal microscopy.
Results: Olfactory dysfunction was observed in behavioral tests before exhibiting memory impairment in 5-month 5xFAD. Observing the pathological changes, we found that dopaminergic periglomerular neurons were decreased in the olfactory bulb and that increased infiltration of CD45 positive immune cells were observed in the endoturbinate regions of the olfactory epithelium.
Conclusions: Further experiments are planned to prove whether regulations of immune cells rescue the olfactory dysfunction and AD progression. It is expected to understand the correlation between the infiltration of immune cells in the olfactory system and AD, and to suggest early diagnosis and therapeutic targets for AD.

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P0206 / #1420

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

AN OPTIMIZED MALDI-TOF MS MATRIX FOR STUDYING PHOSPHORYLATED AMYLOID-BETA PEPTIDES

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Aims: To develop an optimized MALDI-TOF-MS matrix formulation allowing for the improved detection of synthetic phosphorylated amyloid-beta species by MALDI-TOF-MS.
Methods: Different matrix preparations substituted with selected additives were deposited on a Ground Steel Target and tested on a MALDI-TOF/TOF mass spectrometer for their performance in detecting synthetic amyloid-beta peptides phosphorylated at Ser8 or Ser26.
Results: MALDI-TOF detection of synthetic phosphorylated amyloid-beta peptides was substantially improved by addition of n-octyl-β-D-glucopyranoside (OGP), α-cyano-4-hydroxycinnamic acid (CHCA) and phosphoric acid (PA) to a 2',4',6'-trihydroxyacetophenone (THAP) / diammonium citrate (DAC) matrix. The optimized matrix (referred to as "TOPAC") allowed the detection of synthetic pSer8-amyloid-beta with high signal intensities minimal loss of phosphoric acid, and an optimized ratio between non-oxidized and oxidized species of more than 2:1.
Conclusions: We propose the novel TOPAC matrix as a valuable tool for future studies aiming for the mass spectrometric verification of phosphorylated amloid-beta variants in biological samples.

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P0208 / #1760

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

IMMUNOPHENOTYPING AND EPITOPE MAPPING FOR ALZHEIMER'S DISEASE-RELATED T CELLS

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Aims: Priming of the adaptive immune system by Alzheimer's Disease (AD)-associated antigens is still a matter of debate. The existence of protective antibodies against β-amyloid aggregates in healthy aged donors indicates that the peripheral immune system can 'sense' the brain, most likely via drainage of brain-derived solutes through dural lymphatics. In exploratory immunophenotyping studies, we reported changes in T-cell profiles in blood of subjects with early cerebral β-amyloidosis. We hypothesize that AD-associated epitopes elicit specific adaptive immune responses detectable in the periphery starting in preclinical AD.
Methods: We designed cross-sectional and longitudinal immunophenotyping studies to assess blood donors characterized by β-amyloid-PET and AD plasma biomarkers. We included healthy control subjects and mild cognitive impairment (MCI) patients. We analysed peripheral blood mononuclear cells (PBMCs) via multiparameter mass cytometry and characterized clonally expanded cells via single-cell RNA-sequencing and paired T- and B-cell receptor profiling. Finally, we investigated T-cell specificity *in vitro* with antigen-presentation assays.
Results: We observed that increases in specific antigen-experienced subpopulations such as CD8+ TEMRA/effector T-cells in blood were associated with increased cerebral β-amyloid load and detectable as early as in preclinical AD stages. Moreover, we found memory and TEMRA/effector T-cells with reactivity towards AD-related peptide epitopes in the blood of still β-amyloid-free cognitively healthy donors.
Conclusions: While the relationship between T-cell reactivity and cognitive outcomes in AD has been widely explored, the association of peripheral immune cell alterations with key pathological biomarkers such as β-amyloid deposition has not yet been studied in detail. Our study suggests that changes in adaptive immune responses might be detected already in an early phase of cerebral β-amyloidosis, at a stage when cognitive deficits are not yet present.

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P0209 / #1603

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

ACUTE AND CHRONIC AB OLIGOMERS TOXICITY IN PRIMARY CULTURE OF CORTICAL NEURONS: TWO DISTINCT MECHANISMS

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Aims: Alzheimer's disease (AD) is characterized by the extracellular accumulation of senile plaques composed of beta-amyloid (Aβ) and the intracellular deposition of neurofibrillary tangles composed of hyperphosphorylated tau (Tp). Aβ oligomers (AβO) induce damage beginning with loss of synapses, followed by neurite network disorganization and neuronal death. In this study, we investigated and compared acute direct neurotoxicity and chronic neuroinflammation induced by AβO.
Methods: Using primary culture of rat cortical neurons, the AβO toxicity was investigated in presence or absence of microglial cells in the culture by applying different doses of AβO. Survival of cortical neurons, integrity of their neurite network and neurotoxicity was studied by immunostaining (Cytochrome C, caspase 3, AT100). Furthermore, activation of microglial cells was analyzed by immunostaining against different microglial markers and cytokines measurement.
Results: We showed in our models that AβO toxicity induced synapses disorganization and neuronal loss by different mechanisms. High doses of AβO caused acute neuronal death involving direct neurotoxicity, and synapses loss was observed after low doses of AβO. We also shown that in presence of microglial cells low dose of AβO induced an exacerbate microglial activation that can be beneficial to phagocyte AβO, but induced a strong neuroinflammation causing neuronal death.
Conclusions: Altogether, these findings showed us that neuronal death induced by AβO toxicity is due to different pathways involving both neuroinflammation and neurotoxicity. It highlights that microglial activation is necessary to phagocyte AβO in order to protect neurons, but in a controlled way to not induce a neuroinflammation causing neuronal death.

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P0210 / #1506

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

EXTRACELLULAR VESILE PROTEIN SIGNATURES AS EARLY DIAGNOSTIC MARKER FOR NEURODEGENERATIVE DISEASES

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Aims: Dementia is a prevalent disease of the 21st century that poses a major challenge to societies worldwide. The pathogenesis of this disorder remains unclear. To improve the prevention and treatment of dementia, there is an urgent need to identify disease-specific markers that enable early diagnosis and elucidate the underlying molecular mechanisms. Using differential mass spectrometry in combination with bioinformatics approaches, we aimed to investigate extracellular vesicles (EVs) from blood plasma of patients of the " VOGEL" study to identify novel biomarker features for dementia development.
Methods: Initially, different plasma EVs isolation methods (ExoQuick, qEV35 and ME kit) were compared using mass spectrometry (MS)-based proteome profiling. In addition, targeted MS-based approach for EV quality control (QC) using specific biomarkers was established. The optimal EV isolation method was utilized to perform a quantitative proteomic plasma EV profiling within the " VOGEL" cohort (six-year longitudinal study: baseline (controls) and after six years (control and mild cognitive impairment (MCI)) to identify distinct disease-related protein signatures.
Results: For the isolation and proteomic analysis of plasma EVs, a combination of size exclusion chromatography, urea lysis, and liquid digestion proved optimal, providing the highest number of identified and quantified protein groups. Furthermore, utilization of the developed EV-QC approach allows quick sample quality assessment with regard to EV isolation, which so far required time-consuming methods. The established EV proteomic sample processing and QC workflow was used for plasma EV proteome profiling in the “VOGEL” cohort including 179 sample.
Conclusions: By using optimal sample processing methods and incorporating specific quality controls, quantitative profiling of plasma EV proteomes provides protein signatures that could be useful for neurodegenerative disease diagnosis.

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P0211 / #1389

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

DETERMINANTS OF COGNITIVE AND BRAIN RESILIENCE TO TAU PATHOLOGY: A LONGITUDINAL ANALYSIS

Anna Svenningsson[1], Diana Bocancea[2,3], Anna Van Loenhoud[2,3], Colin Groot[1,2,3], Frederik Barkhof[4,5], Olof Strandberg[1], Ruben Smith[1], Michael Pontecorvo[6], Gil Rabinovici[7], Wiesje Van Der Flier[2,3], Oskar Hansson[1], Rik Ossenkoppele[1,2,3]
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Aims: Mechanisms of resilience against tau pathology are insufficiently understood. Longitudinal data are necessary in revealing factors relating to preserved cognition (cognitive resilience) and brain structure (brain resilience) despite tau pathology and clarifying whether they relate cross-sectionally or longitudinally.
Methods: We included 366 β-amyloid positive individuals with mild cognitive impairment or Alzheimer's disease dementia with baseline [^{18}F]flortaucipir positron emission tomography (tau PET) and longitudinal cognitive assessments (Mini Mental State Examination). A subset (n=200) additionally underwent longitudinal magnetic resonance imaging. We used linear mixed effects models with longitudinal cognition and cortical thickness as outcomes to investigate determinants of cognitive resilience and brain resilience. Models assessed whether age, sex, education level, *APOE*ε4 status, intracranial volume, and cortical thickness moderated the association of tau pathology (temporal region of interest) with cognitive decline or cortical thinning.
Results: Significant moderation effects revealed that the negative association of baseline tau PET with rate of cognitive decline was enhanced with older age, higher education level, and larger intracranial volume. Younger age and higher education were associated with better cognitive performance at baseline, and higher cortical thickness was associated with better cognition at baseline and slower cognitive decline, independent of tau. Education modified the association between tau PET and cortical thinning, with higher education enhancing the negative impact of tau. Older age was associated with lower baseline cortical thickness and higher rate of cortical thinning independent of tau. No associations were seen for sex or *APOE*ε4 status.
Conclusions: In symptomatic individuals with underlying Alzheimer's disease neuropathological changes, education is positively associated with baseline cognitive performance but negatively moderates the impact of tau burden on cognitive decline and cortical atrophy.

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P0212 / #1753

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

SIGNIFICANT CHANGE IN BIOMETAL DISTRIBUTION IN BRAINS OF ALZHEIMER´S DISEASE (TGSWDI) MICE

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Aims: Neuronal demise in Alzheimer's disease (AD) occurs years later than the accumulation of amyloid-beta plaques and neurofibrillary tangles, but the mechanisms underlying neuronal death remain unresolved. Increasing accumulation of biometals (e.g. iron, zinc, copper, and manganese) increases oxidative stress, and their accumulation is worsened by cerebral amyloid angiopathy (CAA) which causes microbleeds with the deposition of iron. We hypothesized that AD studied in a mouse model with CAA (TgSwDI) causes pathological deposition of biometals with resulting dyshomeostasis.
Methods: Brains of TgSwDI mice, which deposit amyloid plaques and CAA from 3-6 months, and C57Bl/6j control mice, aged 7, 12, and 24 months (n=6-12 per age) were dissected into the cortex, hippocampus, thalamus, and cerebellum. The content of iron, zinc, copper, and manganese was measured using ICP-OES. The hippocampus and thalamus were also examined for gene expression of selected iron-handling proteins using TaqMan qPCR, and the hippocampi from 24 months mice were examined for their protein content using LC-MS/MS.
Results: The content of biometals varied among different brain regions, ages, and genotype. Combining the biometal content of each brain region revealed that TgSwDI mice had significantly different biometal profiles compared to controls. The gene expression of ferritin light and heavy chains significantly decreased in TgSwDI mice at all ages, while the expression of the transferrin receptor was unaffected. The LC-MS/MS analysis showed that TgSwDI mice had severe gliosis without significant changes in iron-handling proteins.
Conclusions: Our findings show that the content of biometals is significantly changed in different brain regions of TgSwDI mice with a simultaneous reduction in ferritin expression. The suppressed expression of ferritin isoforms combined with the change in biometal content likely contribute to oxidative stress and neuronal damage in TgSwDI mice.

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P0213 / #1527

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

AN INTEGRATED MACHINE LEARNING MODEL FOR TRANSCRIPTOMIC SIGNATURES FOR ALZHEIMER'S DISEASE PATIENTS WITH HISTORY EXPOSURE TO HEAVY METALS

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Aims: Many Alzheimer's disease patients with a history of exposure to heavy metals have specifically altered signatures in their genomic and transcriptomic profiles. The aim of this work is to develop an integrative machine learning workflow to identify such signatures and achive better understanding of the etiology.
Methods: We revisited a publicly available single cell RNAseq (scRNA-Seq) dataset comparing the transcriptomics profiles for various cell types within the brains of AD vs. non-AD patients. We decided to focus on the 35 patients with definitive diagnosis and consistent pathology profiles for non-AD vs. AD. We also modeled the response to different metals using in-house RNA-Seq data from iPSC cells originated from AD and healthy human subjects treated with aluminum or lead.
Results: From the public scRNA-Seq data, differentially expressed genes (DEG) between non-AD vs. AD patients were identified in the five cell types in brain. We built a gene network illustarting the interaction between cellular response to metal ion and Amyloid beta binding, indicating that interruptions of this sub-network in brain microenvironment may be related to the onset and progression of AD. From the in-house RNA-Seq data we identified differentially expressed pathways when iPSC cells were treated with aluminum or lead. KEGG pathway HSA05010 (Alzheimer's Disease-Homo sapiens) was significantly up-regulated in both aluminum and lead treated cells, yet the lead treated cells showed much broader pathway changes.
Conclusions: This analysis is one of the first efforts to systematically model the defect response to different types of metal ions in transcriptomics profiles from both AD patients' tissues and human-based iPSC cells. The panels of differentially changed pathways would provide novel hypotheses on the role of heavy metal exposure in the onset and progression of AD.

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P0214 / #2744

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

DIFFERENTIATION OF PMN310 FROM OTHER AMYLOID-BETA-DIRECTED ANTIBODIES: ABILITY TO SELECTIVELY TARGET TOXIC BRAIN OLIGOMERS DESPITE COMPETING MONOMERS AND PLAQUE

Johanne Kaplan[1], Ebrima Gibbs[2], Juliane Coutts[2], Beibei Zhao[3], Neil Cashman[4]
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Aims: Compare PMN310 to other Abeta-directed antibodies for selectivity and ability to avoid plaque and to maintain interaction with toxic oligomers in the presence of competing monomers.
Methods: Surface plasmon resonance was used to assess the binding of multiple Abeta-directed antibodies (PMN310, donanemab, aducanumab, lecanemab, crenezumab, solanezumab, gantenerumab) to a toxic oligomer-enriched low molecular weight fraction of soluble brain extract from AD patients, with and without pre-exposure to competing monomers. Binding to Abeta plaque was examined by immunohistochemistry on AD brain sections.
Results: Abeta-directed antibodies showed varying degrees of binding to the isolated toxic oligomer-enriched fraction. Exposure to monomer competition, unavoidable in vivo, completely inhibited the ability of solanezumab, crenezumab and gantenerumab to bind toxic oligomers, correlating with the negative clinical data observed so far with these antibodies. Antibodies with more selectivity for aggregated Abeta which have produced positive clinical data (donanemab, aducanumab, lecanemab) were less impacted by monomer competition and maintained higher levels of binding to toxic oligomers. By comparison, PMN310 was the least impacted by monomer competition resulting in a toxic oligomer binding level overall greater than that of the other antibodies. In contrast to other Abeta antibodies, PMN310 did not bind plaque.
Conclusions: PMN310 distinguishes itself from other Abeta antibodies by its enhanced selectivity for toxic oligomers, allowing it to withstand competition by monomers and plaque thereby preserving the effective dose reaching toxic oligomers. Plaque avoidance by PMN310 could also potentially reduce the risk of ARIA and its complex associated monitoring, while possibly allowing for safe administration of higher doses.

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P0215 / #1717

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

TARGETING ALZHEIMER'S DISEASE WITH NATURAL COMPOUNDS-BASED NANOMEDICINE

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Aims: Molecules inhibiting amyloid β (Aβ) aggregation and/or increasing Aβ fibril disruption are a promising approach to the prevention and treatment of Alzheimer's disease (AD). Gallic acid (GA) has recently shown strong anti-amyloidogenic effects. However, its sensitivity to oxygen, light, and high temperatures, as well as its short half-life and fast body clearance, hamper its clinical use. Therefore, the main goal of this research is to develop an optimized liposomal formulation for delivering GA to the brain while overcoming its limitations.
Methods: Different approaches were used to prepare GA-loaded liposomes to establish the formulation with the best physicochemical parameters. The surface of the liposomes was then functionalized with transferrin (Tf) to direct them to the brain and improve their passage across the blood-brain barrier (BBB) due to Tf receptors overexpression. The *in vitro* release of GA from Tf-functionalized liposomes was evaluated, and stability studies were conducted. Afterward, the ability of the drug delivery system (DDS) to inhibit the $A\beta_{1-42}$ aggregation and disrupt preformed fibrils was investigated.
Results: Reverse-phase evaporation technique proved to be the most suitable in terms of NPs' physicochemical characteristics for producing GA-loaded liposomes. GA-loaded Tf-functionalized liposomes exhibited mean sizes of 130 nm, low polydispersity index values, and neutral zeta potential. The nanosystem promoted the sustained release of GA over 5 days and showed physical stability for 1 month. Additionally, GA-loaded Tf-functionalized liposomes interacted strongly with $A\beta_{1-42}$ monomers, slowing the Aβ monomer-to-oligomer and oligomer-to-fibril transitions and reducing the number of fibrils produced by 56%. Furthermore, the NPs disrupted around 30% of mature Aβ fibrils.
Conclusions: The developed Tf-targeted DDS for the brain delivery of GA may represent a promising approach for preventing and treating AD.

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P0216 / #1066

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

EFFECTS OF CITALOPRAM TREATMENT ON ABETA PATHOLOGY AND BEHAVIOUR DEFICITS IN THE 5XFAD AND TG4-42 ALZHEIMER'S DISEASE MOUSE MODELS

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Aims: Given the need for disease-modifying therapies for Alzheimer's diseae (AD), drug repurposing may be a promising approach. It has previously been shown that long-term use of selective serotonin reuptake inhibitors (SSRI) delayed the conversion from mild cognitive impairment to AD in patients with a previous depression for several years (Bartels et al., 2018). The aim of the current study was to investigate the effects of Citalopram treatment on the behaviour deficits and Abeta pathology in two different AD mouse models.
Methods: 5XFAD and Tg4-42 AD mice were treated with Citalopram in two consecutive studies. In a dose-finding study, 10-week-old mice received 5 mg/kg, 10 mg/kg or 40 mg/kg Citalopram for 2 weeks. In the following long-term trial 10-week-old 5xFAD and Tg4-42 mice were treated with 10 mg/kg Citalopram for 6 months. Behaviour tests were performed assessing memory, motor functions & anxiety after the long-term treatment (Rotarod, Novel Object Recognition, Elevated-Plus-Maze, Dark/Light & Water Maze). Abeta levels in the blood plasma and the Abeta load in the brain were measured in all mice after the treatment.
Results: Short-term-treatment with Citalopram significantly and dose-dependently decreased the concentration of $A\beta_{40}$ and $A\beta_{42}$ in the blood plasma of 5XFAD and Tg4-42 mice. Long-term-treatment with Citalopram normalized the anxiety behaviour and locomotor activity in 5XFAD mice. Additionally, Citalopram improved recognition and working memory of 5xFAD and Tg4-42 mice. In addition, the effects of long-term Citalopram treatment on the Abeta pathology will be presented.
Conclusions: In conclusion, the present study shows that Citalopram treatment can be therapeutic beneficial for several altered parameters in AD including motor deficits, anxiety & memory in two different AD models. Our findings reinforce a SSRI-based medicine as a potential therapy against AD.

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P0217 / #578

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

PBD.C06 MURINE PRECURSOR ANTI-PYROGLU-3 ABETA MAB DOES NOT INDUCE HEMORRHAGES IN PLAQUE-RICH, AGED APP/PS1;APOE4 MICE

Martine Grenon[1,2], Praveen Bathini[2,3], Maria-Giusy Papavergi[1,2], Jens-Ulrich Rahfeld[4,5], Torsten Hoffmann[5], Stefan Tasler[5], Stephan Schilling[4,5], Cynthia Lemere[2,3]
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Aims: Pyroglutamate-3-amyloid-beta (pGlu-3-Abeta) is a modified, N-terminally truncated, toxic form of Abeta, highlighting it as a potential therapeutic target. Amyloid-Related Imaging Abnormalities (ARIA), including microhemorrhages, have been observed in clinical studies testing plaque-binding anti-amyloid antibodies. Here, we tested a novel CDC-mutant anti-pGlu-3-Abeta monoclonal antibody (mAb), 07/2a-k (murine PBD.C06), engineered to minimize the risk for vascular-related inflammation by blocking C1q activation upon Abeta binding.
Methods: Sixteen-month-old APP/PS1;APOE4 mice were immunized weekly for 15 weeks with 350 µg intraperitoneal injections of 07/2a-k, 3D6-L (a murine analog of bapineuzumab), or an IgG2a-isotype control antibody. hAPOE4 control mice were injected with PBS. Cognition was assessed with the Spatial Novelty Y Maze (SNYM), Novel Object Recognition (NOR), and the Barnes Maze (BM).
Results: All groups performed similarly in the SNYM and in the NOR discrimination index. However, 07/2a-k-treated mice showed the same novelty preference (NOR) as PBS-injected hAPOE4 mice, suggesting some benefit. 3D6-L-treated mice appeared to perform more like hAPOE4 mice in the BM, suggesting a learning treatment effect. ELISA analysis revealed lowering of Abeta-x-42 and pGlu-3-Abeta levels by 3D6-L only. No effect was observed on Abeta-x-40. Thioflavin-S hippocampal plaque staining was reduced after treatment with 3D6-L and 07/2a-k. 3D6-L treatment also lowered general Abeta and pGlu- Abeta staining by immunohistochemistry. In contrast to 07/2a-k-treatment, 3D6-L-treatment induced significantly more microhemorrhages in parenchyma and visible microbleeds on the brain surface.
Conclusions: While both 3D6-L and 07/2a-k showed modest effects on cognition in aged mice, only 07/2a-k treatment was free of hemorrhages. Thus, the removal of the C1q site on antibodies might help to reduce antibody-related side effects. Further studies will be required to assess the apparent differences in Abeta clearance. Funding: 1RF1 AG058657 (CAL).

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P0219 / #671

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

SAFE AND NEUROPROTECTIVE EFFECTS OF A SYNTHETIC COUMARIN DERIVATIVE ZN014 FOR EARLY-PHASE ALZHEIMER'S DISEASE

Hsiu-Mei Hsieh[1], Chia-Yu Li[1], Ying-Chieh Sun[2], Guey-Jen Lee-Chen[1], Chiung-Mei Chen[3], Kuo-Hsuan Chang[3], Wen-Wei Lin[2]
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Aims: Alzheimer's disease (AD) is the most common neurodegenerative diseases and is without effective therapeutics currently. The signaling pathways of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TRKB) play a pivotal role in axonal sprouting, proliferation of dendritic arbor, synaptic plasticity, and neuronal differentiation. Studies have also proved that abnormalities BDNF in AD patients promote Aβ aggregates. Currently, 7,8-dihydroxyflavon (7,8-DHF) is known as the best synthetic TrkB agonist, which binds to the TrkB receptor and effectively triggers downstream signaling. In addition, synthetic coumarin derivatives were identified to enhance the BDNF production in our previous study. In this study, we evaluated 15 compounds (ZN001-ZN015) with similar structures to 7,8-DHF (flavone) or coumarin using AD hippocampal primary culture and model mice.
Methods: Immunocytochemical analysis was performed to evaluate the neuroprotective effect of compounds on mouse hippocampal primary culture. Cognitive behavioral and immunostaining were conducted in AD model mice to identify the therapeutic potential of ZN014 in vivo.
Results: Our results showed that ZN014 effectively promoted the neurite outgrowth in the primary culture under Aβ toxicity. Further in vivo study proved ZN014 ameliorated the memory impairment in AD model mice. Immunostaining showed that ZN014 reduced the neuronal cell loss, increased the mature BDNF/pro-BDNF ratio and alleviated the neuroinflammation in the mouse hippocampus.
Conclusions: We suggest ZN014 might be potential to be further developed as a compound in AD treatment.

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P0220 / #2103

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

ADAMTS1 IS A SECOND ADAMTS PROTEASE FAMILY MEMBER THAT IS EXPRESSED IN GLIAL CELLS AND GENERATES N-TRUNCATED ABETA4-X PEPTIDES

Vidya Kesireddy[1], Loretta Hamacher[1], Carolina Münch[1], Hermeto Gerber[2], Claus Pietrzik[3], Patrick Fraering[2], Oliver Wirths[4], Sascha Weggen[1]
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Aims: N-truncated Abeta4-x peptides can be generated through proteolytic processing of APP by the secreted metalloprotease ADAMT4, which is exclusively expressed in oligodendrocytes (Walter 2019 Acta Neuropathol 139:239-257). However, in the brains of 12-month-old 5xFAD/ADAMTS4 KO mice, only a 50% reduction in Abeta4-x peptide levels was observed. This indicated that other proteases might participate in Abeta4-x peptide generation, with other ADAMTS family members being potential candidates.
Methods: HEK293 cells with stable co-expression of human APP695sw and ADAMTS1 were established, and APP processing and secreted Abeta levels were analyzed by Western Blotting, ELISA and mass spectrometry. ADAMTS1 KO reporter mice were used to study ADAMTS1 expression in the adult murine brain.
Results: Inducible overexpression of ADAMTS1 in HEK293 cells resulted in the secretion of Abeta4-40 but unchanged levels of Abeta1-x peptides, similar to our previous observations with ADAMTS4. Further studies revealed important functional distinctions between ADAMTS1 and ADAMTS4. First, mass spectrometry analysis showed subtle differences in the proteolytic products generated by the two proteases, with ADAMTS1 spectra lacking signals for Abeta12–40 peptides. Second, while ADAMTS4 overexpression resulted in strongly reduced levels of the secreted APP ectodomain (APPs), this effect was less prominent with ADAMTS1. Third, the expression pattern of ADAMTS1 in the murine brain was different from ADAMTS4 with prominent expression in astrocytes.
Conclusions: N-truncated Abeta4-x peptides are highly aggregation-prone and abundant in brain samples of AD patients. Our findings demonstrate that at least two members of the ADAMTS protease family contribute to Abeta4-x peptide generation and suggest that these peptides are mainly produced by glial cells in the brain.

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P0221 / #1678

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

A UNIQUE MODE OF ACTION FOR THE TREATMENT OF AD

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Aims: Alzheimer´s Disease (AD) currently affects more than 30 million people worldwide, but to date, no curative or disease modifying treatment is available. We have developed a new mode of action to disassemble toxic Aβ oligomers into functional monomeric Aβ building blocks. This mode of action is realized by an all-d-enantiomeric peptide ligand named RD2 that stabilizes Aβ monomers in their native intrinsically disordered conformation. This is a purely thermodynamic mode of action, which does not require inhibition of enzymes or ion channels, and is therefore not prone to show side effects. The aim of this study was to prove this mode of action.
Methods: We use *in vitro*, *ex vivo* and *in vivo* experiments to demonstrate target engagement and the efficacy of the new mode of action.
Results: We demonstrated *in vitro* by analytical ultracentrifugation that RD2 eliminates toxic Aβ assemblies by stabilizing Aβ monomers in their native intrinsically disordered conformation. Furthermore, we showed that RD2 disassembled Aβ oligomers from brain tissue of former AD patients into Aβ monomers by *ex vivo* treatment. *In vivo* we demonstrated target engagement by showing a significant reduction of Aβ oligomers in the brains of APPswe/PS1ΔE9 mice, which were treated orally for 12 weeks with RD2, compared to placebo-treated mice.
Conclusions: We were able to prove *in vitro*, *ex vivo* and *in vivo* the new anti-prionic mode of action of RD2.

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P0222 / #486

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

PHARMACODYNAMICS ASSESSMENT OF ADUCANUMAB IN 5XFAD MICE : A MODEL-AD PTC STUDY

Paul Territo[1], S Quinney[1], Andi Masters[1], Katy Haynes[2], Zack Cope[2], Gabby Little[2], Scott Persohn[1], Amanda Bedwell[1], Kierra Eldridge[1], Nicholas Seyfried[3], Kristen Onos[4], Michael Sasner[4], Gareth Howell[4], Greg Carter[4], Adrian Oblak[1], Bruce Lamb[1], Stacey Sukoff Rizzo[2]
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Aims: The Model Organism Development for Evaluation of Late Onset Alzheimer's Disease (MODEL-AD) Preclinical Testing Core (PTC) established a rigorous drug testing strategy for unbiased assessments of therapeutic agents. To validate this pipeline, the chimeric murinized antibody aducanumab (chAducanumab), was selected for evaluation in 5XFAD mice.
Methods: Treatment was initiated in 9-month aged male and female 5XFAD mice and WT controls. PK modeling was used to inform chronic dosing. Longitudinal endpoints (n=10-12/sex/genotype/treatment) assessed at baseline and conclusion of chronic treatment included: 18-FDG 18F-AV45 PET/CT, and plasma Aβ. A touchscreen cognitive testing battery and cortical EEG analysis was conducted at the conclusion of chronic treatment. Terminal endpoints included confirmatory autoradiography, IHC, and brain Aβ.
Results: PK/PD modeling revealed $T_{1/2}$ of ~2.5 days, and informed the PD dose regimen (0.1-30 mg/kg Q1W, IP). 12-week treatment with chAducanumab resulted in dose- and sex-dependent reductions in amyloid via 18F-AV45 PET. Glucose uptake via 18F-FDG PET similarly showed a dose dependent reversal of glycolytic loss in key brain regions. Cognitive assessments indicated no effect on task acquisition with a modest improvement in a pattern separation task observed with chAducanumab in females but not males. EEG analysis revealed modest improvements in delta, alpha, and beta oscillations with treatment. Multi-omics analysis are in progress.
Conclusions: chAducanumab treatment resulted in reductions in brain amyloid consistent with clinical findings, and a unique glycolytic restoration with improvements in some aspects of brain function in 5XFAD mice, thus supporting pipeline validation of the MODEL-AD PTC for evaluating therapeutic antibodies.

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P0223 / #896

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

MULTI-FREQUENCY LUMINAIR INHIBITS THE SECRETION OF AMYLOID-B AND THE PHOSPHORYLATION OF TAU PROTEIN IN SH-SY5Y CELLS

Tzyh Chyuan Hour[1,2,3], Chen-Wen Yen[1,4,5,6], Hsi-Wen Chang[1,2], Ming-Hui Chen[1], Ling-Chun Huang[7], Yuan-Han Yang[1,7,8,9]
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Aims: Alzheimer's disease (AD) is the most common cause of dementia and can not be cured. Previous research showed that non-invasive scintillation gamma frequency, 40 Hz, oscillation enhanced recognition and memory in AD mice model, but the molecular change in cell model was still unclear. Meanwhile, how to adapt the flicker light to avoid uncomfortable experiences is crucial for clinical application. We are going to examine the effects of gamma frequency in SH-SY5Y cells through multi-frequency luminaire emerging 40 Hz light.
Methods: A multi-frequency luminaire emerging 40 Hz light was provided by Delta Electronics Incorporation and confirmed by Industrial Technology Research Institute. SH-SY5Y cells were exposed to the multi-frequency luminaire with a fixed lumina to examine the concentrations of Amyloid-β40 (Aβ40) and amyloid-β42 (Aβ42) by enzyme-linked immunosorbent assay. The phosphorylation of Tau, AKT, and mTOR protein levels were examined by Western blotting.
Results: Significant differences of Aβ42 concentration between exposure and control to multi-frequency luminaire group were found ($p<0.05$), exposure: 92.25 ± 5.34, 99.5 ± 5.95, 100.63 ± 11.03 and 97.13 ± 7.77 pg/ml at 15, 30, 45 and 60 min in contrast to 107.6 ± 3.78, 107 ± 2.83, 108 ± 3.32 and 107 ± 3.81 pg/ml, respectively. Moreover, The phosphorylation of AKT, mTOR ,Tau, and 4E-BP1 proteins were inhibited by the multi-frequency luminaire in SH-SY5Y cells.
Conclusions: Our study showed the multi-frequency luminaire involved in the inhibition of secretion of Aβ42 and inhibition of p-Tau protein expression through the mTOR/4E-BP1/Tau signaling pathway in SH-SY5Y cells. Exposure to the multi-frequency luminaire may possibly improve the symptoms of AD patient. The detailed mechanisms and possible clinical benefits for the multi-frequency luminaire should be determined.

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P0224 / #2679

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

ANTI-AMYLOID BETA ANTIBODIES INDUCES NEUROTOXICITY FOLLOWING ACTIVATION OF ALLERGENIC-RELATED PROTEINS: IMPLICATION FOR AMYLOID-RELATED IMAGING ABNORMALITIES.

Mourad Tayebi, Utpal Adhikari
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Aims: Recent published clinical trial safety data showed that 41% of Alzheimer patients experienced amyloid-related imaging abnormalities (ARIA), marks of microhemorrhages and oedema in the brain, following administration of Biogen's Aduhelm/ aducanumab (amino acids 3-7 of the Aβ peptide). Similarly, Janssen/Pfizer's Bapineuzumab (amino acids 1-5 of the Aβ peptide) and Roche's Gantenerumab (amino acids 2–11/18–27 of the Aβ peptide) also displayed ARIA in clinical trials, including microhemorrhage and focal areas of inflammation or vasogenic oedema respectively. The molecular mechanisms underlying ARIA caused by therapeutic anti-Aβ antibodies remain largely unknown, however, recent reports demonstrated that anti-prion antibodies activate both the neuronal apoptotic and allergenic proteomes following cross-linking the cellular prion protein.
Methods: Liquid Chromatography and Mass Spectrometry Flow Cytometry Bioinformatics
Results: We report that treatment of human primary neurons and human induced pluripotent stem cells (iPSC) co-cultured with human primary microglia with anti-Aβ1-6, or anti-Aβ17-23 antibodies activate a significant number of both apoptotic and allergenic-related proteins as assessed by mass spectrometry. Interestingly, a large proportion of the identified proteins included cytokines such as IL-4, IL-12, and IL-13 suggesting a type-1 hypersensitivity response. Following flow cytometry analysis, several proinflammatory cytokines such as GM-CSF, IL-6, IL-9, IL-12, IL-17A, IFN-α, and TNF-α were significantly elevated following anti-Aβ1-6, or anti-Aβ17-23 antibody treatment.
Conclusions: These results justify further investigation of the molecular mechanisms of ARIA during immunotherapy study trials of AD.

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P0225 / #2304

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

IMMUNOGENICITY AND EFFICACY OF NOVEL MULTITEP-BASED ADJUVANTED VACCINES TARGETING PYROGLUTAMATE-MODIFIED ABETA PEPTIDES, PE3ABETA AND PE11ABETA

Anahit Ghochikyan[1], Karen Zagorski[1], Olga King[1], Armine Hovakimyan[1], Irina Petrushina[2], Tatevik Antonyan[1], Jean Paul Chadarevian[3], Gor Chailyan[1], Manush Ghazaryan[1], Hayk Davtyan[4], Matt Blurton-Jones[5], David Cribbs[2], Michael Agadjanyan[1]
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Aims: Our long-standing tenet is that the Aβ vaccine initiated in non-demented at-risk subjects can prevent/delay pathological processes and disease onset. The pyroglutamate-modified Aβ variants are neurotoxic and aggregation-prone, playing a role in triggering amyloid pathogenesis. pE3Aβ is found in the extracellular plaques and intraneuronal depositions as early as preclinical AD. We have previously demonstrated that our proprietary vaccine platform MultiTEP is highly immunogenic in adult non-human primates (NHP) and AD mouse models, capable of generating robust antibody responses against Aβ, Tau, and α-Synuclein. Now, we developed MutiTEP-based vaccines targeting pE3Aβ and pE11Aβ.
Methods: A genetically engineered variant of MultiTEP was generated to enable chemoselective bioconjugation of synthetic peptides under mild aqueous conditions. An AD mouse model (5XFAD) and adult NHPs were immunized with adjuvanted vaccines intramuscularly. Antibody titers were tested via ELISA. The reduction of brain pathology in 5xFAD mice was determined via biochemical assessment (MSD, ELISA) and IHC.
Results: Both vaccines induced robust immune responses in inbred mice and outbred monkeys with immune systems similar to humans. The generated antibodies were highly selective for pE3Aβ and pE11Aβ, respectively, and recognized Aβ plaques in brains from AD cases. Importantly both vaccines significantly reduced AD-like pathology in 5xFAD mice.
Conclusions: Elly-Lilly reported that patients injected with anti-pE3Aβ monoclonal antibody (mAb) donanemab showed a 32% slower decline on iADRS than placebo. While promising, the regular injections of monoclonal antibodies in the preventive setting are not practical due to the frequent and invasive nature of the costly treatment. Our vaccines targeting pE3Aβ and pE11Aβ are feasible alternatives to mAbs. We believe that preventive vaccination will maintain a therapeutic level of antibodies to inhibit the aggregation of pathological Aβ and delay the disease onset.

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P0226 / #1830

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

INDUCTION OF AN EFFECTIVE ANTI-AMYLOID-B HUMORAL RESPONSE IN AGED MICE

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Aims: Objective. Aging-related decline in immune functions, termed immunosenescence, is a primary cause of reduced vaccine efficiency in the elderly, due to impaired induction of cellular and humoral responses to new antigens, especially if the response is T cell dependent. Consequently, the elderly are susceptible to a more severe morbidity following infections, and exhibit more prolonged and frequent hospitalization, and a higher mortality rate than in the general population. Therefore, there is an increasing need to develop vaccination strategies that overcome immunosenescence, especially for aging-related diseases such as Alzheimer's disease (AD). This study aimed to develop a new vaccination strategy that harnesses memory-based immunity, which is less affected by aging.
Methods: Methods. Aged 5xFAD mice, which model early onset AD, as well as aged wildtype mice exhibit a dramatic reduction in anti-Amyloid-beta (A-beta) antibody (Ab) production. We therefore aimed to reverse this process by inducing memory response at a young age. To this end, young mice were primed with a DNA vaccination against the vaccine carrier Hepatitis B surface antigen (HBsAg). At an advanced age, primed mice were immunized with an A-beta$_{1-11}$ fused to HBsAg.
Results: Results. This vaccination scheme elicited a markedly higher A-beta specific antibody titer than vaccinating aged unprimed mice with the same construct. Importantly, this vaccine strategy more efficiently reduced cerebral A-beta levels and altered microglial phenotype
Conclusions: Conclusions. Overall, we provide evidence that priming with an exogenous antigen carrier can overcome impaired humoral responses to self-antigens in the elderly, paving the route for a potent immunotherapy to AD.

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P0227 / #2232

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

NEUROTOXIC AB42 OLIGOMERS CAN BE SELECTIVELY DETECTED AND NEUTRALIZED BY SINGLE DOMAIN ANTIBODIES

Liliana Napolitano[1], Alessandra Bigi[1], Devkee Vadukul[2], Francesco Aprile[2], Fabrizio Chiti[1], Cristina Cecchi[1], Roberta Cascella[3]
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Aims: Extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles of the hyperphosphorylated tau protein are the main hallmarks of Alzheimer's disease (AD). Aβ aggregation consists of a complex chain of nucleation events producing soluble oligomer intermediates, which are the major neurotoxic agents. The transient nature of these oligomers makes their isolation and characterization very challenging. Single domain Abs (sdAbs), composed only of a variable domain of the heavy chain with high specificity and affinity, appear as promising tools for an early accurate diagnosis and therapy for AD.
Methods: An *in vitro* and *in vivo* screening of different sdAbs was performed, selecting those targeting $A\beta_{42}$ oligomers or fibrils with high specificity using immunoassays and the super resolution stimulated emission depletion (STED) microscopy. The potential of sdAbs to prevent $A\beta_{42}$-induced cytotoxicity in neuronal cells was also investigated. Then, the sdAbs were used to selectively detect $A\beta_{42}$ assemblies in the cerebrospinal fluid (CSF) of AD patients and controls by ELISA and dot-blot analysis. Finally, the ability of sdAbs to counteract the detrimental effects caused by $A\beta_{42}$ was also investigated in cultured neuronal cells treated with CSF samples.
Results: sdAbs can detect neurotoxic Aβ assemblies both *in vitro* and in cultured cells and prevent the associated neuronal dysfunction in our cell models. Notably, sdAbs can significantly distinguish Aβ oligomers and fibrils in the CSF of AD patients and controls and neutralize their toxic behaviour.
Conclusions: All these data provide a solid foundation for the development of sdAbs-based immunodiagnostic tools that can selectively detect aggregate conformations in complex mixtures such as biological samples for an early differential diagnosis of AD. Furthermore, our study contributes to the generation of novel therapeutic approaches for AD and other neurodegenerative disorders.

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P0228 / #721

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

NOVEL VACCINE CANDIDATES AGAINST MISFOLDED AB PEPTIDE

Aishwarya Sriraman, José Flores-Fernandez, Razieh Kamali Jamil, Yongliang Wang, Holger Wille
Centre for Prions and Protein Folding Diseases, University of Alberta, Department Of Biochemistry, Edmonton, Canada

Aims: Alzheimer's disease (AD) is thought to be caused by the misfolding of the amyloid beta (Aβ) and tau proteins, which both adopt a beta-sheet rich conformation and form oligomers and amyloid fibrils. Diverse attempts have been made to develop vaccines as prophylactics for AD employing these proteins and peptides in their linear form, but they lacked structural specificity and functionality. Here, we present a novel approach to design vaccine candidates based on the structure of Aβ fibrils that present the epitopes in a structurally-controlled manner.
Methods: The innocuous HET-s prion that adopts a beta-sheet rich conformation natively was engineered in a structurally-controlled manner to design vaccine candidates based on recent structures of Aβ fibrils solved by cryo-EM. Constructs were expressed in *E. coli* cells, purified, refolded, controlled for their structural fidelity and injected into wild-type mice. The specificity of the immune responses was tested against non-neurologic controls and Alzheimer disease brain homogenates.
Results: The purified and refolded Aβ vaccine candidates exhibited the expected self-assembly into amyloid fibrils by negative stain electron microscopy. The antisera from wild-type mice, immunized with these recombinant antigens, were found to be specific for disease-specific antigens in AD brain samples, but did not recognize non-neurologic control samples.
Conclusions: The Aβ vaccine candidates elicited specific immune responses targeting AD disease antigens. Next, we are going to test their efficacy in a transgenic mouse model of AD and watch for a delay or reduction in the formation of pathogenic assemblies.

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International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 28 - April 1, 2023 | Gothenburg, Sweden
AD/PD 2023 March 28 - April 1 GOTHENBURG

P0229 / #2707

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

IN VITRO AND IN VIVO PROFILE OF AC-0027875, A NOVEL GAMMA-SECRETASE MODULATOR FOR THE PREVENTION AND TREATMENT OF ALZHEIMER´S DISEASE

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Aims: In light of recent developments in the field, gamma-secretase modulators have re-emerged as a promising class of small-molecule anti-amyloidogenic agents for the treatment of early stages of Alzheimer´s disease.AlzeCure Pharma has therefore developed the novel gamma-secretase modulator AC-0027875 within its research platform, Alzstatin. The subsequent in vitro profiling of the compound and the assessment of its in vivo properties were the focus of the presented studies.
Methods: The in vitro effect of AC-0027875 on the production of various Abeta-peptides was explored in HEK/APPswe cells, mouse primary cortical neurons and human induced pluripotent stem cell-derived cortical neurons using immunoassays specific for Abeta42 and additional gamma-secretase-generated Abeta products. In the in vivo studies, AC-0027875 was administered orally to C57BL/6J mice, and plasma and brain were collected. The compound exposure in plasma and brain tissue was determined by LC-MS/MS. The reduction of soluble Abeta42 in the brain was determined by ELISA.
Results: The GSM AC-0027875 displayed high potency in HEK/APPswe cells, mouse primary cortical neurons and human cortical neurons in reducing Abeta42 and Abeta40 levels. The compound showed a clear Abeta modulation pattern in line with the effect of a gamma-secretase modulator with increased levels of the shorter peptides, Abeta37 and Abeta38. AC-0027875 also showed potent effects in vivo, displaying significant reduction of Abeta42 levels in brains of C57BL/6J mice.
Conclusions: The GSM AC-0027875 shows a promising in vitro and in vivo profile and therefore is a suitable candidate for further development for the prevention and treatment of Alzheimer´s disease.

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P0230 / #2494

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

BACE1 DELETION IN THE ADULT REVERSES EPILEPTIFORM ACTIVITY AND SLEEP-WAKE DISTURBANCES IN AD MICE MODELS

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Aims: Alzheimer's disease (AD) increases the risk for seizures and sleep disorders. It is unclear whether β-site amyloid precursor protein (APP) cleaving enzyme-1 (BACE1) deletion will ameliorate these phenotypes in AD mouse models.
Methods: We performed video-EEG/EMG recordings in 12-hour light/12-hour dark cycle in nine-month-old 5xFAD and APP KI (APP $^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$) mice treated with or without BACE1 inhibitor AZD3293 as well as adult BACE1$^{fl/fl/thyCre}$, BACE1$^{fl/fl/aldh1l1CreERT2}$, and BACE1$^{fl/fl/ubcCreERT2}$ mice. The epileptiform and sleep-wake activity were scored with Sirenia Seizure and Sleep Pro software. Animals were euthanized at the end of EEG recordings and brains were collected for immunohistochemistry and western blotting.
Results: We show that germline deletion of (BACE1) in neurons, and not astrocytes, increases epileptiform activity, while BACE1 deletion at adult ages shows no alteration to the normal EEG waveform. Sequentially deleting BACE1 in the adult is able to reverse epileptiform activity in 5xFAD mice, while the BACE1 inhibitor AZD treatment dramatically increases epileptiform spiking in both 5xFAD and APP KI mice. Also, sleep-wake pathologies of increased wakefulness and decreased NREM and REM sleep are evident in both 5xFAD and APP KI mice, but BACE1 inhibition in the adult reverses plaque load and sleep disturbances only in 5xFAD mice but not APP KI mice. Further mechanistic studies show that APP KI mice had more diffuse plaques and impaired plaque-associated microgliosis compared to 5xFAD mice, suggesting that the reversal of plaques and functional differences may be due to differences in microglial dysfunction of Aβ clearance.
Conclusions: Our study provides insight into functional impairments of epileptiform activity and sleep disruption in two AD mouse models, BACE1 deletion and inhibition rescues deficits in 5xFAD mice but not APP KI mice.

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POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

CHARACTERIZATION BY FLIM AND EM OF GLUTAMATE TRANSPORTER GLT-1 AND PS1/Γ-SECRETASE INTERACTION IN ALZHEIMER'S DISEASE CONTEXT

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Aims: Presenilin 1 (PS1)/γ-secretase mutations cause early-onset familial Alzheimer's disease (fAD). Clinical data revealed that patients with presenilin mutations have significantly higher incidence of epileptiform activity, suggesting that fAD PS1 mutations could contribute to hyperactivity. We have recently discovered an interaction between PS1, and the glutamate transporter GLT-1/EAAT2 in AD context. This interaction plays a role in GLT-1 trafficking and function where PS1 acts as a chaperone. Our objectives are: i) Where the interaction site is located; ii) Designing a cell permeable peptide (CPP) to modulate this interaction iii) Establish a 3D structure of the GLT-1/PS1 interaction and CPP binding site by cryo-EM.
Methods: To identify the PS1/GLT-1 interaction site, we have have performed an alanine scanning within GLT-1/PS1 proteins paired with FLIM in intact cells. Next, we sought to determine if it is possible to block these interaction sites using CPP. These CPPs present sequence from HIV and sequence from native GLT-1/PS1 proteins, coupled to a fluorophore for cells uptake monitoring. Finally, a protocol for GLT-1 and PS1 purification has been created to establish the cryo-EM structure of the PS1/GLT-1 complex and the exact binding site of the CPP.
Results: Based on the alanine mutants scanning performed by FLIM, we discovered two potential interaction sites in GLT-1 transmembrane domain (TM) 4 and TM5, while PS1 presents one interaction site in the TM6. The purification protocol allowed to observe the GLT-1/PS1 complexes by EM.
Conclusions: The identification of PS1/GLT-1 interaction sites are critical for modulation of both PS1 and GLT-1 function. CPP as drug could potentially induce functional changes in GLT-1 and PS1. The regulation of glutamate uptake in the synaptic cleft could be beneficial for controlling epileptiform activity in AD patients and beyond.

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P0232 / #1600

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

BACE INHIBITION AND SYNAPTIC DYSFUNCTION: MECHANISTIC INSIGHTS FROM IPSC-DERIVED HUMAN NEURONS

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Aims: Amyloid precursor protein (APP) β-cleavage by β-site APP-cleaving enzyme (BACE) is believed to be the rate-limiting step of amyloid generation, and therefore a focal target for Alzheimer´s disease (AD) treatment. Several BACE inhibitors reached phase-III clinical trials, showing reduction in amyloid load in the brain, but had to be discontinued, with reported cases of cognitive side effects. Multiple animal studies have shown that BACE inhibition decreases spine density, impairs synaptic transmission and plasticity; however the mechanisms are still under investigation. Here we test the hypothesis that reduced β-site cleavage of APP in neurons results in accumulation of APP in synapses, leading to impaired synaptic functionality.
Methods: Human cortical neurons derived from induced pluripotent stem cells (iPSC) were exposed to the BACE inhibitor LY2886721. Presynaptic and axonal protein levels in the cell supernatant were investigated using IP-MS or ELISA, as markers of synaptic or neuroaxonal degeneration. APP accumulation in synapses was investigated using immunocytochemistry or western blot of cell lysates or isolated synaptic terminals.
Results: Treatment with LY2886721 decreased secretion of Aβ and soluble APPβ by 75%, with no changes in soluble APPα secretion. Increased levels of presynaptic proteins, but unchanged levels of neurofilament light chain in the cell supernatant of treated neurons suggested synaptic degeneration without neuroaxonal damage. Furthermore, BACE inhibition was associated with time-dependent intracellular accumulation of full-length APP, particularly in isolated synaptic terminals. Down-regulation of APP prior to the treatment will prove if the accumulation of APP at the synaptic compartment is responsible for BACE inhibition-dependent synaptic loss.
Conclusions: BACE inhibitors are still a precious resource to delay or prevent AD progression. Unraveling the mechanisms by which these drugs affect synaptic functionality is important for a reassessment of this treatment strategy.

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P0233 / #941

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

GAMMA-SECRETASE EXOSITES AS TARGETS FOR SUBSTRATE-SELECTIVE LOWERING OF ABETA GENERATION

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Aims: Processing of the amyloid precursor protein substrate C99 into harmful amyloid-β peptide (Aβ) species by γ-secretase is critically implicated in Alzheimer´s disease (AD) pathogenesis. We previously reported that recruitment of C99 involves binding of its N-terminal extracellular domain to exosites, substrate-binding sites that are remote from the γ-secretase active site. Following up on these findings, we now asked whether C83 also interacts with these exosites or bypasses them, and whether the exosite interactions of C99 might be targetable to inhibit Aβ generation.
Methods: A combination of established cell-free and cell-based methods including substrate photocrosslinking and cleavage assays as well as brain Aβ analysis in transgenic mice was used.
Results: We show that the N-terminally shorter extracellular domain of the non-amyloidogenic C83 substrate also interacts with γ-secretase exosites, but more weakly than C99. Moreover, we interestingly found that bulky aromatic mutations within the 16 amino acid extension of C99 interfere with exosite-binding and inhibit substrate cleavage. Likewise, peptides binding to the C99 N-terminus that selectively inhibit Aβ production in a Notch-sparing manner and lower Aβ in an AD mouse model interfere with exosite-binding of C99.
Conclusions: The N-terminal extracellular domains of C99 and C83 both interact with γ-secretase exosites. Exosite-interactions of the C99 N-terminal region with γ-secretase can impact on substrate cleavage and indicate that interfering with exosite-interactions of C99 may provide a means for selectively modulating amyloidogenic substrate processing to lower Aβ.

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P0234 / #165

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

ELUCIDATING ANTI-AMYLOID POTENTIAL OF ORIENTIN - IN SILICO AND IN VITRO APPROACHES

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Aims: Alzheimer's disease (AD), neurodegenerative disorder that continues to burden the global due to increase in number of elderly individuals. Beta-amyloid hypothesis suggests that beta-amyloid (Aβ) is the main culprit in AD pathogenesis. Therefore, targeting Aβ biosynthesis could be one of the therapeutic interventions. Orientin has been known to possess neuroprotective properties, yet its role in Aβ biosynthesis remains unexplored. This study characterises and validates the ability of orientin to bind and inhibit secretases activities via *in silico* and *in vitro* studies.
Methods: The molecular docking of orientin against secretases performed through AutoDock tools, binding energy and RMSD values were analysed. The binding characteristics of orientin against secretases were further validated through *in vitro* cell-based ELISA assay on Aβ -stimulated SH-SY5Y cells.
Results: The molecular docking analysis revealed that orientin binds to α, β and γ-secretase with binding energy of -9.07, 11.84 and -11.64 kcal/mol respectively. The binding interactions suggested that orientin is more favorably bind to β-secretase, with the following arrangement β-secretase > γ-secretases > α-secretase. While the *in vitro* result suggested orientin (10 μM) exhibited 7% inhibition on α-secretase, 14% on β-secretase and 8.7% on γ-secretase; while 20 μM exhibited 10% of inhibition on α-secretase, 13.9% on β-secretase and 17.6% on γ-secretase.
Conclusions: This study suggested orientin has inhibitory effects especially on β- and γ-secretases. Further studies on beta-amyloid biogenesis could investigate the overall gene expression of secretases on APP and the inhibitory effects of orientin on secretases using knock out genes via *in vivo* study for more holistic perspective.

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P0235 / #2706

POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

EFFECTS ON NEUROPROTECTION AND NEUROPLASTICITY BY THE CLINICAL COMPOUND ACD856, A NOVEL POSITIVE MODULATOR OF TRK-RECEPTORS FROM THE NEURORESTORE® PLATFORM.

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Aims: Given that the neurotrophins are known to exert neuroprotective effects and to increase neuronal plasticity, the major objective of this study was to assess the effects of the clinical stage compound ACD856, a positive allosteric modulator of Trk-receptors, on neuronal plasticity and neuroprotection.
Methods: In vitro effects of ACD856 were investigated in embryonal primary cortical or hippocampal neurons by measuring metabolic activity, phosphorylation of ERK1/2 and synaptic markers. Effects on synaptic markers were also studied in PC12 cells. Effects on neuronal plasticity were further investigated in fear-conditioning cognition model and a model of depression in vivo.
Results: ACD856 demonstrated neuroprotection against energy-deprived or amyloid-beta induced neurotoxicity. The neurotrophins BDNF and NT-3 had a substantial effect on phosphoERK1/2 levels in cortical neurons when compared to other neurotrophic factors. Interestingly, ACD856 demonstrated an effect on the levels of phosphorylated ERK1/2 in neurons, suggesting that one of the effects of the compound is to modulate phospho-ERK1/2 levels. The synaptic protein SNAP25 was increased after treatment with ACD856, and the in vivo experiments suggest a long-term effect of ACD856 on neuronal plasticity as judged by enhanced cognitive abilities and a sustained anti-depressant effect.
Conclusions: The results indicate that ACD856 can act in a neuroprotective manner, modulate phospho-ERK1/2 levels and improve neuronal plasticity or in other ways increase network connectivity. The fact that ACD856 shows both symptomatic and potential disease-modifying effects is of high importance for the future treatment of patients with Alzheimer's disease and other neurodegenerative disorders.

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P0236 / #1767

POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

ROSMARINIC ACID EXHIBITS ANTICANCER EFFECTS VIA MARK4 INHIBITION

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Aims: Microtubule affinity regulating kinase (MARK4) is a potential drug target for different types of cancer as it controls the early step of cell division. In this study, we have screened a series of natural compounds and finally identified rosmarinic acid (RA) as a potential inhibitor of MARK4.
Methods: Molecular docking and 500 ns all-atom simulation studies suggested that RA binds to the active site pocket of MARK4. Additionally, fluorescence-based binding and Isothermal titration calorimetry were used to ascertain the actual binding. Moreover, cell-based tau-phosphorylation studies were carried out to have further insight.
Results: Molecular docking and 500 ns all-atom simulation studies suggested that RA binds to the active site pocket of MARK4, forming enough number of non-covalent interactions with critical residues and MARK4-RA complex is stable throughout the simulation trajectory. RA shows an excellent binding affinity to the MARK4 with a binding constant (K) of 10^7 M^{-1}. Furthermore, RA significantly inhibits MARK4 activity (IC_{50} = 6.204 µM). The evaluation of enthalpy change (ΔH) and entropy change (ΔS) suggested that the MARK4-RA complex formation is driven by hydrogen bonding and thus complexation process is seemingly specific. The consequence of MARK4 inhibition by RA was further evaluated by cell-based tau-phosphorylation studies, which suggested that RA inhibited the phosphorylation of tau. The treatment of cancer cells with RA significantly controls cell growth and subsequently induces apoptosis.
Conclusions: Our study provides a rationale for the therapeutic evaluation of RA and RA-based inhibitors in MARK4 associated cancers and other diseases.

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POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

LEUCETTINIB-21, A DYRK1A KINASE INHIBITOR DRUG CANDIDATE AIMING AT THE CORRECTION OF COGNITIVE DISABILITIES IN PEOPLE WITH DOWN SYNDROME OR ALZHEIMER'S DISEASE

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Aims: Some cognitive disabilities associated with **Down syndrome** (**DS**) and **Alzheimer's disease** (**AD**) can be attributed to an excessive production/activity of **DYRK1A** (dual specificity, tyrosine phosphorylation regulated kinase). Genetic and pharmacological inhibition of DYRK1A corrects cognitive deficits in DS/AD animal models.
Methods: Inspired by **Leucettamine B**, a marine sponge natural product, we synthesized, optimized and extensively characterized >500 analogues, **Leucettines**, followed by a second-generation family, **Leucettinibs** (>620 analogues).
Results: Leucettinibs display high inhibitory potency towards DYRK1A (0.5-10 nM IC50 values). A comparative study carried out with 56 reported DYRKs/CLKs inhibitors shows that Leucettinibs is among the most potent inhibitors of this kinase. Leucettinibs inhibit the phosphorylation of several proteins at DYRK1A-specific sites in cell cultures. Leucettinibs are orally available, brain permeable and inhibit endogenous brain DYRK1A. Pharmacokinetics studies show dose-dependent uptake in blood plasma. Leucettinibs (p.o., 0.3-0.5 mg/kg) correct spatial and learning memory disorders in various DS/AD animal models. This strong proof-of-concept supports the idea that pharmacological inhibition of DYRK1A might correct memory disorders in DS and AD patients. A clinical drug candidate, **Leucettinib-21**, was selected following a stringent multiparametric GO/NO GO decision tree. *In vitro* and *in vivo* safety studies show that Leucettinib-21 is extremely well tolerated. Regulatory preclinical toxicity studies (rats, mini-pigs), formulation and synthesis of a GMP batch have been carried out, in preparation to clinical phase 1 studies in healthy volunteers. An overview of the chemical, biological, pharmacological and safety properties of Leucettinib-21 will be presented.
Conclusions: Leucettinib-21 display favorable pharmacological and encouraging safety properties. Pending confirmation of its safety in animals (2022) and in healthy volunteers (2023), this DYRK1A targeting drug candidate will be evaluated for its ability to correct cognitive disabilities associated with DS and AD.

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POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

MARK4 INHIBITED BY ACHE INHIBITORS, DONEPEZIL AND RIVASTIGMINE TARTRATE: INSIGHTS INTO ALZHEIMER'S DISEASE THERAPY

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Aims: Microtubule affinity-regulating kinase (MARK4) plays a key role in Alzheimer's disease (AD) development as its overexpression is directly linked to increased tau phosphorylation. MARK4 is a potential drug target of AD and is thus its structural features are employed in the development of new therapeutic molecules. Donepezil (DP) and rivastigmine tartrate (RT) are acetylcholinesterase (AChE) inhibitors and are used to treat symptomatic patients of mild to moderate AD. In keeping with the therapeutic implications of DP and RT in AD, we performed binding studies of these drugs with the MARK4.
Methods: We performed computational analysis, namely, Molecular docking and molecular dynamic simulation analysis. Computational observations were further validated by in vitro binding assays, viz. fluorescence binding experiments at different temperatures and Isothermal titration calorimetry.
Results: Both DP and RT bound to MARK4 with a binding constant (K) of 10^7 M^{-1}. The temperature dependency of binding parameters revealed MARK−DP complex to be guided by static mode while MARK−RT complex to be guided by both static and dynamic quenching. Both drugs inhibited MARK4 with IC_{50} values of 5.3 μM (DP) and 6.74 μM (RT). The evaluation of associated enthalpy change (ΔH) and entropy change (ΔS) implied the complex formation to be driven by hydrogen bonding making it seemingly strong and specific. Isothermal titration calorimetry further advocated a spontaneous binding. In vitro observations were further complemented by the calculation of binding free energy by molecular docking and interactions with the functionally-important residues of the active site pocket of MARK4.
Conclusions: This study signifies the implications of AChE inhibitors, RT, and DP in Alzheimer's therapy targeting MARK4.

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P0239 / #1062

POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

FRAGMENT-BASED DISCOVERY OF A NOVEL, BRAIN PENETRANT, ORALLY ACTIVE HDAC2 INHIBITOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Aims: Histone deacetylase (HDAC) enzymes play a key role in the regulation of chromatin unfolding and gene expression. Increased levels of HDAC2 have been observed in the brain of mouse models of neurodegenerative disease and in patients with Alzheimer's disease. HDAC2 was found to be responsible for the reduction of histone acetylation and the decrease of expression of key genes associated with learning and memory, suggesting that brain penetrant HDAC2 inhibitors could be beneficial for the treatment of neurodegenerative diseases.
Methods: We have applied our fragment-based drug discovery (FBDD) platform to screen our proprietary fragment library against the full length human HDAC2 using a combination of protein thermal shift (Tm) and X-ray crystallography.
Results: Fragment screening enabled us to identify several fragment hits which bound throughout the catalytic site of the protein, from the "entrance tunnel" to the deepest part of the "foot pocket". Guided by numerous protein-ligand crystal structures, we successfully evolved the initial fragment hits into a novel, potent, brain penetrant HDAC inhibitor capable of significantly increasing histone H4K12 acetylation levels in the brain when dosed orally to mice.
Conclusions: HDAC inhibitors have been primarily developed for cancer treatment. It has been reported that a number of HDAC inhibitors have low brain uptake due to poor blood-brain barrier permeability, highlighting their limitations as clinical candidates for the treatment of neurodegenerative diseases. We have shown that FBDD is a suitable technology for the identification of potent HDAC2 inhibitors with *in vivo* distribution characteristics suitable for CNS indications.

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P0241 / #1394

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

NEUROPROTECTIVE EFFECTS OF FLUOROETHYLNORMEMANTINE (FENM) AFTER CHRONIC INFUSION BY ALZET PUMPS IN THE AB25-35 MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Fluoroethylnormemantine (FENM) is an analogue of Memantine (MEM) originally synthesized as a precursor for PET imaging. FENM, administered intraperitoneally (ip), prevented the toxicity, neuroinflammation and learning deficits in Swiss mice intracerebroventricularly (icv) injected with oligomerized $A\beta_{25-35}$ peptide, an acute model of Alzheimer's disease. The drug showed some superior efficacy to MEM and an absence of direct amnesic effect at high doses. We here compared the efficacy of FENM after ip repeated injections and subcutaneous (sc) chronic infusion with Alzet pump, in $A\beta_{25-35}$-treated C57Bl/6J mice.
Methods: At different timepoints, memory deficits were evaluated using spontaneous alternation in the Y-maze and a novel object test. Toxicity in the mouse hippocampus or cortex was analyzed biochemically or morphologically, using markers of apoptosis, neuroinflammation and oxidative stress. Expression of NMDA receptor subunits and its scaffold protein PSD-95 were also analyzed in hippocampal homogenate or synaptosomal preparations by western blotting.
Results: Data showed that sc-infused FENM is effective at doses in the 0.03-0.3 mg/kg/day range. Learning deficits, neuroinflammation (astrocytic and microglial reactions, cytokines release), oxidative stress and apoptotic markers were attenuated after sc-infusion of FENM. Expression levels of PSD-95 and GluN2A/GluN2B ratio were also analyzed. Finally, long-term effects of FENM and MEM was compared after repeated ip-injections (0.3 mg/kg) in $A\beta_{25-35}$-treated mice. Animals' spatial working memory was evaluated once-a-week using spontaneous alternation. FENM effect was maintained during 2 months of treatment while MEM effect was lost after 4 weeks. When drug treatment was stopped, FENM-treated mice maintained mnesic scores for 20 days, suggesting long-term effects.
Conclusions: These data showed efficacy of sc-infused FENM in the $A\beta_{25-35}$ mouse model. Moreover, evidence was obtained suggesting a long-term and putatively disease-modifying effect of FENM, absent for MEM.

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P0242 / #975

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

NEUROPROTECTIVE EFFECT OF TROPISETRON IN STREPTOZOTOCIN INDUCED ANIMAL MODEL OF ALZHEIMER'S DISEASE.

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Aims: Aim:- Neuroprotective effect of tropiosetron in STZ induced Animal Model of Alzheimer's disease. Objectives:- To investigate the effect of Tropisetron on cognitive functions and memory in STZ induced animal model of Alzheimer's disease. To determine the potential of Tropisetron on behavioral, biochemical and histopathological alterations in STZ induced animal model of Alzheimer's disease.
Methods: All the experimental animals were divided into 6 groups with 8 animals in each group. After 14 days of surgery, injection of treatment drug (Tropisetron) and administration of standard drug (donepezil) has been started and continued for further 15 days. The protocol schedule, behavioural parameter and the biochemical analyses has been formulated into experimental design Body Weight Behavioural analysis 1. Open Field Test 2. Object Recognition Test 3. Morris Water Maze Biochemical analysis 1. Catalase 2. GSH 3. Lipid Peroxidation(MDA) 4. Nitrite Estimation 5. AChE Histopathology analysis

Region	Stain	Inference
Hippocampus	Haematoxylin & Eosin	Neurodegeneration
Cerebral cortex	Haematoxylin & Eosin	Narrowing of cortical ribbons

Results: The current study indicates the neuroprotective effect of tropisetron against ICV-Streptozotocin induced animal model of Alzheimer's disease. In the current study tropisetron has shown a significant decrease in the behavioral, biochemical and histological alterations caused by ICV-STZ infusion.
Conclusions: In conclusion, the present study is designed to explore the neuroprotective effect of Tropisetron in ICV-STZ induced neurotoxicity in rats. On the basis of obtained results in the present study, the following findings are concluded.

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P0243 / #1952

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

ALZHEIMER'S DISEASE & THE GLUTAMATERGIC SYSTEM: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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Aims: Glutamate is the major excitatory neurotransmitter in the human brain, and regulating its homeostasis is paramount for brain functioning. Increases in glutamate concentration in the synaptic cleft lead to a phenomenon called glutamatergic excitotoxicity, causing progressive neuronal death. This has been described as a common feature in neurodegenerative disorders, including Alzheimer's Disease (AD). Thus, we sought to perform a systematic review with meta-analysis to assess whether the glutamatergic system is consistently altered in AD patients.
Methods: PubMed and Web of Science databases were searched for articles evaluating the glutamatergic system in AD. Included reports quantified glutamate-related selected outcomes in healthy age-matched controls and AD individuals. Pooled effect sizes were determined with standardized mean differences(SMD) using Hedge G method with random effects and adjusted by false discovery rate. Risk of bias was investigated using adapted JBI questions for Case-Control Studies, and heterogeneity was examined by I^2 statistics. This review complied with PRISMA (2020) guidelines and was registered at PROSPERO(CRD 42022299518).
Results: We included 62 reports, comprising 2047 healthy age-matched controls and 2160 AD individuals.In a composite of cortical and subcortical regions termed "whole brain"(WB), we observed functional changes, including hypofunctional NMDAR (9 studies;N=93C/97AD;SMD=-0.41;I^2=91.53%;adj.p<0.001) and decreased glutamate uptake (12 studies;N=80C/92AD;SMD=-0.81;I^2=82.70%;adj.p<0.001) in AD patients.In the same composite of regions, AD patients also presented decreased expression of the NMDAR regulatory subunit NR2B (4 studies;N= 23C/28AD;SMD =-1.07; I^2=41.81%; adj.p <0.001), decreased AMPAR-GluA2/3 (7 studies;N=68C/75AD;SMD=-0.63;I^2=95.55%;adj.p=0.046).

A

Marker	Region	SMD	Adj. p-value	Control (N)	AD(N)	Bias score
AMPAR - GluA1	EC	-1.08	0.003	18	21	3 0 0
AMPAR - GluA1	HP	-1.20	< 0.001	22	22	0 1 2
AMPAR - GluA2/3	WB	-0.63	0.046	68	75	1 2 4
NMDARa	WB	-0.60	< 0.001	93	97	3 5 1
NMDARa	CX	-0.58	0.006	73	79	2 4 1
NMDAR - NR2B	WB	-1.07	< 0.001	23	28	1 2 1
NMDAR - NR2B	EC	-1.49	0.005	20	20	1 1 1
NMDAR - NR2B	HP	-0.94	0.004	23	28	1 3 0
Glu uptake	WB	-0.80	< 0.001	80	92	6 5 1
Glu uptake	CX	-1.04	< 0.001	79	89	6 4 1
Glu uptake	HP	-0.76	0.015	26	22	1 3 0

High risk Some concerns Low risk

B

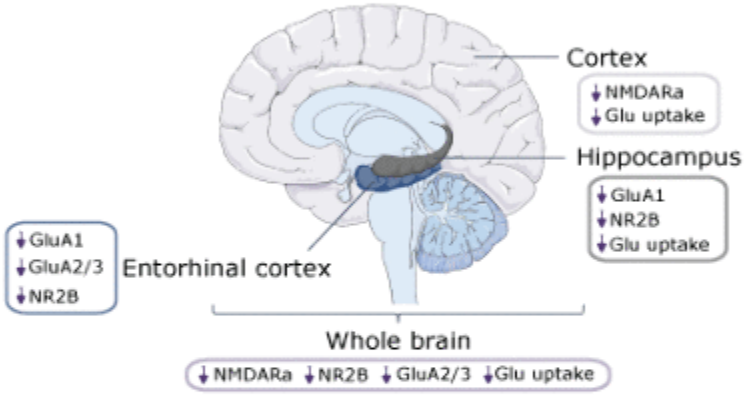

Figure 1. Significant glutamatergic changes in the AD brain. A. Effect estimate is represented as standard mean difference (SMD) by analyzed region. Bias score categories are illustrated by colored circles and the number of studies in each category is indicated on the right side. **B.** Brain illustration indicating the analyzed regions with significant alterations in the selected glutamatergic outcomes.

Abreviations: whole brain (WB); cortex (CX); entorhinal cortex (EC); hippocampus (HP); glutamate (Glu); NMDARa (N-methyl-D-Aspartate receptor activated); NMDAR subunit (NR); alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR); AMPAR subunit (GluA);

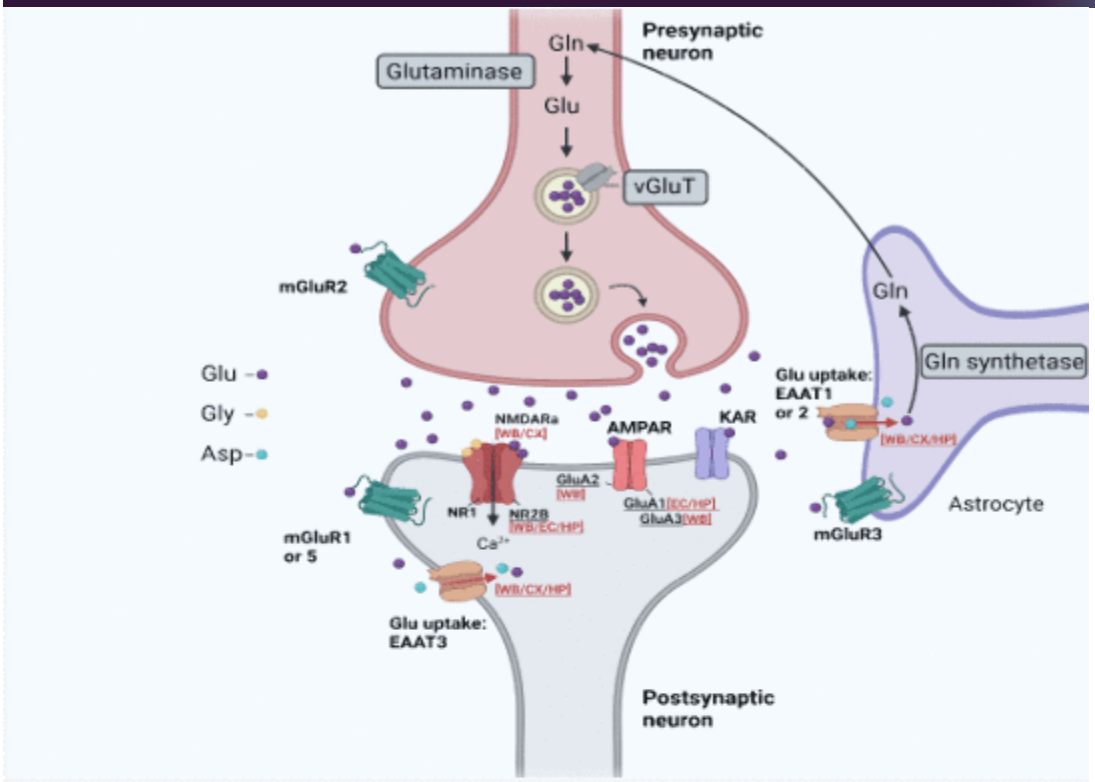

Figure 2. Main components of the glutamatergic synapse included in the meta-analysis. The main components are illustrated in the figure and their alterations in AD - solely reductions - (NMDARa, NR2B, GluA1, GluA2/3 and the glu uptake system) are accompanied by the respective altered brain regions written in red and underlined.

Abbreviations: whole brain (WB), cortex (CX), entorhinal cortex (EC), hippocampus (HP), glutamine (Gln); glutamate (Glu); vesicular glutamate transporter (vGluT); metabotropic receptor (mGluR); glycine (Gly); NMDARa (N-methyl-D-Aspartate receptor activated); NMDAR subunit (NR); alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR); AMPAR subunit (GluA); kainate receptor (KAR); excitatory amino acid transporter (EAAT); aspartate ('asp').

Conclusions: This study comprises the most comprehensive meta-analysis of the glutamatergic system in AD. The results of this meta-analysis suggest a reduction of specific glutamatergic components in AD. Our findings corroborate the idea of glutamatergic system dysfunction in AD and reinforce the need of further studies to advance our understanding of AD neurotransmission imbalance.

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P0244 / #2135

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

CHARACTERIZATION OF CANCER CELL LINE-BASED MODELS AS TOOLS FOR PRECLINICAL SCREENING OF NOVEL CHOLINERGIC MODULATORS

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Aims: Acetylcholine (ACh) signaling dysfunction leads to several neurodegenerative diseases including Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS). The diseases are characterized by lower production of ACh, because of degeneration of the cholinergic neurons and/or hypoactivation of ACh synthesizing enzyme choline-acetyltransferase (ChAT). However, development of effective therapeutic require robust cellular model for screening and preclinical evaluation as well as studying why cholinergic neurons are selectively vulnerable in AD and ALS. This study aimed to screen, characterize, and validated several cell lines as surrogate of cholinergic models.
Methods: Several cancer cell lines were screened by flow cytometry for the expression of cholinergic markers including ChAT, the ACh degrading enzymes (AChE/BChE), nicotinic and muscarinic ACh receptors (n- and mAChRs). The expression of these markers was also checked with other biochemistry methods. ACh levels were also measured in cell lysates and culture medium using HPLC.
Results: Three small cell lung cancer cell lines (A549, H82 and H69) were found to express all the cholinergic biomarkers. The cells also produced and released ACh in the medium. In addition, preliminary analysis of isolated mitochondria from these cells indicated that mitochondria not only possessed α7-nAChR but also M1 mAChR, BChE and ChAT. These cell lines are currently subjected to pharmacological analyses by a set of ChAT inhibitors as well as a unique class of compounds, called ChAT Potentiating Ligands (CPLs) that been shown to strongly boost the activity of ChAT in vitro.
Conclusions: The characterized cholinergic cell models may prove invaluable for studying etiology of diverse cholinergic selective disorders, such as AD, ALS, and apparently lung cancer as well as preclinical testing of therapeutic candidates targeting the cholinergic system.

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P0245 / #1050

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

SYNERGISTIC MODULATION OF THE CHOLINERGIC SYSTEM IN A TRANSGENIC RAT MODEL OF AD

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Aims: Since current treatment strategies for AD show limited efficacy and side effects, new approaches are needed to provide successful therapy within a worldwide aging population. The aim of this study is to pin down synergistic effects of chronic co-treatment using cotinine, a positive allosteric modulator of alpha7-nicotinic acetylcholine (ACh) receptors plus galantamine, an ACh-esterase inhibitor (AChEI). Single and combined preclinical therapeutic efficacy of both components is evaluated in APP-transgenic rats with endpoints in (i) information processing, cognition and memory *in vivo* and (ii) amyloid plaque load and neuroinflammatory markers *ex vivo*.
Methods: 5-month-old McGill-R-Thy1-APP rats receive a combination of galantamine and cotinine via drinking water for 94 days. Sensorimotor function (information processing), behavioral flexibility, attention (cognition) and object recognition (memory) are assessed *in vivo* by using both, classical and automated behavioral assays. Amyloid deposition load and markers of neuroinflammation are quantified *ex vivo* using a 3D reference atlas of the rat brain.
Results: Compared to administration of either cotinine or galantamine alone, we expect potentiated benefits by a combined treatment with both compounds, resulting in improved working- as well as episodic-like memory, attention and information processing. Additionally, we anticipate reduced amyloid plaque burden and neuroinflammation after chronic co-treatment.
Conclusions: Cotinine has promising effects on cognitive deficits in preclinical AD models, but can only exert its full activity in presence of sufficient levels of endogenous ligands. This co-treatment effect can be achieved by AChEIs such as galantamine, which increases the synaptic concentration of ACh. Not only cholinergic deficits but also amyloid plaques and neuroinflammation represent neuropathological origins of cognitive decline and disease burden in AD. This approach tackles all three patho-mechanisms by boosting the cholinergic neurotransmission in a dual manner using two compounds with additional anti-aggregation as well as immunomodulatory properties.

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P0246 / #2408

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

THE N-TYPE CALCIUM CHANNEL AS THERAPEUTIC TARGET IN NEURODEGENERATIVE DISEASES

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Aims: Ca^{2+}-signaling plays a central role in numerous cellular processes; especially in excitatory cells, such as neurons. The elevation of cytosolic calcium levels initiates the activation of downstream signaling cascades critical for protein-synthesis-dependent synaptic plasticity and long-term potentiation (LTP). Recently, it was shown that cytosolic calcium levels are affected in neurodegenerative diseases. In part, this Ca^{2+} influx is mediated by the family of Voltage-Gated Calcium Channels (VGCCs), which regulate Ca^{2+} transmembrane fluxes in response to membrane depolarization. Here, we present a potential new therapeutic target for the treatment of neurodegenerative diseases, the N-type VGCC ($Ca_V2.2$).
Methods: Crude membrane fractions of brain-homogenates from the cortex and cerebellum from APPswe/PSEN1dE9 mice were analyzed via Western Blots with regard to relative expression levels of $Ca_V2.2$. Stably transfected CHO-cells, expressing α_1b-, β_3- and $\alpha_2\delta_1$-subunits of the $Ca_V2.2$-channel, were used as input for $Ca_V2.2$ purification. Binding of purified $Ca_V2.2$ to a known and a potential new inhibitor was analyzed in surface-plasmon-resonance (SPR)-experiments.
Results: The $Ca_V2.2$ expression was found to be significantly increased in the cortex, but not in the cerebellum of APPswe/PSEN1dE9 mice at old age (28 m) compared to age-matched WT animals and a positive correlation with age and disease progression was observed. Binding of purified $Ca_V2.2$ to the known inhibitor confirmed successful purification of the protein in native form and additional binding to the new potential inhibitor ADP1 could be observed.
Conclusions: Overexpression of the N-type calcium channel may, in part, be responsible for progressive neuronal dysfunction caused by excitotoxicity in a mouse model of AD. Furthermore, we could show in preliminary results the lead optimization of the known compound ADP1 as inhibitor of the $Ca_V2.2$-channel for a general neuroprotection approach.

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P0247 / #723

POSTERS: A02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: APOE & LIPOPROTEIN-BASED

SELECTIVE ACTIVATION OF LXRS AND RXRS REGULATES SYNTHESIS, RELEASE AND LIPIDATION OF HEPATIC APOE IN HEPATOCARCINOMA CELL LINES

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Aims: Apolipoprotein E (ApoE) is an important lipid transporter, whose lipidation is mediated by the ATP-binding cassette transporter A1 (ABCA1) activity. Transcription of *APOE* and *ABCA1* is controlled by the ligand-dependent transcription factors Liver X (LXRs) and Retinoic X (RXRs) receptors. The liver is the main site of peripheric ApoE production accounting for 90 % of plasma ApoE. Low plasma ApoE levels have been associated with higher Alzheimer's disease (AD) risk and amyloid-beta pathology in the brain, and ABCA1 deficiency was linked to cognitive impairment. Here we studied basal and agonist-induced hepatic ApoE synthesis/release to assess how its modulation can affect ApoE lipidation and dimer formation.
Methods: A combination of cell pharmacology, Western Blot, ELISA and SEC was used to study ApoE synthesis/release from *APOE*ε3 homozygous HepG2 and Huh7 hepatocarcinoma cells. Effects of LXR and RXR agonists (T0901917/GW3965 and Bexarotene/9-cis-retinoic acid) on ApoE and ABCA1 levels in cell supernatants and pellets were evaluated after 24/48hrs. Cell supernatants were fractionated by SEC and the total cholesterol, HDL/LDL, VLDL content was determined using colorimetric HDL and LDL/VLDL quantification kit.
Results: Exposure to LXR agonists T0901317 (1 and 10 mM) and GW3965 (2mM) upregulated ApoE secretion (60-70%) without altering intracellular ApoE levels in both cell lines. Furthermore, ABCA1 content was increased in both cell lines after treatment with T0901317 and GW3965. Bexarotene increased ApoE secretion by nearly 50% (24/48 hours) in HepG2 cells, and promoted ApoE heterodimer formation after 48 hours. Conversely, 9-Cis retinoic acid failed to modulate ApoE release in both HepG2 and Huh7 cells.
Conclusions: Hepatic ApoE and ABCA1 synthesis/release from human *APOE*ε3 homozygous hepatocarcinoma cells can be modulated by LXR/RXR agonists with potential implications to ApoE3 dimer and lipoparticle formation

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P0248 / #1260

POSTERS: A02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: APOE & LIPOPROTEIN-BASED

DRUG DISCOVERY FOR BRAIN INFLAMMATION ASSOCIATED WITH APOE4

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Aims: We have recently shown that the brains of persons with APOE4 and dementia show greater measures of chronic unresolved inflammation compared with non-APOE4 carriers. Pathway analysis implicated the activation of calcium-dependent cytosolic phospholipase A2 (cPLA2). Animal and cellular studies confirmed activation of cPLA2 with APOE4 and greater inflammatory signaling. Small molecules capable of selectively limiting brain inflammation associated with APOE4 would be attractive for drug development.
Methods: ApoE4-TR mice were treated daily for seven weeks with vehicle or ASB14780 (10mg/kg, I.P.), a prototype cPLA2 inhibitor, starting at 16 months old. Behavioral testing was subsequently conducted, after which the brains were collected for lipidomic and biochemical analyses. Using high-resolution structural information for cPLA2 (PDBID: 1CJY) catalytic domain and ASB14780 as a prototype, we conducted a virtual screen of more than 19 billion compounds on-demand chemical space, followed by synthesis and in vitro validation. Subsequently, top-scoring compounds with drug-like characteristics were synthesized for *in vitro* validation.

Results: ASB14780 treatment increased brain EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) ratio to Arachidonic Acid (AA) and decreased brain PGE2 levels in ApoE4-TR mice compared to vehicle. ASB14780 inhibited cPLA2 phosphorylation and PGE2 (prostaglandin E2) production *in vitro*, reduced microglia activation, and ameliorated the recognition deficits of ApoE4-TR mice compared to vehicle-treated ApoE4-TR mice *in vivo*. Our initial screening efforts afforded 127 hit compounds that inhibit cPLA2 in vitro. Following validation in cell-based assays, two compounds were selected for optimization: BRI-50054 and BRI-50125. The two identified novel lead series have improved affinities for cPLA2 inhibition compared to ASB14780 and physicochemical properties supporting their bioavailability.

Conclusions: The development of small molecules that can mitigate eicosanoid-driven inflammation by inhibiting cPLA2 have promising effects on reversing AD neuroinflammation.

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P0249 / #2019

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

MODELING APPARENT REVERSALS OF ALZHEIMER'S DEMENTIA: POTENTIAL THEORETICAL LESSONS

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Aims: Data exist to support intensive individualized therapies for improvement of cognitive function among people with Alzheimer's Disease. These programs have been dismissed due to their being individualized and intensive and therefore impractical for a randomized controlled trial. We wanted to explore whether these therapies could be subsumed under the broader category of anti-inflammatory therapies.
Methods: As part of a larger study of life stories and resilience, we recruited 10 people whose Alzheimer's disease had improved using intensive, individualized therapies. These therapies included dietary modifications, daily exercise, anti-inflammatory multi-nutrients, stress reduction using a variety of approaches, and more. We built a system's dynamics, computer simulation model of inflammation in the nervous system using existing literature to inform us of how and where these various factors interact with inflammation. We gathered data from interviews with the participants and entered the information into the computer model.
Results: The computer model successfully predicted within 6 years the onset of cognitive decline using variables extracted from the life stories. We then entered the modifications made by the participants and found that their effects could be plausibly modeled as effects upon inflammation. We were able to adjust model parameters to successfully recreate the slope of improvement in cognitive function within a tolerance of 20% in either direction.
Conclusions: Complex phenomena may need to be studied by complex methods. Multiple, synergistic, interactive variables may be more suitable to computer simulation modeling techniques than randomized, controlled trials. The marker of success is constructing a theoretical, mathematical model that duplicates the outcomes observed. In this case, the model lends credence to an inflammatory model of Alzheimer's disease and shows how multiple, interacting and synergistic factors operating simultaneous can lead to disease improvement.

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P0250 / #2047

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

NEURONAL EXPRESSION OF E2F4DN MODULATES THE IMMUNE RESPONSE OBSERVED IN THE BRAIN OF 5XFAD MICE

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Aims: Alzheimer's disease (AD) is a neurodegenerative disorder in which altered immune response is an important etiological factor. The transcription factor E2F4 participates in tissue homeostasis and regulates gene networks affected in AD, thus constituting a potential target for intervention. Our results are consistent with a beneficial immune response in 5xFAD mice expressing neuronal E2F4DN, which we propose as a therapeutic agent against AD. We have studied whether neuronal expression of a dominant negative form of E2F4 (E2F4DN), unable to become phosphorylated in a Thr motif that controls its activity, can modulate the immune response observed in AD.
Methods: To this aim, we generated Mapt:E2F4DN knock-in mice (E2F4DN mice) that, together with control Mapt:EGFP knock-in mice (EGFP mice), were crossed with 5xFAD mice, a known murine model of AD.
Results: - 5xFAD/E2F4DN mice have a reduction of astrogliosis in the cerebral cortex at 3 months of age.
- 5xFAD/E2F4DN mice present less area occupied by microglia cells in the cerebral cortex of 3 and 6 month-old mice.
- Mice expressing E2F4DN have larger Aβ plaques and the same number than the Alzheimer's mouse model at 3 months of age, and this accumulation of Aβ is slowed down at 6 months of age in cortex.
- E2F4DN triggers attenuated immune response in the hippocampus of 5xFAD mice of 3 and 6 months of age.
Conclusions: Our results are consistent with a beneficial immune response in 5xFAD mice expressing neuronal E2F4DN, which we propose as a therapeutic agent against AD.

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P0251 / #909

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

EFFECT OF ANAKINRA ON LIPOPOLYSACCHARIDE-INDUCED NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) represents a huge economic and societal burden. As the number of patients with AD is expected to grow, finding ways to cure Alzheimer's disease has become a crucial matter. Research has shown that neuroinflammation appears as an early event in AD pathophysiology and could serve as a promising target for AD treatment. Pharmacological blockade of IL-1 signalling has shown to be beneficial in some autoimmune and autoinflammatory diseases, making IL-1β a promising therapeutic target in neuroinflammatory conditions. Anakinra is a recombinant form of the endogenous IL-1 receptor antagonist that blocks IL-1 signalling, relieving proinflammatory activation of amyloidosis and tau phosphorylation and could be instrumental in mainstream anti-AD therapy. The objective of this study is to evaluate the role of Anakinra against neurotoxicity via inflammatory mechanisms.
Methods: The effects of Anakinra on the differentiated human neuroblastoma SH-SY5Y cell line as an in vitro model were investigated. The differentiated SH-SY5Y cells were exposed to 0.125, 0.25, 0.5, 1 & 2 µg Anakinra prior to being exposed to 1 µm LPS to establish its' neuroprotective effects. Cell viability was examined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide) test and additionally, protein array kit studies were also carried out to determine the expression levels of some key inflammatory markers.
Results: Based on our results, Anakinra could be a potential molecule which works via an anti-inflammatory mechanism in Alzheimer's disease.
Conclusions: In conclusion, this study was instrumental in providing a first step in designing an innovative therapy using anti-IL-1 strategy against AD which is extremely important in overcoming the limitation of mainstream anti-AD therapy.

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P0252 / #2241

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

NOVEL SOLUBLE TNF INHIBITOR IMPROVES OUTCOMES IN A MOUSE MODEL OF TRAUMATIC BRAIN INJURY-INDUCED ALZHEIMER'S DISEASE

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Aims: Traumatic brain injury (TBI) is a known risk factor for the later development of Alzheimer's disease (AD). Unfortunately, there are no therapies to 'cure' TBI or AD, and any drugs to improve symptoms have numerous side-effects. Therefore, new pharmacotherapies without side-effects are urgently needed. A major inflammatory cytokine upregulated following TBI and involved in AD pathology is Tumor Necrosis Factor (TNF). The transmembrane form of TNF (tmTNF) preferentially binds TNFR2 promoting predominantly beneficial outcomes (blocking its activity may cause immunological and cardiac dysfunction), while the soluble form of TNF (solTNF) preferentially binds TNFR1 promoting detrimental brain outcomes, including neuronal cell death, amyloid beta plaque and tau neurofibrillary tangle pathology. While traditional TNF inhibitors are non-selective at blocking TNFR1 and TNFR2 activity, a novel second-generation TNF inhibitor (XPro1595, INmuneBio Inc) selectively inhibits only solTNF/TNFR1 activity. In a clinical trial in cancer patients XPro1595 was safe and well-tolerated, and in a second clinical trial in AD patient's interim data shows XPro1595 reverses brain WM neuroinflammatory levels. While TBI accelerates the onset of AD, the role of solTNF/TNFR1 activity in TBI-induced AD pathology has remained unknown.
Methods: AD transgenic mice (3xTg-AD) underwent TBI (CCI injury model), treated with XPro1595 (10 mg/kg, S.C.) 30 minutes post-injury, and allowed survive for 24 hours.
Results: Preliminary data suggests XPro1595 treatment prevents injury-induced increases in glial reactivity (GFAP), APP and amyloid beta (6E10), Tau (Tau46), and phospho-Tau (AT8 and PHF-1) expression.
Conclusions: This data supports the use of XPro1595 clinically following TBI to prevent the later development of AD pathology.

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P0254 / #318

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

PEPTOIDS AS POTENTIAL MODULATORS TO REDUCE S100B-INDUCED RAGE-ASSOCIATED INFLAMMATION IN ALZHEIMER'S DISEASE

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Aims: We demonstrate peptoids (JPT1, JPT1a) as potential inhibitors of RAGE-associated neuroinflammation in Alzheimer's disease (AD). We determined the effect of peptoids on S100B-induced inflammation via measurement of the release of cytokines. We additionally established the binding affinity between sRAGE and peptoids.
Methods: Differentiated THP-1 macrophages were exposed to chronic low-levels of S100B to confirm upregulation of cytokine release. To observe peptoid modulation of S100B-induced inflammation, macrophages were treated with 0-50 micromolar concentration peptoids in the presence of S100B; cytokine analysis via immunoassay was performed for cell culture supernatants. To determine the binding affinity, RAGE (20 nM) was incubated in the presence of 0-500 nM JPT1 or JPT1a to achieve equilibrium. Unbound RAGE was quantified via modified ELISA for calculation of K_d.
Results: S100B-treated THP-1 macrophages elicited anticipated inflammatory response evidenced by dose-dependent upregulation of cytokines. When THP-1 macrophages were incubated with peptoids and S100B, peptoids attenuated these S100B-induced inflammatory responses (Figure 1). Moreover, the peptoids demonstrated nanomolar binding affinity

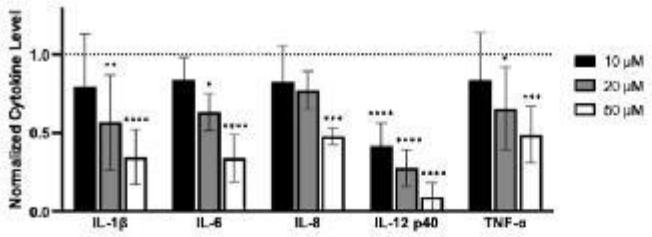

Figure 1. Reduction of S100B-induced proinflammatory cytokine release by peptid JPT1.

for RAGE (Figure 2).

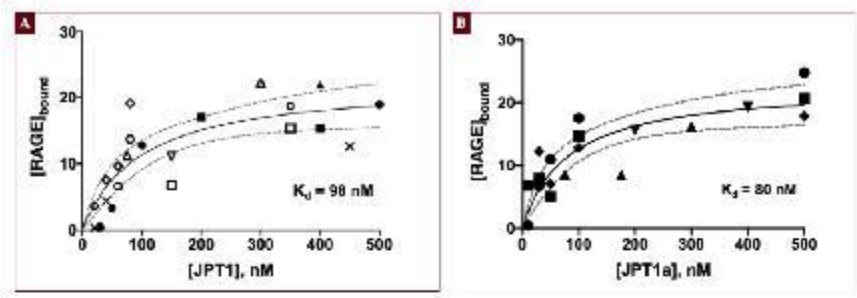

Figure 2. Low nanomolar affinity between sRAGE and JPT1 (panel A) or JPT1a (Panel B) demonstrated.

Conclusions: Peptoids modulate inflammatory responses induced by RAGE ligand S100B, including inflammatory cytokine release. These results implicate peptoids as a potential therapeutic agent for not only AD but also for other inflammation-related illnesses. Because these peptoids have also exhibited the ability to modulate beta-amyloid aggregation and transform the morphology of the aggregates formed, they may function as dual-target therapeutics for AD.

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P0256 / #2583

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

COMPARATIVE ASSESSMENT OF ANTIRADICAL AND CYTOTOXIC ACTIVITIES OF MALAOXON AND CHLORPYRIFOS AGAINST PHYTOCANNABINOIDS: IN VITRO ASSESSMENT

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Aims: Parkinson's disease (PD) is a major neurological disorder characterised by progressive nervous system degeneration and loss of dopaminergic neurons within the basal ganglia. Neuroinflammation and oxidative stress contribute to the neuronal damage observed in PD. Phytocannabinoids can display neuroprotective properties mediated via their antioxidant and anti-inflammatory activities. In contrast, Pesticide exposure can induce neurotoxicity effects, representing an environmental mechanism for the induction of parkinsonian phenotypes. This study investigated the antioxidant and neuroprotective activity of certain phytocannabinoids such as Cannabidivarin (CBDV) and Cannabigerol (CBG). The neuronal toxicity and oxidative stress of malaoxon and chlorpyrifos-oxon to SH-SY5Y neuroblastoma cells were studied.
Methods: Pesticide effects on cell viability were evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) assays. A comparison was performed after the preincubation of SH-SY5Y cells with phytocannabinoids. The ability of phytocannabinoids to limit the production of reactive oxygen species was quantified and ranked by their ability to scavenge free radicals using (2,2′-azino-di-(3-ethylbenzthiazoline sulfonic acid)) ABTS and (2,2-diphenyl-1-picrylhydrazyl) DPPH assays.
Results: Phytocannabinoids exhibited useful free radical scavenging ability and were able to limit cellular redox stress induced by pesticides. Reduced cellular redox stress correlated with improved cell viability. A cell viability curve was observed in the SH-SY5Y cells after being preincubated with CBDV and CBG. After 24 hours of incubation, different concentrations of malaoxon and chlorpyrifos-oxon were exposed to SHSY-5Y cells. MTT and LDH assays were used to quantify the mean effective concentration (EC50). Phytocannabinoids did display a strong antioxidant capacity in scavenging ABTS and DPPH radicals. The half-maximal inhibitory concentration (IC50) of each phytocannabinoid and pesticide were quantified.
Conclusions: These findings point to phytocannabinoids' antiradical and neuroprotective properties that might provide a potential therapeutic strategy for pesticide-induced neurological disorders.

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P0257 / #910

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

A NOVEL SPICE-ANTIOXIDANT-BASED NANO-VEHICLE IN PREVENTION OF AD PATHOGENESIS

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Aims: The present treatment for Alzheimer's disease involves well known synthetic acetylcholine esterase (AChE) inhibitor drugs which besides having short duration of action also have deleterious impact on human health. Therefore, there is a need for natural plant-based biomolecule(s) with potential AChE inhibition activity (ies). The aim of the work is to design a spice-based nano-vehicle as a novel green alternative of synthetic AD drugs by nanoencapsulating a solvent-less supercritical CO_2 extract of small cardamom seeds (SC_E) having a synergistic consortium of five antioxidant molecules, using polyethylene glycol and emulsifiers, selected based on ADMET analyses.
Methods: ADMET analysis, Ellman's assay and enzyme inhibition kinetics of the antioxidant molecules as well as the extract and its nanoliposomal formulation (SC_E-NL) were performed, followed by rigorous molecular docking and dynamics studies using MM-PBSA and umbrella sampling.
Results: Our previous work on acute toxicity tests conducted in Wistar albino rats in accordance with OECD guidelines have revealed LD_{50} of SC_E to be greater than 5000 mg/kg body weight of rats indicating the extract to be perfectly safe. The antioxidants exhibited significant AChE inhibition (*in vitro*) individually (1, 8-cineole exhibited least IC_{50} of 65.53 ± 0.05 µg/mL), and in SC_E (205.62 ± 0.5 µg/mL), as well as in SC_E-NL (575.67 ± 0.5 µg/mL); vis-à-vis rivastigmine (67.52 ± 0.02 µg/mL). Although donepezil reportedly has lower IC_{50} value, it has several side effects. The Lineweaver-Burk plots revealed competitive mode(s) of inhibition of AChE with these antioxidants. Rigorous molecular docking and molecular dynamics-based binding energy analyses suggested very good binding free energies and stable docking/binding complexes.
Conclusions: This study has delivered a nanoliposomal vehicle of food antioxidants as a putative 'green' alternative of synthetic AChE inhibitor drugs, ready for futuristic animal studies.

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P0258 / #643

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

CYTOPROTECTIVE EFFECTS OF NOVEL ANTIOXIDANT CO-DRUG VANL-100 AGAINST BETA-AMYLOID-INDUCED TOXICITY

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Aims: Researchers are exploring the role of antioxidants as novel therapeutics for the treatment of neurodegenerative diseases such as Alzheimer's disease (AD). More recently, strategies such as chemically linking antioxidants to synthesize novel co-drugs have been implemented to counteract the impacts of oxidative stress. The main objective of this study was to assess the cytoprotective effects of the novel antioxidant co-drug VANL-100, the chemical product of covalently linking naringenin (NAR) and alpha-lipoic acid (ALA), in a cellular model of beta-amyloid (Aβ)-induced toxicity. Additionally, the protective effects of VANL-100 were compared to its parent compounds NAR and ALA.
Methods: Cytoprotective and cytotoxic effects of the antioxidant compounds and Aβ, respectively, were measured using the 3-(4,5-dimethylthiazol-2-yl)2-5-diphenyl-2H-tetrazolium bromide (MTT) assay in SHSY-5Y cells in 24-hour pre-treatment and co-treatment experiments. Pre-treatment experiments consisted of 20 μM and 100 μM VANL-100, NAR alone, ALA alone, or NAR+ALA followed by co-incubation with 20 μM non-fibril or fibril Aβ (25-35) 24 hours later. Co-treatment experiments consisted of simultaneous co-incubations of 20 μM and 100 μM treatment of the antioxidant compounds with 20 μM non-fibril or fibril Aβ.
Results: There were no significant differences between the protective effects of VANL-100, NAR, ALA, and NAR+ALA at either dose or with either form of Aβ. Pre-treatment and co-treatment with VANL-100 significantly improved Aβ-induced cell loss. There was no significant difference in the effect of VANL-100 between 24-hour pre-treatment and co-treatment.
Conclusions: The novel co-drug VANL-100 is capable of eliciting cytoprotective effects against Aβ-induced toxicity. The effect of VANL-100 was not significantly different from its parent compounds. These findings provide early evidence of the neuroprotective effects of this novel co-drug in a cellular model of AD.

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P0259 / #154

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

ANTI-OXIDANT AND ANTI-ACETYLCHOLINESTERASE EFFECTS OF COD LIVER OIL IN D-GALACTOSE-INDUCED ALZHEIMER'S DISEASE IN RATS

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Aims: Alzheimer's disease (AD) is a neurodegenerative disease. Nutritional supplements are being investigated as prophylaxis or treatment for AD. Cod liver oil (CL) is rich in omega-3 fatty acids, vitamin A and D. The literature suggested it possesses anti-oxidant, neuroprotective, and mitochondrial protective efficacy. This study was undertaken to evaluate the neuroprotective efficacy of CL in the D-galactose-induced accelerated aging model in rats that causes learning and memory deficiency.
Methods: Disease was induced by administration of D-galactose 100 mg/kg orally for 10 weeks. CL was tested in three doses from week 7 to 10 (CL1: 0.1 ml/kg, CL2: 0.2 ml/kg, CL3: 0.3 ml/kg, orally). At the end of 10 weeks, behavioral parameters (Morris water maze (MWM), Modified Y-maze, and Fear conditioning) were performed and brain samples were collected for further biochemical and histopathological analysis.
Results: The treatment ameliorated the deficits caused due to D-galactose. It reduced the latency to find the hidden platform in MWM, increased the time spent in the closed arm of Y-maze, and increased freezing behavior in comparison to the disease control group. It reduced the acetylcholinesterase activity ($P<0.05$) and levels of malondialdehyde (CL3: $P<0.05$) and increased the levels of superoxide dismutase (CL3: $P<0.0001$), glutathione (CL2 & CL3: $P<0.05$), and catalase. The histopathology showed that treatment ameliorated cell damage by reducing eosinophilia and cell apoptosis.
Conclusions: It can be inferred from the preliminary study that CL possesses acetylcholinesterase inhibitor and anti-oxidant activity and thus can be further researched for the treatment of AD.

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P0260 / #1642

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

OXYGEN SENSING IN NEURODEGENERATIVE DISEASES: CURRENT MECHANISMS, IMPLICATION OF TRANSCRIPTIONAL RESPONSE AND PHARMACOLOGICAL MODULATION

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Aims: O_2 sensing mechanisms in the brain are crucial to maintain tissue homeostasis but, even if it has been demonstrated their implication in NDs, they remain poorly studied. This work aims to review the role of common pathways related to oxygen sensing involved in three major NDs: AD, PD, and ALS.
Methods: The public transcriptomic data related to AD, PD and ALS stored on the GEO repository were downloaded and reprocessed. The DESeq2 package of R was used to identify differentially expressed genes and a functional enrichment analysis was performed to understand which cellular pathways are affected by Alzheimer's Disease, Parkinson's Disease and Amyotrophic Lateral Sclerosis.
Results: The data hereby presented provides a first inspection of the genes and pathways pertaining O_2 sensing mechanisms in the three considered disorders (AD, PD and ALS). It is interesting to observe that most pathways linked to O_2 imbalance are specific for each disease, whilst three of them are in common between PD and ALS and five between PD and AD. This is even more remarked when considering the gene-signature responsible for the pathways' dysregulation. Indeed, no dysregulated gene is shared between the 3 disorders, whilst only one RNA is shared amongst PD and ALS.
Conclusions: Our results show that O_2 sensing related pathways are strongly altered in AD, PD, and ALS, but there is a need of novel strategies to detect these altered mechanisms and their correlation with specific NDs. Moreover, therapeutic approaches targeting this aspect would be of fundamental relevance.

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P0261 / #319

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

GRYLLUS BIMACULATUS AND OXYA CHINESIS SINUOSA EXTRACTS ALLEVIATES H2O2-MEDIATED DISRUPTION OF THE BLOOD BRAIN BARRIER DISRUPTION

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Aims: Blood brain barrier (BBB) protects neurons from various risk factors in the circulation systems, and maintain the central nervous system's internal milieu. Maintaining integrity of BBB plays an important role for the selective control of the chemical composition of brain interstitial fluid, ensuring the normal synaptic functioning and process of information. BBB disruption results in influx of blood-derived toxins, cells, and microbiol pathogens which trigger inflammation an immune responses initiating various neurodegeneration signaling pathways, including Alzheimer disease. Crickets (Gryllus bimaculatus; Gb) and Grasshoppers (Oxya chinesis sinuosa; Ocs) have been used as food sources in many Asia countries. Additionally, Gb and Ocs have been studied in food science research and traditional medicine research focused on anti-oxidant activity. Therefore, we here examined the anti-oxidant activity of Gb and Ocs extracts in primary astrocytes, primary pericytes and endothelial cells.
Methods: We cultured mouse-derived primary astrocytes, pericytes, and endothelial cell line in 48-well, 96-well or insert plates and treated with various concentration of H_2O_2 and/or *Gb* and *Ocs.* Survivability rate was measured by MTT assay. BBB integrity was measured by EVOM3.
Results: Mouse-derived primary astrocytes and pericytes were protected by *Gb* and *Ocs* extracts while there is no response in endothelial cells. When we check the effects of these extracts in the in vitro BBB model system after treatment with H_2O_2, the BBB TEER values were higher after the combined treatment with *Gb* and *Ocs* extracts
Conclusions: Endothelial cells had the most resistance to oxidative stress, follow by pericytes and astrocytes came last. *Gb* and *Ocs* exerted cytoprotective effect in primary astrocytes and pericytes. *Gb* and *Ocs* protected BBB integrity in H_2O_2-treated in vitro BBB models which are containing 3 types of cells: endothelial cells, primary astrocytes and primary pericytes.

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P0262 / #753

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

SERINE RACEMASE INHIBITION IMPROVES MEMORY AND PREVENTS NEURONAL AND SYNAPTIC LOSS IN ALZHEIMER'S DISEASE

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Aims: There is evidence that neuronal toxicity in Alzheimer's disease (AD) could be mediated by overactivation of N-methyl-D-aspartate receptors (NMDARs) by amyloid-β. Activation of NMDARs depends on the binding of glutamate and a co-agonist, D-serine or glycine. D-serine is generated by serine racemase (SR), which catalyses the racemization of L-serine to D-serine. In this study, we targeted the glycine/D-serine site of NMDARs with a specific SR inhibitor (SRi) to investigate whether reducing D-serine levels would improve AD-related memory loss and neurotoxicity.
Methods: The SRi L-aspartic acid β-hydroxamate (LAH) was injected into 7-month-old 5xFAD/Thy1-GFP and wild-type (WT) mice intraperitoneally at a dose of 3mg/kg once daily for 14 days. Following treatment, behavioural assessment of learning and memory was performed using the fear conditioning test. Amyloid pathology, neuronal loss and synaptic expression were assessed using immunohistochemistry and western blots.
Results: We observed that LAH treatment reversed hippocampal-dependent learning and memory deficits in 5xFAD mice, without changes in WT mice. These improvements were not related to changes in Aβ pathology. Interestingly, SRi treatment led to a 34% increase in neuronal density in the subiculum and in synaptic markers in hippocampus in 5xFAD mice. Analysis of dendritic spines in 5xFAD/Thy-1-GFP double transgenic mice revealed a reduction in 5xFAD mice compared with WT mice, which was reversed by SR inhibition.
Conclusions: These results demonstrate that SR inhibition could have potential therapeutic value in late-stage AD.

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P0263 / #2732

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

A NOVEL THERAPEUTIC APPROACH FOR ALZHEIMER´S DISEASE BASED ON BRI2 PROTEIN

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Aims: Development of pro-neurogenic therapies for compensating the neuronal loss and restoration of degenerated synaptic networks in Alzheimer´s disease (AD) have been difficult to achieve, which calls for new strategies to promote adult neurogenesis and counteract neurodegeneration. Recent advances have resulted in the application of different translational approaches for novel therapies, where gene-based therapies have emerged as an exciting possibility. BRI2 is a ubiquitously expressed transmembrane protein that undergoes proteolytic cleavage by distinct proteases originating different BRI2 fragments. The precise physiological function of BRI2 remains elusive, however previous work demonstrated an increase in BRI2 levels during neuronal development, and a strong phenotypic association of BRI2 and its processing with neuronal differentiation. This work aims to explore the contribution of BRI2 proteolytic fragments to neuronal differentiation.
Methods: In this work, a human recombinant BRI2 fragment fused with the Myc tag for detection purposes was produced. SH-SY5Y cells and mouse primary neuronal cultures (PNC) were incubated with different concentrations of BRI2 fragment, and its cellular uptake was analysed. Moreover, the effects of BRI2 fragment on SH-SY5Y and PNC were evaluated by performing a detailed morphometric analysis to characterize its differentiation phenotypes, and by determining the ability of the fragment to inhibit Aβ42 aggregation.
Results: Our results indicate that the recombinant BRI2 fragment is internalized by cells in a dose-dependent manner and showed high stability in the conditional media. Remarkably, preliminary evidence suggests that the recombinant BRI2 fragment is also able to reduce Aβ42 aggregation.
Conclusions: With this work, we expect to contribute to unveiling BRI2 as a neuronal differentiation modulator, which will be valuable to propose an innovative pro-neurogenic therapy for neurological conditions characterized by neuronal loss and atrophy, such as AD.

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P0264 / #291

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

TRANSCRANEAL PULSE STIMULATION FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT AND EARLY ALZHEIMER'S DISEASE

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Aims: Brain stimulation with transcranial pulse stimulation (TPS) is currently being studied for their increasing popularity as an approach to modulate and stimulate the human brain. Several publications have reported the benefits that TPS can deliver to the patients with a varied number of neurologic disorders, being specially so in patients with cognitive impairment due to Alzheimer's disease and other causes . Here we present the promising results from a short - medium follow-up of subjects with cognitive impairment treated with TPS.
Methods: The treatment protocol includes an initial evaluation with a neurologist and a neuropsychologist and an MRI scan. We perform an extensive cognitive battery, which includes MoCA test, clinical dementia rating (CDR), functional activities questionnaire (FAQ) and specific test to evaluate all cognitive domains. All patients received 6000 pulses/session. The session duration is 25 minutes. Subjects received 6 sessions delivered over 2 weeks, and a reinforcement session was administrated after 10 weeks. The protocol includes the evaluation of the patients after 3, 6 and 12 months post-treatment.
Results: Patients have experienced a sustained improvement in the following categories: orientation and attention. Improvement in fluency of language has also been documented. This study is yet to be concluded after collecting 12 month follow-up results.
Conclusions: Patients presented good tolerability and no side effects. This method shows promising results to slow down the progression of the disease and improve certain areas on the cognitive behavior. Shockwave stimulation is a non-invasive and well-tolerated technique that could support or enhance pharmacological treatment of patients with MCI and EAD.

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P0265 / #1907

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

ALLOPREGNANOLONE AS A REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S DISEASE: A RANDOMIZED, PLACEBO-CONTROL, PHASE 2 PROOF-OF-CONCEPT CLINICAL TRIAL

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Aims: This is a proof-of-concept phase 2 clinical trial to investigate the long-term safety and efficacy of allopregnanolone (Allo) to function as a regenerative therapeutic to restore structural integrity and cognitive function of the brain in participants with mild Alzheimer's disease (AD) dementia.
Methods: Design: multi-center, double-blind, parallel-group, randomized-controlled clinical trial. A total of 20 sites will recruit 200 participants with mild AD; 100 per treatment arm. Eligible participants are male or female, age 55-80 years old, diagnosed with probable AD, MMSE between 20–26 and APOEe4 genotype (3/4 and 4/4). Participants will be randomized to 4 mg Allo (administered IV over 30 minutes, once-per-week) or matching placebo, 1:1 allocation, for a 12-month period. After 12 months, all participants in the placebo group will be crossed-over to receive Allo for the remainder of the study. Brain imaging to evaluate the primary endpoint will be conducted at baseline, 6 and 12 months.
Results: Primary Endpoint is mean rate of change in hippocampal volume at 12 months. Secondary Endpoints include mean rate of change in CANTAB-PAL, ADAS-Cog11, and ADCS-iADL; safety outcomes at 12 months. Exploratory endpoints include regional brain volumes, white matter fiber tract diffusion measures, average intrinsic connectivity, and cerebral region cerebral blood flow; blood-based biomarkers of target engagement and other cognitive and functional outcomes. Additionally, change from baseline to 6, 12 and 18 months in open-label treatment participants in the above endpoints.
Conclusions: Herein we present design of a phase 2 proof-of-concept trial to assess the efficacy of allopregnanolone as a regenerative therapeutic using an imaging biomarker endpoint. Results from this study will validate previous findings indicating that allopregnanolone may exert both regenerative and neuroprotective effects on structure and connectivity in the Alzheimer's brain.

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P0266 / #2284

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

FOSGONIMETON IS NEUROPROTECTIVE AND RESCUES COGNITIVE PERFORMANCE IN MODELS OF NEUROINFLAMMATION

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Aims: Positive modulation of the hepatocyte growth factor (HGF)/MET system has demonstrated neurotrophic effects, highlighting its potential as a therapeutic strategy for neurodegenerative disorders. We have previously shown that fosgonimeton, a small molecule positive modulator of HGF/MET, protects against several components of neurodegeneration including mitochondrial dysfunction, oxidative stress, and excitotoxicity. Here, we sought to assess the ability of fosgonimeton to mitigate lipopolysaccharide (LPS)-induced neuroinflammatory cognitive deficits in vivo, as well as cytokine release and neurotoxicity in vitro.
Methods: To evaluate the pro-cognitive effects of fosgonimeton after neuroinflammatory insult, adult mice received a single, intraperitoneal injection of LPS followed by daily subcutaneous doses of fosgonimeton for 14 days. Cognitive performance was assessed in the T-maze spontaneous alternation task. In addition, LPS-stimulated, THP-1 differentiated macrophages were treated with the active metabolite of fosgonimeton (fosgo-AM) and levels of secreted proinflammatory cytokines were measured via homogenous time resolved fluorescence. Finally, the effect of fosgo-AM on neuronal viability in response to LPS treatment was evaluated in vitro.
Results: Fosgonimeton significantly attenuated LPS-induced cognitive impairment in vivo, as measured by percentage of spontaneous alternations. In vitro, THP-1 differentiated macrophages treated with fosgo-AM exhibited a significant reduction in LPS-induced proinflammatory cytokine release. Furthermore, treatment with fosgo-AM protected neurons from LPS-induced cytotoxicity.
Conclusions: Here we demonstrate the ability of fosgonimeton to protect against neuroinflammation-induced cognitive deficits in vivo. We also provide in vitro evidence of potential mechanisms by which fosgonimeton exerts these effects, including a reduction in proinflammatory cytokines that are central to neuroinflammation and mitigation of neuroinflammatory cytotoxicity. These data suggest that fosgonimeton has pro-cognitive and neuroprotective properties with potential therapeutic value for neurodegenerative disorders, including Alzheimer's and Parkinson's disease, in which neuroinflammation is a known contributor to neuronal decay.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

DISCOVERY OF POTENT CHOLINESTERASE INHIBITION-BASED MULTI-TARGET-DIRECTED LEAD COMPOUNDS FOR SYNAPTOPROTECTION IN ALZHEIMER'S DISEASE

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Aims: Multiple biological mechanisms act in concert during the etiological manifestation of Alzheimer's disease (AD). Drug development efforts mainly focused on single targets failed to provide an effective treatment. Therefore, there is a pharmacological need for simultaneous targeting of multiple disease mechanisms and functional validation pipelines involving animal models. In this study, we aimed to design novel multi-target compiunds and test their in vivo efficacy on synaptic protection and drug likeness.
Methods: We designed cholinesterase inhibition (ChEI)-based multi-target-directed ligands (MTDLs) that simultaneously target symptomatic AD-related receptors. We built a library of seventy 4-methylbenzothiazole-piperazine propanamide derivatives, sequentially screened for *in vitro* ChEI; determined σ_1R, σ_2R, NMDAR-GluN2B binding affinities and P2X7R antagonistic activity; performed molecular docking studies for potent ligands/inhibitors on their corresponding targets.
Results: We designated nine hit compounds, which fulfill *in silico* drug-likeness criteria and do not cause toxicity *in vitro* in human neuroblastoma, liver hepatoma, embryonic kidney cells. Seven compounds displayed *in vitro* cytoprotective activity in human neuroblastoma, and primary human fetal cortical astrocytes with two different stress inducers (H_2O_2 and Amyloid-β42). We screened neuroprotective activity of hit seven compounds *in vivo* in a zebrafish model of acute amyloidosis-induced synaptic degeneration. Compared to benchmark drug donepezil, six showed equal/better synaptic-protective activity. Two compounds with P2X7R antagonistic activity alleviated activation state of microglia *in vivo*. Blood-brain barrier and gastrointestinal tract permeabilities of lead candidates were determined. Four lead compound candidates did not display CYP450 3A4, 2D6, 2C9 inhibition.
Conclusions: We identified four of our ChEI-based lead MTDLs as promising drug candidates for synaptic integrity protection. These compounds could serve as disease-modifying AD treatment. Our study also demonstrates zebrafish as a useful pre-clinical tool for drug discovery and development.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

HUGGING IT OUT: EPIGENETIC EDITING OF OXYTOCIN IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's Disease (AD) is a progressive fatal neurodegenerative disease characterized by neuronal loss, brain atrophy, and cognitive disturbances. Accumulating evidence suggests that oxytocin also plays a role in memory formation, mainly by maintaining long-term potentiation (LTP). Recently a link between AD-specific DNA methylation signatures and the oxytocin promoter was established in brains of patients suffering from AD. The first aim of the project is to examine the effects of oxytocin treatment on AD pathology *in vivo*. The second project aim is to investigate the epigenetic signature of the oxytocin promoter in AD and its effect on pathology by means of epigenetic editing. This will be achieved by using CRISPR-dCas9 first *in vitro,* using the murine hippocampal cell line HT22, as well as *in vivo* using APP/PS1 mice.
Methods: To investigate the first aim of this project we use APP/PS1 mice as a model for AD. They perform behavioural tasks (Object location task, Y-maze, sociability assessment) and memory performance and overall sociaiblity are assessed. To investigate biologically relevant markers of AD we mainly use qpcr and ELISA to investigate the effects of treatment. For the second aim of the project we use CRISPR, specifically dcas9 to epigenetically edit methylation of the OXT promoter.
Results: APP/PS1 mice treated with oxytocin were able to recover the cognitive deficit as observed in saline treated age-matched controls of APP/PS1 mice. Intranasal administration of oxytocin increased hippocampal oxytocin levels, and increased mTOR levels.
Conclusions: Oxytocin treatment restores cognitive deficits in APP/PS1 mice. While the exact mechanism by which the effects are exerted, either by indirectly boosting LTP through an increase of synaptic plasticity, or by more directly working on LTP via mTOR signalling remains to be elucidated further.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

PREGNANE-LIKE CAUDATIN ACTIVATES PPARA-MEDIATED AUTOPHAGY AND MITIGATES ALZHEIMER'S DISEASE PATHOLOGY IN MICE MODEL

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Aims: To evaluate Caudatin's potential in Aβ and phospho Tau clearance in cell and animal models of AD.
Methods: AD mice model and treatment schedule: The animal handling and experiments were performed with an approved animal license (20-27) in DH/HT&A/8/2/6 Pt.1. Caudatin was orally administered in Female 3XTg-AD mice models. The 3XTg-AD (N = 8 per group) transgenic mice were orally given Caudatin (20 mg/kg or 40 mg/kg, N = 8) and lithium chloride (LiCl, 20 mg/kg) was used as a positive control group. Caudatin administration started from six months of age and continued till the 14th month. The experimental animals were subject to behavior analysis in the 14th month and at the end of 14th month, all the animals were sacrificed for further experiments. **In vitro studies:** Mouse microglial cell line , CHO 7PA2) cells, mouse Hippocampal Neuronal Cell Line (HT-22), and mouse Neuroblastoma (N2A) cells-overexpressing tandem fluorescent-tagged LC3 (tfLC3) were used for the in vitro studies.
Results: Oral administration of Caudatin decreased AD pathogenesis and ameliorated cognitive dysfunction in the 3XTg-AD mice model. Thus, PPARα is an important therapeutic factor, regulating ALP for the clearance of Aβ and phospho Tau aggregates in AD cell and mice models. Taken together, we show that Caudatin treatment is a remarkable therapeutic strategy for AD therapy.
Conclusions: The present study is the first preclinical evidence demonstrating the multifactorial efficacy of Caudatin in combating the multiple factors of AD. PPARα and TFEB are essential for the Caudatin-induced autophagy and lysosomal degradation of phospho Tau and APP metabolites in the in vitro and in vivo disease conditions of AD. The current findings of this research study will promote Caudatin as an important clinical drug candidate for AD therapy.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

NX210C: A DISEASE-MODIFYING PEPTIDE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Aims: AD is a neurodegenerative disease affecting million people who suffer from the progressive deterioration of cognitive functions including learning and memory. The few approved treatments such as donepezil are limited to the symptomatic control of AD, therefore there is an urgent need to develop a disease-modifying treatment to halt AD-induced cognitive deficits. The subcommissural organ (SCO)-spondin is a brain-specific glycoprotein which contributes to neuronal development. Here, we sought to evaluate the protective effects of a SCO-spondin-derived peptide (NX210c) on learning and memory in a mouse model of AD.
Methods: Mice were subjected to an intracerebroventricular injection of $A\beta_{25-35}$ oligomers and treated with intraperitoneal injections of vehicle and NX210c according to different doses (ranging from 0.1 to 30 mg/kg) and therapy paradigms (early or late stand-alone treatments, combination with donepezil or second-line treatment). Cognitive functions were evaluated using the Y-Maze, the step-through latency passive avoidance (STPA) and the Morris water maze (MWM) tests for up to 4 months.
Results: Early-stage daily treatment with NX210c decreased the levels of common markers of AD such as $A\beta_{1-42}$, phosphorylated Tau and TNF-α, and increased synaptogenesis. Regardless of the experimental paradigm used, NX210c prevented AD-induced decreased spontaneous alternations (Y-Maze) and step-through latency into the dark compartment (STPA), and AD-induced increased time to find the immersed platform during the learning phase and decreased time in the target quadrant during the retention phase (MWM).
Conclusions: This study provides the first evidence that a clinical-stage drug candidate peptide reduces common hallmarks of AD pathology and restore learning and memory at both early and late pathological stages. Overall, we shed light on the therapeutic potential of this innovative disease-modifying peptide to restore memory function in AD patients.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

CHOLINERGIC ALTERATIONS IN CEREBRAL CORTEX OF A HUMANIZED APP-KNOCK-IN (APPNL-G-F) MODEL OF ALZHEIMER'S DISEASE

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Aims: Objectives: Early loss of basal forebrain cholinergic neurons (BFCNs) and altered cholinergic pathways are well-known changes in Alzheimer's disease (AD), also linked to memory dysfunction. BFCNs innervate wide areas in the cerebral cortex, which displays profound cholinergic activity and acts as one of the sites for nerve growth factor (NGF) synthesis. Typical AD is identified by the pathological hallmarks amyloid beta (Aβ) plaques and tau tangles. Recently, the anti-amyloid antibody Aducanumab was approved for AD therapy by the United States of America Food and Drug Administration but whether Aβ deposition modulates cholinergic activity is not well established.
Methods: Methods: To delineate the specific role of Aβ deposition towards modifying cholinergic activity, a humanized APP-knock-in mouse model of AD, termed *App*$^{NL-G-F}$, was employed. Tissues from parietal cortex from *App*$^{NL-G-F}$ mice and wildtype control (C57BL/6JRj) were isolated at different stages of amyloid pathology – 2-month age (pre-plaque stage), 7-month age (plaques present + initiation of cognitive deficits), and 12-month age (advanced amyloid pathology), respectively. The isolated tissues were then processed in various extraction buffers (soluble, ionic and detergent soluble fractions) and pooled together to recover total tissue homogenates. Enzymatic assays for acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), choline acetyltransferase (ChAT) along with NGF levels were measured.
Results: Results: Age-dependent changes were observed in *App*$^{NL-G-F}$ wherein an increased cholinesterase activity (AChE and BuChE; 7 and 12-month) and reduced ChAT activity (7-month) were observed, as compared to wild-type controls. The cholinergic index (ChAT/AChE) was significantly decreased in *App*$^{NL-G-F}$ mice from 7 months onwards coinciding with altered neurobehavior. Total NGF levels were also found to be suppressed in *App*$^{NL-G-F}$.
Conclusions: Conclusions: Significant age-dependent alteration in cholinergic activity is evident in cerebral cortex of *App*$^{NL-G-F}$mice, when compared to wild-type counterparts.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

BENZOPYRAN DERIVATIVE PENETRATES THE BLOOD–BRAIN BARRIER, ELIMINATES SYNAPTIC DEFICIENCY AND RESTORES MEMORY DEFICIT IN 5XFAD MICE

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Aims: Synapse loss in the brain of Alzheimer's disease (AD) patients correlates with cognitive dysfunctions. Drugs that limit synaptic loss are promising pharmacological agents. The transient receptor potential cation channel, subfamily C, member 6 (TRPC6) regulates the formation of an excitatory synapse. Positive regulation of TRPC6 results in increased synapse formation, enhances learning and memory in animal models. Thus, TRPC6 channels constitute an attractive molecular target. We have previously shown that TRPC6 channels are key regulators of store-operated calcium entry (nSOCE) in hippocampal neurons (Zhang at al 2016, J Neurosci). TRPC6-dependent nSOCE is necessary to support mushroom spines and protect them from amyloid toxicity in vitro. It has been shown that TRPC6 positive regulators can restore LTP deficit in brain slices taken from AD transgenic mouse models. However, previously all TRPC6-targerting compounds tested by us failed to cross brain-blood barrier (BBB).
Methods: molecular docking, spine quantification, PK, LTP, behavior
Results: Recently, novel selective TRPC6 agonist, 3-(3-,4-Dihydro-6,7-dimethoxy-3,3-dimethyl-1-isoquinolinyl)-2H-1-benzopyran-2-one (C20), has been identified (Hafner et al 2019, Cell calcium). Herein, we investigated the therapeutic profile of novel selective TRPC6 positive modulator. We demonstrated that C20 binds TRPC6 in its extracellular part in the agonist binding site. C20 shows synaptoprotective properties in vitro and recovers synaptic plasticity in brain slices of aged 5xFAD mice. C20 efficiently penetrated BBB. 14 days long i.p. injections of 10mg/kg of C20 increase both hippocampus-dependent context and hippocampus-independent cued fear memory in 5xFAD mice.
Conclusions: C20 is a perspective TRPC6-specific compound that might reduce cognitive decline. The research was funded by Russian Science Foundation Grant No 20-75-10026.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

PRO-BDNF PREDICTS MEMORY GAINS IN ELDERLY PERSONS AFTER LIFESTYLE CHANGES- A SUBGROUP ANALYSIS AMONG ADHERENT PARTICIPANTS IN THE FINGER STUDY

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Aims: Brain-derived neurotrophic factor (BDNF), including the mature form (mBDNF) and its precursor (proBDNF), has an important role in brain plasticity, and is possibly also involved in neuroprotective mechanisms against development of dementia. In this study we relate, for the first time, serum levels of both mBDNF and proBDNF with cognitive changes in elderly persons at risk of dementia during a comprehensive life-style intervention.

Methods: A sub-sample of 151 participants from the Finnish Geriatric Intervention Study to prevent cognitive impairment and disability (FINGER), aged between 60 and 79 years, and with high adherence to the intervention protocol were included in the analysis. The multidomain intervention combined several lifestyle changes in parallel (diet, exercise, cognitive training, social stimulation, and vascular risk management) over 24 months. Serum mBDNF and proBDNF levels were measured at baseline and after after 24 months, and were related to changes in cognitive performance using multiple linear regression models.
Results: We found a positive association between proBDNF levels at baseline and improved memory performance over the 24-month intervention period. This association was especially strong for changes in complex memory performance. In addition, participants with larger increases in their proBDNF levels over the intervention period also had larger gains in memory performance. We found no associations between levels of mBDNF, or changes in mBDNF levels, and performance changes in any cognitive domain.
Conclusions: These results suggest that proBDNF may have a key role in molecular processes underlying memory improvement, and that proBDNF availability can serve as a predictor of memory benefits from comprehensive lifestyle changes in elderly persons.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

BENEFICIAL EFFECTS OF CAFFEINE AND PHYSICAL ACTIVITY IN MOUSE MODELS OF ALZHEIMER'S DISEASE

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Aims: Regular physical activity has been associated with healthy brain aging, reflected by beneficial effects on cognition and learning and memory. In addition, nutritional supplements such as caffeine have been shown to act as cognitive enhancers and may possess neuroprotective properties. Caffeine is the most frequently consumed psychoactive substance worldwide and epidemiological evidence suggest a correlation between reduced dementia risk and caffeine consumption as well as physical activity. Our aim was to investigate the effects of physical activity and caffeine in transgenic Alzheimer's disease (AD) mouse models and control animals with regard to potential synergistic effects.
Methods: Long-term oral caffeine treatment as well as increased physical activity in the form of enriched environment housing as well as combined treatment paradigms are assessed on the behavioral, biochemical and neuropathological level.
Results: Caffeine treatment of the Tg4-42 mouse model of AD improved behavioral deficits, alleviated neuron loss and triggered hippocampal neurogenesis. In 5XFAD mice, a model with robust amyloid-β plaque deposition, beneficial effects on behavioral parameters were detected, albeit with unaltered amyloid-β pathology. A combination of enriched environment housing and oral caffeine treatment triggered learning and memory performance in wildtype mice but did not show further synergistic effects in Tg4-42 mice.
Conclusions: These results suggest potential synergistic effects of caffeine and physical activity. In contrast to previously published data, our results do not support an anti-amyloidogenic effect of caffeine but rather point to boosted neurogenesis as an important mode of action.

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POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

PIPERAZINE DERIVATIVE BINDS G-ACTIN IN SILICO AND STABILIZES ACTIN FILAMENTS IN VITRO

Nikita Zernov[1], Viktor Ghamaryan[2], Ani Makichyan[2], Daria Melenteva[1], Lernik Hunanyan[2], Elena Popugaeva[1]
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Aims: Alzheimer's disease (AD) is characterized by synaptic dysfunction, which is expressed through the loss of dendritic spines and changes in their morphology. Pharmacological compounds that are able to protect spines in AD brain are suggested to be novel drugs that would be able to slow down the disease progression. We have recently shown that a positive TRPC6 modulator, the compound 51164 (N-(2-chlorophenyl)-2-(4-phenylpiperazine-1-yl) acetamide), causes upregulation of postsynaptic neuronal store-operated calcium entry, increases mushroom spine percentage and recover synaptic plasticity in amyloidogenic mouse models of Alzheimer's disease. The purpose of the present study is to investigate the synaptoprotective mechanism of 51164.
Methods: Confocal microscopy, calcium imaging in dendritic spines, molecular docking, molecular dynamics.
Results: We present experimental data indicating that 51164 possesses an alternative synaptoprotective mechanism. We demonstrated that 51164 can restore mushroom spine percentage in neurons with the downregulated activity of TRPC6-dependent neuronal store-operated calcium entry. Moreover, we report binding of 51164 to G-actin in silico. We observed that 51164 interacts with Lys 336, Asp157, Ser14 of G-actin, amino acids involved in the stabilization/polymerization of the G-actin structure. We showed that interactions of 51164 with G-actin are much stronger in comparison to the well-characterized F-actin stabilizing and polymerizing drug, jasplakinolide.
Conclusions: Obtained results suggest an alternative neuroprotective mechanism of 51164 that is related to the preservation of actin filaments in vitro. This research was funded by Russian Science Foundation Grant No 20-75-10026.

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POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

THERAPEUTIC EFFICACY OF NOVEL PEPTIDE APTAMERS TO TARGET CELLULAR PRION PROTEIN IN NEURODEGENERATIVE DISEASES

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Aims: Alzheimer's disease (AD) and prion diseases are incurable neurodegenerative diseases. The objective of our research is to develop peptide aptamers (PAs) as therapeutics to treat AD and prion diseases by targeting cellular prion protein (PrP^C), which plays a significant role in both diseases. PrP^C acts as a substrate for replication of infectious prion (PrP^{Sc}) and as a high affinity receptor for amyloid beta oligomers (AβO). PAs consist of a combinatorial peptide moiety inserted into a protein scaffold, here the *E. coli* thioredoxin A (TrxA).
Methods: We synthesized and purified recombinant PAs. We used prion infected neuronal cells cellular and primary culture as models for prion disease and AD, respectively. We tested the stability of PAs and carried out *in vivo* experiments using transgenic 5XFAD mice. The 5XFAD mice were treated with PA8 and scaffold protein TrxA (as a control) at a 14.4 ug/day dosage for 12 weeks by intraventricular infusion usingosmotic pumps. Behavioral and biochemical/immunohistological experiments were performed.
Results: Our *in vitro* results of prion infected neuronal cells indicate that PA treatment inhibits the propagation of PrP^{Sc}. We also found that PA treatment prevents the interaction of AβO with PrP^C and reduces AβO-induced neurotoxicity in N2a cells and primary hippocampal neurons. For the first time, we observed that treatment with PA8 improves memory functions of 5XFAD mice as compared to TrxA-treated 5XFAD mice. We found that PA8 treatment significantly reduces AβO pathologies in the brain tissue of 5XFAD mice. Interestingly, PA8 significantly reduces AβO-PrP interaction and its downstream signaling such as phosphorylation of Fyn kinase, reactive gliosis as well as neurodegeneration in the brain of 5XFAD mice.
Conclusions: Overall, our *in vitro* and *in vivo* results indicate that PAs targeting PrP^C act as novel anti-prion compounds and reduce AD pathologies.

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POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

THE NOVEL NASAL FORMULATION AS THE TREATMENT FOR ALZHEIMER'S DISEASE

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Aims: Since multiple factors have been linked to the onset of AD, we believe that the most effective method to conquer AD is to develop a multitargeting therapy by the combination of medications. The novel formula should have the synergistic effect on targeting the broad range of pathological factors and increase the drug bioavailability. Our aim is to develop a multi-targeting intranasal formulation as therapeutic agent for AD and other neurlogical diseases.
Methods: *MIT preparation:* The THC was dissolved in oil phase containing an antioxidant, ethanol. The melatonin and insulin were dissolved in water. The oil was transferred into water phases beaker sonicated for about 10-15 minutes to make an emulsion. This formulation contained 83 mg/ml THC, 167 mg/ml melatonin, and 20 U/ml insulin. *Treatment*: MIT nanoformulation was administered intranasally every day for three months. The administered dose of THC, melatonin, and insulin in the MIT nanoformulation were 0.02, 0.04, and 0.008 mg/kg, respectively. *Radial Arm Water Maze was used for behavior testing. Immunostaining, ELISA assays were used for the blood and brain tissues.*
Results: MIT nanoformulation treatment can improves APP/PS1 aged mice cognitive performance, induce a decrease of Aβ in the brain, induced an increase in total tau and p-GSK3β ,and modulation of mitochondrial proteins
Conclusions: The results suggest that intranasal administration of MIT nanoformulation is beneficial for the memory rescue of APP/PS1 mice. The memory-improving effect of MIT is associated with its inhibitory effect on Aβ production in the brain areas responsible for memory, improvement of mitochondrial functions, and subsequent improvement of the neuropathologic profile in aging APP/PS1 mice. Continuous nasal delivery of MIT opens up a new pharmacotherapy path and could revolutionize the treatment of AD and other neurodegenerative disorders.

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P0278 / #2788

POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

COV-1, A NEW PEPTIDE THAT INHIBITS THE MECHANISM OF SUMOILATION, AS A POSSIBLE THERAPEUTIC STRATEGY FOR NEURODEGENERATIVE PATHOLOGIES

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Aims: SUMOylation, is a post-translational modifications fundamental in regulating several cellular processes: cell division, migration, tumorigenesis, DNA repair, homeostasis mitochondrial and stress responses. Perturbations in SUMOylation at the neuronal level contribute to numerous pathological conditions like Alzheimer's. Tau protein, in Alzheimer's disease, forms insoluble aggregates that accumulate at the level of neurons, process also influenced by SUMOylation. Understanding the basic mechanisms in the cell under normal and pathological conditions is critical for drug discovery.
Methods: COV-1, is a novel cell permeable peptide able to prevent protein SUMOylation. We are testing how SUMOylation perturbation influence Tau aggregation by using (i) Western blotting analysis; (ii) biochemistry techniques. (iii) Immunofluorescence assay on SH-SY5Y cellular lines.
Results: Through biochemical and immunofluorescence analyzes on neuroblastoma cells we have defined the doses and timing in which the peptide is efficient in decreasing global SUMOylation, also verifying its toxicity. Preliminary immunofluorescence data on neuroblastoma cells indicate that, by inducing hyperphosphorylation of Tau with okadoic acid and at the same time treating with the COV-1 peptide, they highlight how, as the SUMOylation decreases, a decrease in aggregate Tau appears to correspond. Furthermore, to better study Tau aggregation we transfected neuroblastoma cells with a Venus-tau 173/155 plasmid and these data corroborate with those of immunofluorescence showing how COV-1-induced de-SUMOylation leads to less protein aggregation.
Conclusions: After verifying that de-SUMOylation through the use of COV-1 induces less aggregation of Tau, in the future we would like to use this model to study how SUMOylation affects phosphorylation and aggregation of Tau in vivo, by injecting the Cov peptide in mouse models C57BL-6 and Tg2576 to highlight the possible involvement of SUMOylation on Tau aggregation in a pathological and control genetic background.

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P0279 / #1976

POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

CARNOSINE AND ITS DERIVATIVES AS ACTIVATORS OF IDE AND THE PROTEASOME

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Aims: L-Carnosine is an endogenous dipeptide that has high potential for therapeutic purposes, being an antioxidant with metal chelating, anti-aggregating, anti-inflammatory and neuroprotective properties. Despite its potential therapeutic values, the biomolecular mechanisms involved in neuroprotection are not fully understood. Here, we aim to demonstrate, at chemical and biochemical level, that insulin-degrading enzyme plays a pivotal role in carnosine neuroprotection. We propose to use carnosine and its derivatives as activators of both Insulin-degrading enzyme (IDE) and the proteasome.
Methods: We first investigated the toxic potential of Aβ1-42 oligomers in the absence or presence of Carnosine and/or a highly selective IDE inhibitor (6bK). We then investigated Carnosine/IDE interaction and the molecular mechanisms underlying the protective effects of Carnosine. For this purpose, we have applied high-performance liquid chromatography-mass spectrometry (HPLC-MS), Surface Plasmon Resonance (SPR), dynamic light scattering (DLS) and fluorescent methods to determine the effect of Carnosine on IDE activity, oligomerization and cooperativity. Results indicate that the neuroprotective effect of Carnosine is due to a modulation of IDE activity and oligomerization.
Results: Carnosine prevents the toxicity of Aβ1-42-induced in mixed neuronal cultures via IDE; Carnosine induces IDE oligomerization; Carnosine differently modulates IDE activity in vitro towards long and short substrates; Carnosine increases IDE cooperativity.
Conclusions: Carnosine does not bind to the IDE catalytic site, being a heterotropic modulator, as it is able to regulate the enzyme activity by binding to the exosite or to other not identified sites, causing a different interaction between the enzyme and long substrates, changing their reciprocal affinity and, in turn, IDE catalytic activity (it is an IDE activator). Carnosine derivatives also show interesting properties to be unveiled. References: ACS Chemical Neuroscience (**2022**) 13, 1588−1593. Analytical and Bionalytical Chemistry (**2022**) 414, 4793−4802.

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P0280 / #1364

POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

CYTOSKELETAL PROTEINS ARE NOVEL BINDING PARTNERS OF BRI2-BRICHOS DOMAIN

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Aims: Accumulation of misfolded proteins, mainly extracellular amyloid beta (Aβ), is the pathological hallmark of Alzheimer Disease (AD). Molecular chaperones prevent misfolding and aggregation of proteins. The Bri2 BRICHOS domain (Bri2-BRICHOS) is an extracellular molecular chaperone which efficiently prevents Aβ aggregation and neurotoxicity. A recent *in vivo* study using intravenous treatment with recombinant human (rh) Bri2-BRICHOS attenuated Aβ pathology and markedly reduced the plaque-associated astro- and microgliosis in *App* knock-in AD mice. However, biological functions of Bri2-BRICHOS need to be further evaluated. In this study, we aimed to identify novel biding proteins of Bri2-BRICHOS to get further insights into its biological functions.
Methods: We performed co-immunoprecipitation experiments of brain homogenate from App^{NL-F} knock-in AD mice, using rh Bri2-BRICHOS-mCherry or mCherry alone and subsequent nano-LC-MS/MS to identify bound proteins. Binding between rh Bri2-BRICHOS and identified proteins was validated by pull-down with rh Bri2-BRICHOS conjugated to magnetic beads. The binding of rh Bri2-BRICHOS-mCherry to the identified protein was also assessed in mouse brain slices and the SH-SY5Y cell line.
Results: We identified seven cytoskeletal proteins as binding proteins; spectrin alpha and beta chain, myosin-10, myosin-Va, drebrin, tubulin and actin. Interestingly, spectrin beta is a component of Aβ plaques, and drebrin expression is decreased in the hippocampus of AD patients. The identified proteins could be confirmed with Bri2-BRICHOS bound to magnetic beads. Immunofluorescence staining of mouse brain slices showed partial co-localization of added rh Bri2-BRICHOS-mCherry and tubulin β III signals. In addition, microtubules were stained by rh Bri2-BRICHOS-mCherry in SH-SY5Y cells.
Conclusions: We identified cytoskeletal proteins including spectrin, drebrin and tubulin as novel Bri2-BRICHOS biding proteins. Further understanding of Bri2-BRICHOS function in relation to the cytoskeleton may help evaluation of rh Bri2-BRICHOS as an AD therapy.

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P0281 / #1738

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

TREM2 AGONISM ACTIVATES HUMAN MICROGLIA IN THE CONTEXT OF AMYLOID PATHOLOGY IN VIVO

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Aims: Pharmacological activation of TREM2 represents a novel therapeutic approach to slow Alzheimer´s disease progression. Loss-of-function variants in *Trem2* have been linked to early- and late-onset AD and can accelerate amyloid pathology in animal models. Genetic ablation of TREM2 function has been suggested to lock microglia in a homeostatic state, preventing a switch to the disease-associated state supporting the phagocytotic clearance of misfolded proteins and cellular debris. The mechanisms behind TREM2-mediated activation of phagocytosis remain poorly understood. Monitoring the impact of TREM2 activation *in vivo* requires humanized animal models due to low gene sequence homologies, inherent differences in immune responses and phenotypical disparities *in vitro* and *in vivo* between mouse and human microglia. Here we study the impact of TREM2 agonism on xenografted human microglia in a mouse model of amyloid pathology.
Methods: Transgenic APP^{NL-G-F} mice transplanted with human embryonic-stem-cell-derived microglia were systemically treated with TREM2 small molecule agonists. Human microglia were sorted from the brain and subsequently assessed using multi-omics technologies. Responses were compared to corresponding endpoints in *in vitro* microglia studies.
Results: Small molecule pharmacological activation of TREM2 leads to significantly increased activation of xenografted human microglia as assessed by cytokine and chemokine expression in the presence of amyloid pathology in APP^{NL-G-F}, but not in APP^{wt} mice. Other changes in the transcriptome profile are observed that suggest a switch to disease-associated phenotypes. These effects are observed at exposures consistent with activation of TREM2 *in vitro* as monitored by pSYK and sTREM2 levels.
Conclusions: The human microglia xenograft mouse model is a valuable tool to study the impact of pharmacological TREM2 activation and other manipulations on human microglia in the presence and absence of AD neuropathology.

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P0282 / #1068

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

A MONOCLONAL ANTIBODY AGAINST TREM2 MODIFIES MICROGLIAL INTERACTION WITH THEIR LOCAL ENVIRONMENT

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Aims: To use a novel monoclonal antibody against TREM2 to investigate the role this receptor plays in mediating microglial state and interaction with their environment.
Methods: Two *ex vivo* techniques were applied in this study. First, Acute brain slices from adult Iba1-GFP mice were treated for 1 hour with an anti-TREM2 antibody or a control isotype antibody prior to being fixed for morphological analysis or live imaged for surveillance analysis. Furthermore, organotypic hippocampal slice cultures from neonatal mice were treated for 24 hours with an anti-TREM2 antibody or a control isotype antibody prior to being fixed and immunostained.
Results: We found that short-term (1 hour) treatment of *ex vivo* acute brain slices with this anti-TREM2 antibody increases morphological complexity of microglia that drives enhanced surveillance activity, potentially increasing contacts between microglia and neurons. Furthermore, prolonged (24 hour) treatment with this antibody in organotypic brain slice cultures elevates lysosomal volume in microglia, potentially indicating that these cells are in a heightened activation state and phagocytosing more synapses.
Conclusions: This work has shown that TREM2 is involved in regulating microglial activation state in non-disease conditions and exogenous stimulation of this receptor may alter how microglia engage with other cells in their environment.

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P0283 / #1817

POSTERS: A02.L. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CD33

INHIBITION OF CD33-SIALIC ACID BINDING IN LATE-ONSET ALZHEIMER'S DISEASE

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Aims: While Alzheimer's disease pathogenesis is still poorly understood, genetic studies have clearly indicated a causal role for microglia, the innate immune cells of the CNS. Despite the progress made in identifying genetic risk factors, such as CD33, and underlying molecular changes, there are currently limited treatment options for LOAD. Based on the known function of CD33 being an inhibitory molecule, we hypothesize that CD33 activation leads to microglial suppression, resulting in the inability to resolve inflammatory processes and mitigate pathogenic amyloid plaques, which may heighten susceptibility to neuronal loss and contribute to AD progression. Here, we investigate the effects of sialic acid binding peptides on CD33 inhibition and downstream microglial response.
Methods: Sialyated glycoproteins were immobilized onto microtiter plates overnight and then incubated with recombinant hCD33-Fc and increasing doses of peptide. CD33 binding was detected using an anti-human IgG-HRP antibody and fluorescent intensity was quantified to determine the effect of the peptides on CD33-sialic acid binding. Following treatment with peptides in human monocyte-derived microglia-like cells (MDMi), the effect of the peptides on microglial function and immune signaling is determined by measuring gene expression changes in markers of microglial activation by qPCR and amyloid-beta uptake by flow cytometry.
Results: Treatment with peptide 1 resulted in a dose-dependent decrease in hCD33-Fc binding to immobilized sialyated glycoprotein. The effect of peptide 1 on markers of microglial activation and amyloid beta uptake will be discussed.
Conclusions: Sialic acid binding peptides were determined to inhibit CD33 binding to sialyated glycoproteins *in vitro*. Ongoing experiments aim to determine if inhibiting CD33 using sialic acid binding peptides is sufficient to resolve amyloid beta induced suppressed microglial immune signaling and increase microglial phagocytosis, response, and mitigate pathology.

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P0284 / #414

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

HARNESSING IPSC-DERIVED MICROGLIA TO DELIVER THERAPEUTICS IN THE BRAIN

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Aims: Delivery of effective therapeutics to the brain has been limited by the protective qualities of the blood-brain barrier. Studies have sought to circumvent the BBB via noninvasive techniques like transport/carrier and chimeric constructs. However, brain-specific vs systemic uptake remains elusive, let alone potentially problematic in cases of peripheral toxicity. More invasive techniques like direct injection of peptides or viral vectors have also been proposed. However, these methods require multiple treatments for long-term therapeutic efficacy with limited diffusion through the brain. Recently, immune cell therapies are becoming mature options for a variety of diseases. Coupled with advancements in gene editing techniques, they offer long-term therapeutic efficacy that address many of these limitations. As the innate immune cell of the brain, microglia stand out as the ideal candidate for immune cell therapies in the CNS.
Methods: Patient-derived iPSCs were CRISPR-engineered to produce membrane-bound neprilysin (NEP) and secreted neprilysin (sNEP) under the control of the endogenous CD9 promoter. iPSCs were differentiated into microglial progenitors and transplanted into WT-MITRG and 5x-MITRG transgenic mice at 2 months of age. After 4.5 months, mice were sacrificed and whole brains were harvested for IHC and biochemical analysis.
Results: CRISPR-engineered microglia delivered neprilysin payloads in response to β-amyloid pathology in the hippocampus and cortex of 5x-MITRG chimeric mice. In comparison to WT cells, NEP and sNEP transplanted microglia reduced levels of AB-plaques and oligomers in the brain. Biochemical analysis further revealed delivery of neprilysin prevented synaptic degeneration and reduced astrogliosis. Moreover, transcriptomic activation of neprilysin production in response to pathology demonstrated therapeutically favorable outcomes without off-target degradation of homeostatic neuropeptides.
Conclusions: These results indicate iPSC-microglia can be engineered *ex vivo* to deliver therapeutics with specificity at the sites of pathology in the brain.

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P0285 / #487

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

ENGINEERING AN INHIBITOR-RESISTANT HUMAN CSF1R VARIANT FOR MICROGLIA REPLACEMENT

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Aims: Recent efforts have sought to develop therapeutic strategies for the replacement of dysfunctional microglia with peripheral macrophages. However, such approaches require hazardous conditioning methods like chemotherapy or irradiation to promote engraftment of peripheral myeloid cells that, despite long-term brain residence, remain transcriptionally and functionally distinct from microglia. One potential solution would be to efficiently deliver stem cell-derived microglia that closely mimic the transcriptional and functional characteristics of human microglia in the brain. However, achieving robust engraftment into the occupied microglia niche remains challenging. We sought to develop an alternative approach by generating iPSC-microglia (iMG) carrying a single amino-acid point mutation within CSF1R that maintains canonical signaling while conferring resistance to CSF1R-inhibitors (CSF1Ri).
Methods: Comparative analysis of the crystal structure of CSF1R bound to PLX3397 and PLX5622 led to the identification of the 795-position as an optimal target for inhibitor resistance. CRISPR-editing was used to introduce three homozygous point mutations into an isogenic series of human-iPSCs. RNA sequencing of WT- and variant-iMG cultured with CSF1Ri identified G795A as the ideal variant for transplantation studies in xenotolerant MITRG chimeric mice.
Results: Biochemical and cell-based assays show G795A confers broad CSF1Ri resistance with no discernable gain or loss of function of CSF1R signaling. Xenotransplantation studies demonstrate G795A-iMG exhibit nearly identical gene expression to WT-iMG after engraftment in the murine brain and respond robustly to systemic inflammatory challenge. Moreover, G795A-iMG progressively expand in the presence of PLX3397, replacing endogenous microglia to occupy the brain, and persist after cessation of inhibitor treatment.
Conclusions: Taken together, these findings demonstrate a novel and translationally impactful tool to enhance the study of microglia function in chimeric models and the development of new therapies involving the delivery of engineered iMG as 'living drugs'.

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P0286 / #1121

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

3D MICROSCOPY UNRAVELS DETAILS IN AMYLOID PLAQUE-MICROGLIA INTERACTION IN APP/PS1 MICE

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Aims: We aimed to visualize details of amyloid plaque – microglia interaction in 3D in transgenic mice at different stages of amyloid plaque formation and at different ages of the mice.
Methods: We cross-bred amyloid plaque forming APP/PS1 mice with CX3CR1-GFP mice expressing green fluorescent microglia. Female offspring were examined at the age of 6 and 13 months. We took 100 µm coronal sections at the level of the dorsal hippocampus and stained them with anti-beta amyloid D54D2 antibody with DAPI in the mounting medium. Isolated clusters of an amyloid plaque and surrounding microglia were imaged in a dense 35 µm stack with a ZEISS LSM 800 confocal microscope and 3D rendered.
Results: We imaged 54 clusters from 13-month-old mice and 29 clusters from 6-month-old ones, n=4. We created a numerical scale to describe characteristic of plaques, microglia-plaque and microglia-microglia interactions. We found that microglia make a contact with the dense plaque core or other microglia surrounding the plaque, but not with the diffuse amyloid-beta halo around the plaque.
Conclusions: 3D imaging and rendering of amyloid plaques shed new light into microglia-plaque interactions and help to better understand the function of microglia at different stages of amyloid plaque formation

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P0287 / #331

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

AN IN VITRO PRIMARY RODENT MICROGLIA MODEL TO ENABLE DRUG DISCOVERY FOR NEURODEGENERATIVE DISEASES

Dawn Lau[1], Carmen Navarron Izquierdo[1], Marcus Pendery[1], Leena Patel[1], Alexandra Van Ingelgom[1], Leela Phadke[1], Kathryn Costelloe[1], Melissa Salazar[2], Sharan Rajakumar[1], Dervis Salih[2], Carlo Sala Frigerio[2], Paul Whiting[1], Lorenza Magno[1]
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Aims: Microglia have been shown to be a key contributor to several neurodegenerative diseases, such as Alzheimer's disease (AD). Recent genome-wide association studies have identified several risk genes, specific to or highly enriched in microglia, for AD, highlighting an increasing focus on microglia-targeted drug discovery. However, drug development for microglia-targeted therapeutics is limited and there is a lack of physiologically relevant models for drug discovery. Our aim was to develop a primary rodent *in vitro* microglia model system which is highly robust, amenable for screening, while recapitulating many of the features of *in vivo* microglia.
Methods: We established different culturing conditions to represent homeostatic (serum-free), activated (with serum), and acutely disease-challenged microglia populations, and characterised gene expression by single-cell RNA sequencing as well as morphology. We designed a suite of functional assays relevant to neurodegenerative disease and suitable for target validation and identification, including phagocytosis, cytokine production, and calcium flux.
Results: We show that the homeostatic microglia are transcriptionally and morphologically heterogeneous, in line with *in vivo* microglia, and respond differently to acute challenges in comparison to activated microglia in the various phenotypic assays. We also used tool compounds to validate our *in vitro* model system and assays.
Conclusions: We have developed a robust, high throughput *in vitro* primary microglia model to enable identification and validation of novel microglia targets for drug discovery.

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P0289 / #2115

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

CLEC5A DEFICIENCY AMELIORATES THE AB-INDUCED NEURODEGENERATION IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly. The β-amyloid (Aβ) accumulation, one of the pathological hallmarks of AD, increases the risk of dementia via the toxicity to neurons and induces neuroinflammation in the diseased brain. C-type lectin domain family 5 member A (CLEC5A), a pathogen recognition receptor, was found to participate in microglial inflammasome activation under virus infection. In this study, we hypothesize the CLEC5A involved in the microglial activation against the Aβ-induced AD pathology.
Methods: For in vivo study, the AD mouse model was crossed with CLEC5A knockout (KO) mice to identify the behavioral and pathological changes. For in vitro study, CLEC5A expression was knockdown using shRNA in microglial cell line (BV2). Immunohistochemistry (IHC), qPCR, ELISA were used to identify the impact of CLEC5A on neuroinflammation in both models.
Results: In AD mouse with CLEC5A KO, their spatial memory was improved and the hippocampal Aβ deposits were decreased. In BV2 cells with CLEC5A knockdown, the phagocytosis of Aβ was increased and the inflammatory cytokine, TNF-α, was also decreased under Aβ stimulation.
Conclusions: Lack of CLEC5A improved memory function and decreased Aβ deposits in AD mice. The reduced inflammatory signaling and increased Aβ phagocytosis were also found in CLEC5A deficient microglia. This study implied that the microglial CLEC5A may involve in the Aβ clearance and inflammatory signal in AD.

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P0290 / #630

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

EFFECTS OF PALMITOYLATED ANALOG OF PROLACTIN-RELEASING PEPTIDE IN 3XTG-AD MODEL

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Aims: Prolactin-releasing peptide (PrRP), is a neuropeptide with anorexigenic and antidiabetic properties. Because of the suggested link between obesity and/or type 2 diabetes and Alzheimer's disease (AD) development, anorexigenic and/or antidiabetic compounds were repurposed as potential neuroprotective compounds.
Methods: In this study, we examined the neuroprotective properties of palmitoylated PrRP analog and liraglutide, a glucagon-like peptide 1 receptor agonist. The study was made in triple transgenic 3xTg-AD mice, a model of both, AD-like β-amyloid (Aβ) and Tau pathology. Mice were treated subcutaneously once daily for four months with palm^{11}-PrRP31 (5 mg/kg) or liraglutide (0.2 mg/kg). Potential neuroprotective and anti-inflammatory properties were immunohistochemically measured.
Results: Using 3xTg-AD model of neurodegeneration, we tested potential beneficial effects of PrRP analog palm^{11}-PrRP31. 3xTg-AD mice developed Aβ and Tau pathology and furthermore, microgliosis and astrocytosis in hippocampus, cortex and amygdala. These pathologies were significantly reduced by four months treatment with palm^{11}-PrRP31.
Conclusions: In summary, lipidized analogs of PrRP seem to be potential neuroprotective agents but the exact mechanism of action must be further studied.

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P0291 / #997

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

PHARMACOLOGICAL MODULATION OF INFLAMMATORY PATHWAYS IN PRIMARY MICROGLIA

Carmen Navarron Izquierdo[1], Dawn Lau[1], Marcus Pendery[1], Hannah Woodward[1], Melissa Salazar[2], Kathryn Costelloe[1], Fiona Jeganathan[1], Carlo Sala Frigerio[2], Dervis Salih[2], Paul Whiting[1], Lorenza Magno[1]
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Aims: Neuroinflammation has been recently described as one of the main hallmarks of neurodegenerative diseases. Novel GWAS studies have associated microglia genes with increased risk of Alzheimer's disease (AD) pointing out potential new targets for the treatment of AD with microglial cells in the center of new promising therapeutic approaches. Among them, oligoadenylate synthetase 1 (OAS1) as well as phospholipase C-gamma 2(PLCG2) variants have been recently related to increased and decreased risk of Alzheimer's disease (AD) respectively, making them potential candidate targets for AD treatment. Our main objective is to validate microglia-related potential new targets for the treatment of neuroinflammation associated with neurodegenerative diseases.
Methods: To address this objective, we use primary rat microglia cell cultures in serum-free microglia (recently shown that mimic better the in vivo homeostatic microglia) and classical serum-containing media. Rat brain microglia are plated in 96 or 384 formats and automation is used to support high-throughput assays, using LPS as a well-established model of neuroinflammation. In particular, we have optimized a compound addition protocol in combination with secretome assays, inflammasome activation and gene expression levels as endpoints.
Results: To evaluate Oas1 and Plcg2 as potential targets for AD, we here focused on addressing microglia inflammatory response upon treatment. We show that pharmacological targeting of these pathways with available and in-house developed tools modulates microglia inflammasome, secretome, and mRNA levels, in a dose-dependent manner.
Conclusions: We integrate here our high-throughput microglia platform upon LPS stimulation together with compound administration to target two relevant pathways for AD. Evaluation of the modulation of the inflammatory response by three different readouts is a first step that gives us key information on how targeting Oas1 or Plcg2 can impact the inflammation associated with AD.

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P0292 / #920

POSTERS: A02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASTROGLIA

OPTOGENETIC ACTIVATION OF ASTROCYTES IN HIPPOCAMPUS RESTORES LTP FORMATION IN ALZHEIMER'S DISEASE MICE MODEL

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Aims: Astrocytes are one of three types of nerve cells that are able to control neuronal activity by means of the gliotranmitters release and calcium level changes. Possible ways to control activity of them is a method of optogenetic. Previously was shown (Gerasimov *et al.*, 2021), that metabotropic opsins (Opto-a1AR) are preferred for an astrocytic activation leading to enhancement of neuronal activity. Evaluation of astrocytes optogenetic stimulation on LTP formation was an objective of the current study.
Methods: Metabotropic optogenetic construct Opto-a1AR-EYFP was expressed in astrocytes in CA1 region of mice hippocampus by stereotaxic surgery; LTP experiments were conducted on an acute brain hippocampal slices of WT and 5xFAD (model with genetic Alzheimer's disease) in age of 6 months. Light parameters for activation of optoconstuct equaled 5 min of 100 ms pulses with interval of 1 sec and were determined in the previous work.
Results: Mean value of slope for last 5 min of one-hour recording were estimated. In WT group the percentage of mean slope value significantly increased after optogenetic stimulation: 162.8±6.5 (n=7) compared with 193,7±13,5 (n=4), p=0,0436, Student's t-test. In 5xFAD group the percentage of this values also significantly increased: 116.3 ±6.5 (n=8) vs 156.4±8.3 (n=4), p<0.0001, Student's t-test. No significant changes were observed between control WT group and 5xFAD group after optogenetic activation of Opto-a1AR: 162.8±6.5 (n=7) vs 156.4±8.3 (n=4), p=0.4742.
Conclusions: In this study was determined that impulse mode of optogenetic stimulation of astrocytes with T = 1 s, t = 100 ms parameters had an effect on formation of long term plasticity and leads to strengthen of synaptic transmission in Alzheimer's disease mice model.

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P0293 / #1207

POSTERS: A02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASTROGLIA

GLYCINE TRANSPORTER-1 EXPRESSION IN ASTROCYTES RESCUES COGNITIVE IMPAIRMENT VIA REGULATING MICROGLIAL PHAGOCYTOSIS IN MOUSE MODELS OF ALZHEIMER'S DISEASE

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Aims: Glycine transporter 1 (GlyT1), expressed predominantly in astrocytes, is responsible for the glycine reuptake from the synaptic cleft in the central nervous system. Previous reports show that glycine concentration is elevated in the cerebrospinal fluid (CSF) of patients with Alzheimer's disease (AD). It could alter glial function which is important for neuroprotection through Aβ phagocytosis. In this study, we aim to evaluate GlyT1 as a novel therapeutic target for Alzheimer's disease.
Methods: To investigate the effect of GlyT1 in the AD brain, we expressed GlyT1 specifically in the astrocytes of the AD model mouse brains by icv injection of AAV with GFAP promoter. Then we evaluated the glial function by immunohistochemistry and ex vivo phagocytosis assay. We conducted behavioral experiments to test the improvement of cognitive function. We also performed in vitro assays using human glial cell lines.
Results: We found that GlyT1 expression is downregulated in the human AD brain, particularly in astrocytes adjacent to Aβ plaques. We revealed that it is mediated by the Aβ-induced PKCβ signaling pathway. To investigate the role of GlyT1 in the AD brain, we expressed GlyT1 using an AAV vector with the GFAP promoter. It resulted in improved microglial phagocytosis, reduced Aβ plaques, and rescued cognitive impairment. In vitro experiments showed a high concentration of glycine mediated by GlyT1 downregulation induces internalization of glycine receptors in microglia, resulting in intracellular Ca^{2+} accumulation and dysfunction of Aβ phagocytosis. GlyT1-overexpressing cells were resistant to the adverse effects of the high concentration of glycine on glial function.
Conclusions: Together, our results demonstrate that Aβ-induced downregulation of GlyT1 in astrocytes results in microglial dysfunction. Thus, we propose AAV-mediated GlyT1 expression in astrocytes as a novel therapeutic method for Alzheimer's disease.

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P0294 / #500

POSTERS: A02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASTROGLIA

TUMOR-INTERACTING ASTROCYTIC SIGNALING RESTRICTS THE PATHOGENESIS OF ALZHEIMER'S DISEASE

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Aims: A 35% lower incidence of Alzheimer's disease (AD) among older cancer survivors was reported versus those without cancer history. Astrocytes are important components for brain tumors and AD pathogenesis. We aim to investigate how brain tumor reduces AD pathogenesis via astrocytic signaling.
Methods: Two mouse brain cancer cell lines were introduced into 5xFAD and APPswe transgenic mice. Mice were sacrificed two weeks after tumor injection. Their brains were processed for amyloid plaque immunostaining and isolation of astrocytes and tumor cells for generating cell-specific RNA sequencing data, which then were analyzed and modeled by the *CCCExplorer* software to predict salient crosstalk signaling between astrocytes and tumor cells.
Results: Significant reduction of amyloid burden was examined in the AD mice injected with tumor in comparison to the mice injected with PBS only. Among the significantly differentially expressed genes in astrocytes of tumor-injected vs PBS-injected AD mice, we found decreased expressions of *APP* and *PS2* and elevated expressions of several enzymes in responsible for Aβ clearance, i.e., *IDE*, *ACE*, and *MMP2* & 9. *CCCExplorer* predicted 45 ligands, 46 receptors and 12 signaling pathways within the astrocytes were activated by interacting with tumors. GO/KEGG enrichment analysis of the astrocytic receptors and ligands identified PI3K-Akt as a top signaling pathway.
Conclusions: Amyloid burden is significantly reduced in AD mice bearing brain tumors. We showed that tumor-astrocyte interaction suppressed Aβ production and increased Aβ clearance. Ongoing work is to validate how activating astrocytic PI3K-Akt signaling alleviate AD, and investigate whether tumor-associated astrocytic receptors and ligands also mediate interactions with other types of cells in the brain to alleviate AD.

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P0295 / #2055

POSTERS: A02.O. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

E2F4DN-BASED GENE THERAPY RECOVERS LONG-TERM POTENTIATION, HIPPOCAMPAL-DEPENDENT MEMORY AND NEURONAL DEATH IN HOMOZYGOUS 5XFAD MICE.

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Aims: Neurons are usually regarded as postmitotic cells, nevertheless they can re-enter cell cycle and survive as hyperploid neurons during the course of different neurodegenerative diseases. Recently, it has been described that cell-cycle reentry, followed by DNA duplication (tetraploidization), and synaptic failure are two early hallmarks of Alzheimer's disease (AD). E2F4 becomes phosphorylated in APP/PS1 mice and in Alzheimer´s patients. We have demonstrated that the phosphorylation of two conserved Thr residues of E2F4 is necessary to induce neuronal tetraploidization and cognitive loss in AD. Therefore, it was developed a novel therapy consisting in neuronal expression of a dominant negative form of E2F4 (E2F4DN), not phosphorylatable. Thus, we hypothesized that viral expression of E2F4DN could correct AD-associated synaptic dysfunction.
Methods: To this aim, we analized the membrane basal properties in hipocampal primary cultures and the synaptic function after the viral expression of E2F4DN
Results: First of all, basal membrane properties were analyzed through whole-cell recordings in hippocampal primary cultures expressing E2F4DN. We demonstrated that it does not alter basal properties of hippocampal neurons. Afterwards, we expressed E2F4DN (intravenous administration of AAV-E2F4DN) in control and homozygous 5xFAD mice. Synaptic function was measured by electrophysiological recordings of field excitatory postsynaptic potentials in hippocampal CA3-CA1 synapses. We found that E2F4DN prevents long-term potentiation (LTP) loss. Furthermore, this LTP maintenance leads to cognitive improvement. 5xFAD mice treated with our therapy present a noticeable improvement in two hippocampal-dependent memory tasks (novel-object location and contextual fear conditioning). This effect correlates with the increase of key LTP regulators and neuronal survival.
Conclusions: Thus, we report here that E2F4DN-based gene therapy represents a promising multifactorial approach for AD treatment with capacity to prevent cognitive decline.

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P0296 / #2489

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROGENESIS AND IPSC AND BRAIN ORGANOIDS

BRAIN ANGIOGENESIS-INFORMED STRATEGY TO DERIVE BRAIN CAPILLARY ENDOTHELIAL CELLS

Habib Baghirov
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Aims: Human induced pluripotent stem cell (hiPSC)-based models of the blood-brain barrier (BBB) hold much promise since hiPSC are species-relevant, scalable, amenable to genetic engineering and can be derived from patient samples. I hypothesized that establishing a bona fide hiPSC model of BCEC requires a comprehensive knowledge of interactions between nascent brain endothelium and neural progenitors at the embryonic stage – in other words, tracing the development of BCEC in the context of cues originating from their environment. Therefore, I sought to formulate a brain angiogenesis-informed strategy for differentiating hiPSC into BCEC.
Methods: I mined public datasets and used a variety of computational approaches to analyze cell development trajectories, direct cell interactions and multicellular programs involving BCEC and neural progenitors at different time points during brain angiogenesis. I subsequently matched the analysis results against open compound libraries to identify ways to simulate those environmental cues chemically.
Results: The computatonal analysis detected a number of interactions known to be crucial in BCEC development, and identified several others, less studied. Based on those results, supplemented with open compound library analysis, I formulated a tentative hiPSC differentiation strategy roughly based on the differentiation of generic endothelial cells but incorporating these angiogenesis-informed findings, with the assumption that they may steer hiPSC toward a specific phenotype that makes BCEC unique in the endothelial landscape.
Conclusions: The analysis of environmental cues during BCEC development may serve as a basis for modeling BCEC from hiPSC. The tentative proposed strategy, nevertheless, requires experimental validation.

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P0297 / #457

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

GLIAL SENESCENCE IN ALZHEIMER'S DISEASE

Nurun Fancy[1], Amy Smith[2], Robert Muirhead[1], Vicky Chau[1], Stergios Tsartsalis[3,4], Karen Davey[5], Aisling Mcgarry[6], Combiz Khozoie[1], Nanet Willumsen[1], Johanna Jackson[1], Paul Matthews[1]
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Aims: The greatest risk factor for Alzheimer's disease (AD) is ageing. One of the major hallmarks of ageing is the accumulation of senescent cells. The aims of this study were to i) quantify senescence load in microglia, oligodendrocyte and astrocyte in *post-mortem* human brain from AD and non-disease control (NDC), ii) determine the major mechanistic driver of increased cell senescence in AD.
Methods: We employed Image Mass Cytometry to co-localise cell type markers (IBA1, OLIG2, GFAP), senescence markers (SA-βGal and p16) and β-amyloid (4G8) to detect senescence in tissues from Middle Temporal Gyrus (MTG) of 10 AD and 10 NDC. snRNA-seq was generated from Entorhinal, MTG and Somatosensory Cortex of 9 AD and 9 NDC. Senescent genesets curated from public databases were used for enrichment analysis in snRNA-seq using AUcell and dream (variancePartition). β-amyloid associated senescence signature was characterised by trajectory analysis using Monocle3.
Results: In AD, 25-35% microglia, oligodendrocyte and astrocyte were positive for SA-βGal resulting in 4 to 5-fold more senescent glia than in NDC. More than 25% microglia within 10 µm around β-amyloid plaques in AD showed expression of SA-βGal while only 3% of microglia >10 µm had associated senescence markers. Geneset enrichment showed significantly increased expression of senescence genes in AD compared to NDC and were positively correlated with greater amyloid load in all three glial cells (not in neurons)**.** Trajectories of the glial nuclei described increased expression of pathways related to replicative senescence, cellular activation and stress response in microglia and oxidative stress in oligodendroglia, and astrocyte.
Conclusions: Our results highlight the high burden of senescent glia and provide evidence for different mechanisms of senescence in microglia (both replicative and stress-induced) relative to oligodendroglia and astrocyte (stress-induced) in AD.

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P0298 / #2702

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

ANALYSIS OF THE EFFECT OF MEMANTINE ON ANTI-PSYCHOTICS IN ALZHEIMER'S DISEASE USING THE COMMON DATA MODEL

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Aims: The effect of N-methyl-d-aspartate receptor antagonist on reduction of neuropsychiatric symptoms of dementia was proven in randomized controlled trials. The aim of this study is to check whether this drug reduce the antipsychotics significantly through common data model.
Methods: This study included approximately 4 million patient-based retrospective cohort data spanning 10 years across three hospitals (Kangwon National University Hospital, Ajou University Hospital, Kyung Hee University Hospital), which was then converted to OMOP CDM. This included standardized data with the same structure to obtain network-wide results through distributed research networks using the same analysis program among collaborating organizations. We conducted a retrospective, observational, cohort study of all outpatients with AD aged over 60 years. AD cohorts were restricted to those who were newly diagnosed and prescribed anti-dementia medications within 6 months from the initial AD diagnosis.The index date was defined as the day of AD diagnosis in each cohort. We included patients within an observational period of over 2 years, comprising 6 months before and 1.5 years after the index date in our database.OMOP CDM version 5.3 was used in this study, which included the OMOP analysis tools on the ATLAS interactive analysis platform. ATLAS version 2.7.6 and FEEDER-NET were used.
Results: For 156 patients with newly diagnosed AD, N-methyl-d-aspartate receptor antagonist was prescribed and 1:3 propensity score matching was made for those using acetylcholine esterase inhibitors. The reduction of anti-psychotics was not observed for any of 3 hospitals as Kangwon National University Hospital (HR 0.35, p=0.19), Ajou University Hospital (HR 2.27, p=0.19) and Kyung Hee University Hospital (HR 1.8, p=0.44)
Conclusions: There were no significant differences in the prescribing of anti-psychotics between groups with N-methyl-d-aspartate
receptor antagonist and acetylcholine esterase inhibitors using OMOP-CDM.

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P0299 / #2219

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

THE INVOLVEMENT OF NMDA RECEPTORS IN THE PREVENTION OF ABETA OLIGOMERS TOXICITY BY TRODUSQUEMINE

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Aims: Alzheimer's disease is characterized by the aggregation of the amyloid β peptide (Aβ) in senile plaques. One of the mechanisms of Aβ oligomer cytotoxicity is the aberrant interaction of this species with the phospholipid bilayer, causing an impairment of Ca^{2+} homeostasis, in which the NMDA receptors plays an important role due to their mechanosensitivity. Recently, the natural aminosterols, such as trodusquemine, showed the ability to bind neuronal membranes and prevent the interaction of aberrant aggregates, thus decreasing their toxicity. In this study we have investigated an additional possible involvement of the NMDA receptors in the trodusquemine protective role.
Methods: The potential effect of trodusquemine on the NMDA receptors opening was evaluated observing the influx of Ca^{2+} on human SH-SY5Y neuroblastoma cells using specific agonist and antagonist of the receptors in the presence or in the absence of the aminosterol and $Aβ_{42}$ oligomers, known as ADDLs. Moreover, the FRET technique was used to inversigate specific interaction between NMDA receptors and trodusquemine.
Results: The data showed that trodusquemine can significantly prevent Ca^{2+} dyshomeostasis caused by $Aβ_{42}$ oligomers. Notably, this protective effect appeared to arise from the modulation of the NMDA receptors opening after the interaction of the aminosterol with the cell membrane.
Conclusions: All these data highlight a further mechanism of action by which trodusquemine prevent oligomer toxicity through the prevention of an excessive opening of NMDA receptors. In particular, in addition to inhibiting the binding of Ab_{42} ADDLs to cell membrane, trodusquemine also appears to prevent the ADDL-induced activation of NMDA receptors in case the oligomers are able to bind to the membrane. Furthermore, this study provides additional evidences that natural aminosterols can be promising molecules in the treatment of neurodegenerative diseases.

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P0300 / #2735

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

MOVING BEYOND TRANSCRIPTOMICS TO IDENTIFY DELIVERY TARGETS AT THE BLOOD-BRAIN BARRIER

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Aims: One approach to CNS drug delivery relies on receptor-mediated transcytosis across brain capillary endothelial cells (BCEC). It requires BCEC shuttle targets enabling this transport. With multi-organ atlases, one can search for targets by viewing BCEC in the context of all cells in the body. Poor correlation between mRNA and protein levels makes it challenging to base target selection on transcriptomics alone. I sought to create a proteomics atlas of cells relevant to biodistribution, and use it to identify plasma membrane-associated targets expressed on and specific to BCEC.
Methods: I integrated publicly available datasets to create a proteomics atlas. I further applied deep learning to deconvolve cell type contribution in bulk samples, and to infer preferential localization of hits to apical or basolateral surfaces. I combined this approach with a transcriptomics-based analysis allowing finer granularity, including isoform identification and target expression on cells beyond the blood-brain barrier. Finally, I analyzed protein turnover, hypothesizing that its rate is crucial for all potential shuttle targets and especially for solute carriers whose use may rely entirely on hijacking their constitutive recycling to direct constructs toward the abluminal membrane.
Results: Despite shallower coverage, the proteomics atlas allows quantitative identification of potential targets. Feature maps derived from combined transcriptomics and proteomics data help identify their contribution in bulk samples. Surface distribution can be predicted with high accuracy using embeddings from transformer architecture-based language models. Turnover data adds another dimension to target choice. Splice isoforms of several hits increase their specificity to BCEC or, vice versa, complicate their potential use.
Conclusions: Combined analysis of proteomics and transcriptomics data allows identifying potential delivery targets on BCEC. Overall, few targets identified using this approach match those commonly used for CNS drug delivery.

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P0301 / #1675

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

PHARMACOLOGICAL PARAMETERS NECESSARY TO SELECT LEAD COMPOUNDS FROM PYRAZOLE-DERIVED ANTI-ALZHEIMER DRUGS

Patricia Melnyk[1], Christophe Mesengeau[1], Pascal Carato[2], Nicolas Renault[1], Mathilde Coevoet[1], Paul-Emmanuel Larchanche[1], Amelie Barczyk[3], Luc Buee[1], Nicolas Sergeant[1]
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Aims: The rationale to define the biological and molecular parameters from structure-activity relationships is mandatory for the lead selection of small drug compounds. Several series of small anti-Alzheimer molecules have been synthesized based on a computer-assisted pharmacophore design derived from two series of compounds whose scaffold originates from chloroquine or amodiaquine. Compounds from this latter series as well as from the first pharmacophore-derived series share in vivo activities towards both amyloid and tau pathology Alzheimer's disease lesional processes. They reduced amyloid deposition et neurofibrillary degeneration, restore cognitive-associated impairments, and reduced neuroinflammation. Their selection was achieved using a cell-system assay including principally the repression of Ab_{1-x} production and increased stability of APP metabolites including carboxy-terminal fragment-a (CTFa) and the amyloid intracellular domain (AICD). The most efficient compounds are potent non-competitive b-secretase inhibitors with various levels of lysosomotropic and autophagy modulatory activities. To further gain into parameters related to these properties, in the present pyrazole-derived series additional markers were considered including $Ab_{x-40/42}$, sAPPa, and sAPPb as well as p62 and LC3-I/LC3-II markers of autophagy and aggrephagy.
Methods: Neuroblastoma SY5Y-APP695WT were treated with incremental concentration of tow series of pyrazole compounds. Abeta1-x, and Abeta x-42/x-40 were determined using ELISA assays. All other markers including CTFs, AICD, p62 and LC3-I/LC3-2 were analyzed by Western-blotting.
Results: Structure-activity around polyamine moieties enabled, together with prior SAR results, to reduce the production of Ab_{1-x} with little modification of $Ab_{x-40/42}$. The non-competitive b-secretase inhibitory activity was associated with a decreased ratio of p62/(LC3-I/LC3-II). Increased stability of CTFa and AICD was rather indicative of the lysosomotropic activity whereas cell toxicity was promoted by the sole p62 enhanced expression driven by the loss of nitrogen moieties.
Conclusions: These parameters enable the selection of potent anti-Alzheimer drugs for the mode of action remains ill-defined.

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P0302 / #2778

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

INTERACTIONS OF AROUSAL STATES WITH THE BENEFICIAL EFFECTS OF 40HZ TREATMENT ON AMYLOID PATHOLOGY

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Aims: Gamma entrainment using sensory stimulation (GENUS) is emerging as a promising treatment for Alzheimer's Disease. In particular, several groups have shown that this non-invasive treatment can reduce the burden of pathological amyloid and tau in mouse models and the first clinical trials have begun to suggest beneficial effects in humans. Therefore, it is paramount to understand how GENUS exerts its beneficial effects and what clinically relevant factors can modulate treatment outcomes. The aim of this study is to characterize the bidirectional interactions between GENUS and brain states, such as sleep or neuromodulatory transmitter release (e.g. acetylcholine, noradrenaline).
Methods: We use the 5xFAD mouse model of amyloid accumulation, wherein the amyloid-reducing effects of GENUS are well characterized. In 5xFAD mice, we employ closed-loop electrophysiological recordings in freely moving mice to characterize the effects of GENUS on arousal states. Moreover, we use genetically encoded fluorescent sensors for neuromodulatory neurotransmitters to assess how GENUS affects the brain's neuromodulatory state. Finally, we combine in-vivo pharmacology with biochemical assays (i.e. ELISA) and immunohistochemistry to characterize how arousal state modulates the effects of GENUS on amyloid burden.
Results: We find that the beneficial effects of GENUS significantly depend on brain state. Interestingly, we find that this effect is unlikely to be mediated by differences in brain entrainment to stimulation at gamma frequency. On the other hand, we find no indication that GENUS exerts its beneficial effects via modulating the arousal state of the brain.
Conclusions: Our data suggest that the clinical outcome of GENUS may depend significantly on the brain state. Moreover, our data suggest that local entrainment of brain activity to stimulation at gamma frequency can be mechanistically decoupled from the beneficial effects of GENUS.

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P0303 / #1366

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

COMBINATION OF CIPROFLOXACIN/CELECOXIB AS A NOVEL THERAPEUTIC STRATEGY FOR AD

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Aims: The pathophysiology of Alzheimer's disease (AD) is complex and underlies multiple pathways including neuroinflammation, impaired recycling processes, and autophagy. Dysregulations of miRNA expression and alterations in dicer activity demonstrated in AD brain, impact brain size, behavior, and longevity. Due to the disease's complexity and diverse manifestation, combined multi-targeted therapy is needed. To target the various relevant pathways, the combination of ciprofloxacin, which induces dicer activity and regulates microRNA synthesis, and celecoxib, an NSAID COX-2 inhibitor, which reduces inflammation, oxidative stress, and amyloid aggregation(Aβ), were selected. The study objective was to evaluate the effect of a fixed-dose combination of ciprofloxacin and celecoxib in AD. The use of a similar combination showed a beneficial synergistic effect in ALS, where it altered key pathologies such as neuroinflammation, autophagy, and TDP-43 levels in both pre-clinical and clinical studies. Therefore, we aim to investigate the relevance of this combination as a potential treatment for AD.
Methods: The applicability of the combined postulated mode of action (MOA) in AD was assessed clinically in blood samples and in neuronal and microglial cultures. Neuron-derived exosomes, isolated by ExoSORT™, were used to characterize potential target engagement and disease progression biomarkers. The therapeutic effect of each compound alone and in combination were tested in BV-2 cells and SH-SY5Y cells under Aβ-stimulation.
Results: Current findings show alterations in indicative biomarkers related to the combined treatment activity and MOA, such as TDP43 and LC3 ($P<0.05$ and $P<0.01$, respectively). The combined treatment affected the Aβ-induced inflammatory response of microglia, survival, and morphology of neurons.
Conclusions: This work may shed light on a new therapeutic approach to halt AD progression using a combined therapeutic strategy that targets multiple pathways and may identify new biomarkers for target engagement.

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P0304 / #1580

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

TPS (TRANSCRANIAL PULSE STIMULATION): SAFETY AND DOSES EVALUATION

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Storz Medical AG, Business Development, Tägerwilen, Switzerland

Aims: Low intensity shockwaves proved to be efficient for the treatment of non-unions, tendons and muscular pain, wound healing, heart insufficiency, erectile dysfunction and aesthetics since 1990. The working principle is the mechanical stimulation of biological processes called mechanotransduction. Transcranial Pulse Stimulation TPS) uses shockwave pulses for mechanical stimulation of the brain tissue. In spite of the long term (since 1990) practical experience with shock wave application to the soft tissue, the application to the brain tissue required new safety evaluation, in order to exclude negative side effects. Bleeding is considered as the only significant risk factor.
Methods: Two animal trails were performed: 80 Sprague-Dawley rats were divided in 8 groups with 10 animals each and treated with:
0mJ/mm^2, the control group
0.1mJ/mm^2 with 100, 200 and 400 pulses
0.2mJ/mm^2 with 100, 200 and 400 pulses
0.3mJ/mm^2 with 100 pulses 5 Sprague-Dawley rats were treated with 0.2mJ/mm^2 with 400, 4000 and 8000 pulses.
Results: 80 Sprague-Dawley rats trial
The animals were euthanized and the brain histologically investigated with no bleeding found. 5 Sprague-Dawley rats trial
The applied doses correspond to 15, 150 and 300fold human doses. MRI evaluation in-vivo showed minimal bleeding in only one animal treated with 300fold human doses.
Conclusions: This safety margin becomes even higher, when the stronger shockwave attenuation by the human skull compared to the rat skull is considered. Based on these investigations is the treatment with TPS safe.

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P0305 / #1073

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

LIPID-BASED NANOPARTICLES AS CARRIERS OF MEMANTINE: A NEW APPROACH TO IMPROVE THE ALZHEIMER'S DISEASE TREATMENT

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Aims: Alzheimer´s Disease (AD) is the most prevalent form of dementia, affecting more than 46 million people globally. The therapeutic impact of clinically available AD drugs is limited by multiple factors, including their inherent pharmacokinetic and pharmacodynamic features and inability to cross the blood-brain barrier (BBB). Additionally, inadequate targeting induces non-specific distribution and systemic toxicity. To overcome these hurdles and boost drugs' therapeutic effectiveness, nanoparticles (NPs) have been extensively studied. They can protect drugs and have their surface functionalized for a targeted administration, overcoming the BBB. As a result, the drug is released directly into the brain, minimizing the side effects. Thus, this work emphasizes the development of lipid NPs to improve memantine effectiveness, the gold standard drug to treat moderate-to-severe dementia in AD.
Methods: The NPs excipients were selected through a lipid screening, a study that assessed the solubilization potential of different lipids towards memantine. The NPs were synthesized, and their physicochemical parameters were characterized using the dynamic light scattering technique. The memantine encapsulation was optimized and quantified using high-performance liquid chromatography to create stable formulations with the highest quantity of memantine feasible encapsulated.
Results: Lipid NPs were successfully used as carriers for memantine, with an encapsulation efficiency of about 50%. These NPs presented sizes less than 200 nm allowing their passage through the BBB and a zeta potential high enough to guarantee their stability. Results revealed good NPs stability once there was no significant variation in their physicochemical parameters and no signs of aggregation over 6 months.
Conclusions: The memantine-loaded NPs were created with the ideal dimensions to pass through the BBB and zeta potential values that ensured optimal NPs stabilization, making them compatible with systemic administration.

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P0306 / #264

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

NOT ONLY LOW-DOSE (S)-EFAVIRENZ BUT ALSO ITS RACEMIC HYDROXYMETABOLITES ACTIVATE CYP46A1 IN VIVO AND ELICIT THE BENEFICIAL BRAIN EFFECTS

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Aims: To further characterize *(S)*-efavirenz (EFV) as a potential anti-Alzheimer's disease therapeutic that activates CYP46A1, the CNS-specific cholesterol 24-hydroxylase. CYP46A1 controls cholesterol homeostasis in the brain and, thereby, different brain processes. CYP46A1 is an emerging therapeutic target for Alzheimer's disease as it can be activated by low-dose *(S)*-EFV in mice and humans.
Methods: Enzyme assays of purified CYP46A1 with *(S)*- and *(R)*-EFV as well as racemates and *(S)*-isomers of the four phase 1 EFV hydroxymetabolites. *In vivo* treatments of 5XFAD mice with *(rac)*-8,14-dihydroxyEFV and *(rac)*-7,8-dihydroxyEFV.
Results: All tested compounds allosterically activated purified CYP46A1 *in vitro* either by interacting with the allosteric site for *(S)*-EFV, neurotransmitters or both. Mice treated with *(rac)*-8,14-dihydroxyEFV showed many of the brain effects common with those of *(S)*-EFV and were observed either in 5XFAD mice of both sexes or only in male animals. The common sex-independent effects were the activation of CYP46A1 and brain cholesterol turnover, increases in acetyl-CoA and acetylcholine levels, and changes in PSD-95, GFAP, and Iba1 expression. The common sex-dependent effect (only in male mice) was improved performance in the Barnes maze test, which, along with other male-specific effects suggested the desmosterol-acetyl-CoA-acetylcholine-cognition axis. *(Rac)*-8,14-dihydroxyEFV and *(S)*-EFV differed in that the former reduced the brain Aβ42 levels. The characterizations of *(rac)*-7,8-dihydroxyEFV-treated mice are still on-going.
Conclusions: The spatial configuration of all tested compounds neither affected the CYP46A1 activation nor the allosteric sites of binding. *(S)*-EFV should be co-administered with *(rac)*-8,14-dihydroxyEFV and possibly *(rac)*-7,8-dihydroxyEFV to enhance its beneficial effects on the brain.

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P0307 / #384

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

INTRANASALLY ADMINISTERED LOW DOSE METFORMIN IMPROVES SPATIAL LEARNING/MEMORY AND SOCIAL BEHAVIOUR OF SPORADIC ALZHEIMER'S DISEASE-TYPE MODEL RATS

Vladimirs Pilipenko[1], Vladislava Kurtukova[2], Karina Narbute[1], Jolanta Pupure[3]
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Aims: Main pathological processes of sporadic Alzheimer's disease (sAD) can be replicated by intracerebroventricularly (icv) injected neurotoxin streptozocin (STZ). Metformin easily crosses the blood-brain barrier in mammals. Intranasal administration of small molecules is optimal to ensure that administered substance reaches the brain and systemic side effects are avoided. In this study, we investigated the effects of low dose intranasal metformin on spatial learning/memory and sociability of sham-operated and sAD-type model rats.
Methods: sAD was induced in 12-week-old male Wistar rats by icv injection of STZ dissolved in citrate buffer as vehicle. Sham controls received vehicle solution only. Animals were given metformin at 1 and 3 mg/kg doses for 28 consecutive days. Escape latency was then quantified in the Morris water maze (MWM) trainings, whereas time in quadrants and platform crosses – in the MWM probe trial. Sociability (time with unknown animal) and social novelty preference (time with known vs. unknown animal) were assessed in the 3-chamber test. Data were analyzed using two-way ANOVA followed by Holm-Sidak's post-hoc test.
Results: Rats with sAD-type pathology treated with both low doses of metformin had markedly shorter escape latency, higher number of platform crosses and longer time spent in target quadrant than their sAD group counterparts. sAD rats treated with 3 mg/kg metformin spent significantly more time with the unfamiliar rat in the sociability and social novelty preference trial compared to sAD rats.
Conclusions: Low doses of intranasal metformin improve cognition and social behavior in sAD male rats, probably owing to the increased brain concentrations of metformin.

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P0308 / #2010

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

INVESTIGATING THE EFFECT OF SEMANTIC FEATURE ANALYSIS ON ANOMIA IN EARLY ALZHEIMER'S DISEASE : PRESENTATION OF TWO CASES STUDIES

Isabelle Simoes Loureiro[1], Aurélie Miceli[2], Semiz Melike[2], Sandrine Basaglia-Pappas[2]
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Aims: Alzheimer's disease is one of the most common neurodegenerative diseases. In the very beginning of the disease, a semantic memory breakdown is observed. The consequences of this deterioration include difficulties to retrieve words, their meaning and in more general terms, understanding language and being able to express themselves daily. The aim of our study is to evaluate the effectiveness of a method (the " Semantic Features Analysis "- SFA) aimed to reinforce semantic concepts in order to improve lexical retrieval capacities.
Methods: Two participants, MS (87 years old, MMSE : 24/30) and MV (86 years old, MMSE : 20/30) were recruited for the study. Oral picture naming performance was assessed in the pre-intervention, post-intervention and maintenance phases using a naming task. A 16-session individualized program was implemented with two 50-minutes sessions per week for 6 weeks. At each session, the participants were asked to complete a semantic feature analysis form.
Results: Our results show a significative improvement in naming performance only for MS. A generalization of this improvement to the untrained items but semantically related to the trained items and a maintenance of the benefits were also observed. However, for MV, performance did not change significantly. This lack of response could be explained in part by a more important general cognitive and semantic decline.
Conclusions: In conclusion, the treatment of anomia by the SFA made it possible to obtain significant evolutions in one of our participants with AD, by reinforcing the structure of the lexical-semantic network, in the condition of a not too deep semantic deterioration. Our first results provide some evidence-based recommendations to manage anomia in AD even if further research is still needed to support our preliminary findings.

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P0309 / #959

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

EVALUATION OF THE INDIVIDUAL AND SYNERGISTIC NEUROPROTECTIVE EFFECT OF WITHAFERIN A AND TINOSPORA CORDIFOLIA EXTRACT IN NEURON-GLIA CELLS CHALLANGED WITH KAINIC ACID.

Randeep Singh
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Aims: Evaluate the neuroprotective effect of Withaferin A and Tinospora cordifolia extract individually and synergistically in neuron-glia cells challanged with Kainic acid.
Methods: This study used the computational tools like docking softwares to analyse the interaction of various proteins of neuron-glial cells with *Tinospora cordifolia* components, Withaferin A and Kainic acid. The potential role of withaferin A and *Tinospora cordifolia* extract in cell morphometry, migration, expression of plasticity markers, and nuclear factors when challenged with Kainic acid will be studied through immunocytochemistry, wound scratch assay, and western blotting. Elucidation of the role of withaferin A and *Tinospora cordifolia* extract in the signaling pathway involved during the neural glial plasticity when intoxicated with Kainic acid.
Results: A study of the molecular interactions of proteins involved in neurodegeneration with various compounds extracted from Tinospora cordifolia, Withaferin A, and KA is done with the help of molecular docking in Schrodinger's Maestro software. The molecular interactions are demonstrated in terms of docking scores that indicate the binding affinity of ligand (compounds) with the target protein. Docking scores obtained are tabulated below.

	Protein (PDB id)				
	GSK3 (4AFJ)	IL-1β (5R86)	MAPK p38 (5OMH)	TNF-α (5UUI)	Caspase-3 (3KJF)
	-6.738	-3.550	-4.718	-4.406	-3.734
	-6.722	-2.808	-3.264	-4.265	-3.313
	-6.594	-2.672	-2.550	-3.778	-1.779
	-5.364	-2.817	-4.058	-5.147	-4.235
	-4.873	-4.725	-3.126	-4.936	-5.168
	-3.798	-4.132	-4.742	-3.090	-4.059
	-1.771	-2.372	0.963	-3.565	-4.993

Conclusions: A more negative score indicates better binding affinity of the ligand with that protein. Based on docking score and avalaibility of the compound, we are analysing the biological activity of Magnoflorine on Kainic acid-treated neuron and glial cells.

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P0310 / #474

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

THERANOSTIC APPROACH FOR EARLY DIAGNOSIS AND THERAPY OF ALZHEIMER'S DISEASE BY TARGETING AMYLOID-B OLIGOMERS

Kuldeep Tripathi[1,2], Sudipta Senapati[2], Dvir Alfasi[2], Ronen Yehuda[1], Menachem Motiei[3], Rachela Popovtzer[3], Eitan Okun[1], Shai Rahimipour[2]
[1]Bar Ilan University, Gonda Multidisciplinary Brain Research Center, Ramat Gan, Israel, [2]Bar Ilan University, Dept Of Chemistry, Ramat Gan, Israel, [3]Bar Ilan University, Faculty Of Engineering, Ramat Gan, Israel

Aims: Protein misfolding and their accumulation is the basis of several neurodegenerative disorders, including Alzheimer's disease (AD). Amyloid-β accumulation causes severe neuronal damage in the brain way before the appearance of detectable cognitive symptoms. Recent clinical trials suggest the necessity of diagnosing AD at an early stage for effective therapy. The main objective of this study was to develop a novel theranostic method to diagnose and treat AD in its early stage.
Methods: Computed tomography (CT)-detectable gold nanoparticles (GNPs, 20 nm) were synthesized, and their surface was modified with a vector protein to increase BBB permeability, and with the cyclic D, L-α-peptide (CP-2) to selectively targets early Aβ oligomers and modulate their aggregation and toxicity. To study the effect of CP-2 on AD progression and pathology, pre-symptomatic 1.5-month-old 5xFAD mice were treated with CP-2 until five months of age when the earliest behavioral impairment with learning and memory can be detected. *In-vivo* imaging and IHC were used to analyze Aβ pathology and disease progression.
Results: Early Aβ accumulation was detected by CT in 2-month-old pre-symptomatic 5xFAD mice and confirmed with fluorescence imaging using fluorescently labeled CP-2-GNPs. Chronic treatment of 5xFAD with non-toxic CP-2 ameliorated the behavioral and cognition symptoms, reduced Aβ accumulation in the cortex and hippocampus, and decreased relevant inflammatory markers in the brain of treated mice
Conclusions: Our theranostics approach offers a novel promise for early AD diagnosis and therapy by targeting the soluble oligomers.

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P0311 / #647

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

THE ROLE OF SPHINGOSINE-1-PHOSPHATE RECEPTORS AND THEIR MODULATORS IN THE TOXICITY OF AMYLOID BETA OLIGOMERS IN NEURONAL CELLS.

Iga Wieczorek, Robert Strosznajder
Mossakowski Medical Research Institute, Polish Academy of Sciences, Laboratory Of Preclinical Research And Environmental Agents, Warsaw, Poland

Aims: Amyloid β oligomers (Aβo) are commonly recognized as the most toxic form of Aβ, responsible for neurodegeneration in Alzheimer's disease (AD). Another pathological feature of AD is disturbed sphingosine-1-phosphate (S1P)-dependent signaling. Therefore, the aim of the study was to investigate the role of S1P receptors and their modulators in the toxicity of Aβo in neuronal cells.
Methods: The experiments were conducted on mouse hippocampal neurons (HT22 cell line) treated for 24 h with Aβo (1 μM) or with the combinations: Aβo and one of the following S1P receptor modulators: fingolimod ($S1PR_{1,3-5}$), siponimod ($S1PR_{1,5}$), ponesimod ($S1PR_1$), CYM5541 ($S1PR_3$), CYM50308 ($S1PR_4$), A971432 ($S1PR_5$). The expression of genes encoding the following proteins: - S1P receptors ($S1PR_1$, $S1PR_3$, $S1PR_4$, $S1PR_5$) - proapoptotic (Bax, Bad) and antiapoptotic proteins (Bcl2, Bcl-xl) - proinflammatory interleukins (TNF-α, IL-1b, IL-6, IL-18) was determined by the qRT-PCR. Mitochondrial functions were analyzed by MTT assay (metabolic activity) and using 2′,7′-dichlorodihydrofluorescein diacetate (H2DCF-DA) (level of intracellular ROS).
Results: Aβo-treated cells showed a significant lower expression of *Il18* and *Bcl2*, while a significant higher expression of *Il6*. However, restoring of the gene expression to the control level was observed when Aβo was administered together with fingolimod for *Il6* and together with CYM50308 and A971432 for *Bcl2*. Aβo caused a significant decrease in the metabolic activity of HT22 cells and an insignificant increase in the level of free radicals. It was not observed any influence of the investigated modulators on the studied mitochondrial functions.
Conclusions: The obtained results indicate the proinflammatory and proapoptotic effect of Aβo on HT22 cells. Modulation of S1P receptors, mainly $S1PR_4$ and $S1PR_5$, can to some extent counteract the toxicity of Aβo. Supported by grant of National Science Centre, Poland no. 2021/41/N/NZ5/02036.

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P0312 / #2400

POSTERS: A02.R. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

UNDERSTANDING THE EFFECTS OF METFORMIN ON MODELS OF ALZHEIMER'S DISEASE

Dongwei Xu
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Aims: Metformin is a first-line drug for Type II Diabetes, a major risk factor of Alzheimer's disease. A small clinical trial in patients with prodromal Alzheimer's disease and studies on animal models of the disease show benefits of metformin, while epidemiological data-based results suggest a debated role of metformin in Alzheimer's disease. In order to understand the mechanisms underlying the benefits of the drug, we performed a genetic screen in a *Drosophila* model of Alzheimer's disease based on the list of metformin-regulated genes from a yeast screen.
Methods: The elavGS>UAS-Aβ_{42}*Drosophila* model was used for the screen. The expression of Aβ_{42} was induced in neurons when adult flies were fed with mifepristone. We examined the climbing ability of Aβ_{42}-expressing flies with the overexpression or knockdown of 150 metformin-regulated genes. Modifiers from the screen will be further validated and characterised in *Drosophila* and iPSC-based models.
Results: Out of the 150 lines screened, six lines have been identified as suppressors of Aβ_{42}-mediated neurotoxicity, while five lines have been found as enhancers of toxicity.
Conclusions: From the genetic screen, we identified the suppressors and enhancers of Aβ_{42} toxicity, which will be validated in iPSC-based models. Mechanisms underlying the effects of these genes are under investigation.

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P0313 / #1791

POSTERS: A03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

VACSYN STUDY DESIGN – BIOMARKER-BASED DEVELOPMENT FOR ACI-7104, A NOVEL CANDIDATE VACCINE FOR THE TREATMENT AND PREVENTION OF PARKINSON'S DISEASE

Dymitr Kostrica[1], Jonathan Wagg[1], Just Genius[1], Nicolas Fournier[1], Tanja Touilloux[1], Elena Valatsou[1], Olivier Sol[1], Valerie Hliva[1], Marija Vukicevic[2], Marie Kosco-Vilbois[2], Günther Staffler[2], Andrea Pfeifer[2], Johannes Streffer[1,3]
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Aims: Aggregated alpha-synuclein (α-syn) in Lewy bodies (LB) and loss of dopaminergic neurons in the substantia nigra are key pathologic features of PD. Immunotherapies directed against α-syn aim to reduce extracellular α-syn aggregate burden and halt its spread. Here we report an innovative trial design for an optimized active immunotherapy (vaccination) designed to: (i) identify treatment effect(s) on biomarkers early; (ii) leverage interim analyses of biomarker responses to de-risk subsequent development decisions.
Methods: ACI-7104 is an optimized vaccine targeting α-syn for treatment and prevention of PD. ACI-7104 preferentially targeting pathologic α-syn species, including toxic oligomers. Reduction of which has been associated with reported clinical benefit. The study design combines a data-driven approach with continuous and early biomarker analyses to inform subsequent development decisions. Biomarker-rich natural history data sets, such as PPMI and recent clinical studies of α-syn immune therapies enable the selection of relevant markers for decision making and predictors of clinical benefit.
Results: The design of the VacSYN study implements an innovative translational clinical trial design to investigate ACI-7104 in early PD. We will present modelling approaches for this adaptive trial design that support early decision making with multiple interim analyses. Safety and immunogenicity assessments should allow improved dose selection for assessing of α-syn oligomer lowering, an early clinically relevant pharmacodynamic readout in part 1 of the study. This will de-risk the transition into the larger sample size in part 2 including increasingly meaningful markers like advanced MRI, DaTSCAN and clinical function measured by wearable devices and established clinical measures.
Conclusions: Successful development of disease-modifying approaches needs the translation of biological understanding into clinically meaningful measures. VacSYN is a clinical trial design that will allow informed and de-risked transition into pivotal studies.

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P0314 / #2203

POSTERS: A03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

PRE-CLINICAL AND INTERIM CLINICAL PHASE 1 ANTIBODY TITRE ANALYSIS OF ANTI-AMYLOID BETA OLIGOMER VACCINE ALZ-101

Anders Sandberg[1], Zsófia Lovró[2], Niclas Sjögren[3], Mika Scheinin[2], Juha Rinne[2]
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Aims: The first immune therapy candidate targeting amyloid beta (Abeta) to treat Alzheimer's disease (AD), the vaccine AN1792, appeared to provide plaque removal without clinical improvement (Holmes et al., 2008). Four late-stage clinical trials on monoclonal antibodies have recently provided similar results: aducanumab, lecanemab, gantenerumab, and donanemab; all reducing plaque load, but with questionable safety and very modest clinical efficacy. Five different clinical programs have thus demonstrated that plaque removal does not associate with robust clinical benefits. The vaccine candidate ALZ-101 is a very different anti-Abeta approach as it only targets much more toxic, less abundant, soluble oligomeric forms of Abeta. It is now in early clinical development (NCT05328115).
Methods: ALZ-101 is an intramuscularly administered vaccine containing oligomeric forms of the immunogenic Abeta42CC peptide (Sandberg et al., 2010) formulated with aluminium hydroxide. Standard ELISA methods and practices are used to characterize the immune response.
Results: We have previously shown that the immune response to ALZ-101 generates Abeta oligomer-specific antibodies that target a low-abundant toxic form of Abeta in human brain samples with strong neutralising effects. We here provide preclinical data on immunised rabbits demonstrating a half-life of the immune titres in blood of around 3 months and a CSF distribution of 0.3 %. We also show results from an interim IgG titre analysis in the ongoing Phase 1b study on ALZ-101 in participants diagnosed with mild AD or mild cognitive impairment due to AD.
Conclusions: The current evidence supports the continued clinical development of ALZ-101 as a specific, long-acting, and safe immunotherapy for targeting toxic Abeta oligomers in AD.

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P0315 / #2631

POSTERS: A03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

VIVIAD, A PHASE 2B STUDY INVESTIGATING VAROGLUTAMSTAT IN PATIENTS WITH MCI AND MILD AD: UPDATE ON INTERIM BLINDED SAFETY RESULTS

Michael Schaeffer[1], Frank Weber[1], Philip Scheltens[2], Claire Miller[3], Katharina Fuchs[4], Christine Wenzkowski[4], Asger Bihlet[3], Peter Alexandersen[5], Tobias Axelsen[6], John Harrison[7], Everard Vijverberg[2]
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Aims: Objectives: A safety and recruitment update for the phase 2b VIVIAD study of varoglutamstat, a small molecule inhibitor of glutaminyl cyclase, preventing the formation of neurotoxic N3pE-Abeta.
Methods: VIVIAD (NCT04498650) is a multicentre randomized, placebo-controlled, double-blind, parallel group dose finding Phase 2b study in patients with early Alzheimer's disease (AD) and mild cognitive impairment (MCI). The participants' disease status at time of inclusion was confirmed by an Abeta and p-tau biomarker profile. Treatment duration varies between 48 and 96 weeks depending on the time of inclusion, with participants receiving 600mg BID or placebo. The primary outcome is a composite score on the cognitive domains of attention and working memory using theCogstate system ('Cogstate NTB'). To secure a rescueable cognitive deficit in the target domains, inclusion criteria encompassed a score of at least 0,5 SD below age-adjusted mean on the WAIS-IV Coding subtest.
Results: Interim Results: By November 7, 2022, N=250 of 250 patients were enrolled, N=207 had reached week 12, N=84 week 48, and N=22 week 84 of treatment. N=408 patients were screen failures. The occurrence of adverse events normalized per 100 patient 12 week treatment periods was stable at 31. Four treatment emergent adverse events have led to subject discontinuation. All data remain blinded outside the DSMB. With respect to the Coding enrichment strategy, only five participants exhibited normal performance on cognitive tests comprising the Cogstate NTB.
Conclusions: Conclusion: To date, the VIVIAD study data suggest that varoglutamstat is safe and well-tolerated. Furthermore, the strategy of recruiting individuals with evidence of baseline deficits on the Coding test has proven to be an effective method of enriching a study cohort with the necessary rescuable deficits in attention and working memory.

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P0316 / #2023

POSTERS: A03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

IDENTIFICATION OF A DUAL AB-TAU DISAGGREGATOR FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Seung Hoon Han[1,2], Koeun Kim[1,2], Sohui Park[1,2], Jaehoom Jeong[1,2], Yeon Uk Ko[1,2], Hye-Ju Kim[1], Seong Muk Kim[1,2]
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Aims: The accumulation of misfolded protein aggregates is related to neurodegenerative diseases such as Alzheimer's disease (AD), and Parkinson's disease. Because of the accumulation of amyloid β (Aβ) plaques and tau tangles (NFTs) in the brain, neurons slowly degenerate and lose their functions in AD. Recently, many clinical trials for AD therapy with single-target drugs, especially targeted for Aβ or tau aggregates, have failed. As a therapeutic strategy for AD, we therefore propose to introduce a multifunctional anti-AD agent to disaggregate the Aβ plaques and NFTs.
Methods: Hit compound was screened in the functional CNS chemical library with disaggregation efficacy for Aβ and tau aggregates by EC_{50} using thioflavin T (ThT) assay. S603 is selected from patentable derivatives for hit compound. In vitro study, we examined the effects of disaggregation in aggregates system and elimination of intracellular Aβ or tau in cells. In vivo study, we administrated orally to AD mouse model and then analysis of Aβ and tau was performed by molecular biological and histological experiments and behavior tests were conducted.
Results: Our results show that S603 had dual disaggregation capacity for Aβ and tau aggregates. We observed significant decrease of Aβ and NFTs and found the restoration of cognitive decline in S603-treated AD mice.
Conclusions: The study demonstrate that our hit compound was identified as dual functional drug for Ab and NFTs disaggregator. These findings may help to design the next generations of dual or selective disaggregators.

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March 28 - April 1, 2023 | Gothenburg, Sweden

P0316a / #3080

POSTERS: A03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: AGGREGATION INHIBITORS

PHASE 3 CLINICAL STUDIES IN ALZHEIMER'S AND PARKINSON'S DISEASE; INTERIM ANALYSIS OF THE PARKINSON'S CLINICAL STUDY

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Aims: Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function. By inhibiting the translation of neurotoxic aggregating proteins - amyloid precursor protein, tau, alpha-synuclein etc., buntanetap restores axonal transport, lowers inflammation, and protects nerve cells from dying.
Methods: In phase 2a studies, buntanetap showed efficacy in two double-blind, placebo controlled clinical studies in both AD and PD patients. These encouraging data support our further development of buntanetap into phase 3 as a potential treatment for both AD and PD.
Therefore, we started two double-blind, placebo-controlled phase 3 studies to further test buntanetap's efficacy and safety in PD and AD patients.
Results: For the PD study, patients are dosed with either 10mg, 20mg buntanetap or placebo QD. A total of 450 early PD patients are being recruited for a 6-month treatment. Primary endpoint is MDS-UPDRS 2 and 3. We will present the study design and the data from the interim analysis, when 30% of the patients have been treated for 2 months.

Conclusions: For the AD study, patients are dosed with three doses of buntanetap (placebo, 7.5, 15 and 30 mg QD). A total of 320 mild to moderate AD patients are being recruited for a 3-month treatment. Primary endpoints are ADAS-Cog11 and ADCS-CGIC. We will present the study design.

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P0317 / #2206

POSTERS: A03.F. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS

ANIMAL MODELS FOR TESTING SMALL MOLECULES AS MITOCHONDRIAL ENHANCERS IN ALZHEIMER'S DISEASE

Maria Ankarcrona[1,2], Luana Naia[1], Giacomo Dentoni[3], Makoto Shimozawa[4], Erika Bereczki[5], Xidan Li[6], Jianping Liu[7], Nuno Santos Leal[8], Benjamin Portal[9], Maria Lindskog[9], Per Nilsson[10]
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Aims: Mitochondrial dysfunction and decreased energy production occur early in the Alzheimer's disease (AD) process and mitotherapeutics may be valuable disease modifiers. We have previously identified the flavonoid luteolin as a mitochondrial enhancer in primary neurons (Naia et al 2021). We revealed a novel mechanism showing that luteolin increase mitochondria-endoplasmic reticulum (ER) contact, ER to mitochondria Ca^{2+}-transfer and ATP production. Thus, flavonoids may have the potential to enhance mitochondrial function, support synaptic activity and halt the progression of AD. Here the aim was to characterize *App*$^{NL-F}$ and *App*$^{NL-G-F}$ AD-mouse models in terms of mitochondrial function. Such models could then be used to validate our findings with flavonoids and to understand the molecular mechanisms in depth.
Methods: RNA sequencing was performed on hippocampal tissue from knock-in *App*$^{NL-F}$(6, 12, 18 months) and *App*$^{NL-G-F}$(2, 6, 12 months) and wild-type (WT) mice. Primary cortical neurons were derived from *App*$^{NL-F}$ mouse embryos. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured with a XFe96 SeaHorse Analyzer. Mitochondrial Ca^{2+} uptake (Calcium Green-5N) .Patch-clamp recording (miniature EPSCs). Mitochondrial movement (MitoDsRed-transfection) Mitochondria-ER contacts (MERCS) split-GFP-based contact site sensor (SPLICS) analysis.
Results: Time-course transcriptome analysis of the hippocampus revealed energy metabolism as one of the most significantly altered pathways. Functional experiments in mitochondria isolated from young *App*$^{NL-G-F}$ brain showed upregulation of oxidative phosphorylation, combined with higher susceptibility to Ca^{2+}-overload. Subsequently, mitochondrial function was impaired in old *App*$^{NL-G-F}$ brain mitochondria as reflected in the transcriptome analysis. Similarly, *App*$^{NL-F}$primary neurons displayed alterations in mitochondrial and synaptic functions.
Conclusions: We show that *App* knock-in animal models are appropriate for studies with molecules affecting mitochondrial function. We are now performing proof-of-concept studies of the potential protective effect of flavonoids in these AD-models.

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P0319 / #2481

POSTERS: A03.F. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS

MRI CHANGES FOLLOWING TREATMENT OF GLP-1 ANALOGUE, LIRAGLUTIDE IN ALZHEIMER'S DISEASE: ELAD TRIAL

Paul Edison[1], Zuzana Walker[2], Elizabeth Coulthard[3], Christian Hölscher[4], Anthony Passmore[5], Clive Ballard[6]
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Aims: Preclinical evidence in transgenic models of Alzheimer's disease (AD) suggests that liraglutide, a GLP1 analogue, exerts neuroprotective effects by reducing amyloid oligomers, normalising synaptic plasticity and reducing insulin resistance, and increasing the proliferation of neuronal progenitor cells. ELAD is a 12-month, multi-centre, randomised, double-blind, placebo-controlled, phase IIb trial of liraglutide in participants with mild to moderate AD conducted at 24 centres in the UK.
Methods: As a part of this study, a total of 204 Alzheimer's participants were randomised to receive either liraglutide or placebo as a daily subcutaneous injection for 12 months. All subjects underwent volumetric MRI scans at baseline and during follow up. Volumetric changes from baseline to follow up in MRI scans were evaluated using both regional volume analysis and voxel based morphometric analysis
Results: MRI analysis demonstrated that temporal lobe volume ($p<0.001$), total grey matter volume ($p<0.002$) and frontoparietal volume change was lower in liraglutide treated patients compared to the placebo group. Voxel based morphometry (VBM) analysis demonstrated that liraglutide-treated participants showed a slower reduction in whole cortical grey matter, frontal, temporal and parietal lobe volume in participants treated with liraglutide compared to placebo. This was associated with lower decline in cognitive function (ADAS-EXEC) ($p=0.01$). However, there was no difference in glucose metabolism between the two groups.
Conclusions: In the ELAD study, participants with mild to moderate AD who received liraglutide had slower reduction in MRI volume and cognition compared to the placebo demonstrating a potential benefit of liraglutide in the treatment of Alzheimer's disease. These findings highlight the potential of GLP-1 analogues in the treatment of Alzheimer's disease.

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P0320 / #2755

POSTERS: A03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: TRANSCRANIAL MAGNETIC STIMULATION

CORTICAL MICROSTRUCTURAL MRI AS POTENTIAL ENDPOINT IN A 24-WEEK TRIAL OF PRECUNEUS RTMS IN AD: PRELIMINARY RESULTS

Mario Torso[1], Lucia Mencarelli[2], Francesco Di Lorenzo[2], Gerard Ridgway[3], Michele Valotti[1], Ilaria Borghi[2], Sonia Bonnì[2], Martina Assogna[2], Valentina Pezzopane[2], Alessandro Martorana[4], Steven Chance[1], Giacomo Koch[5,6]
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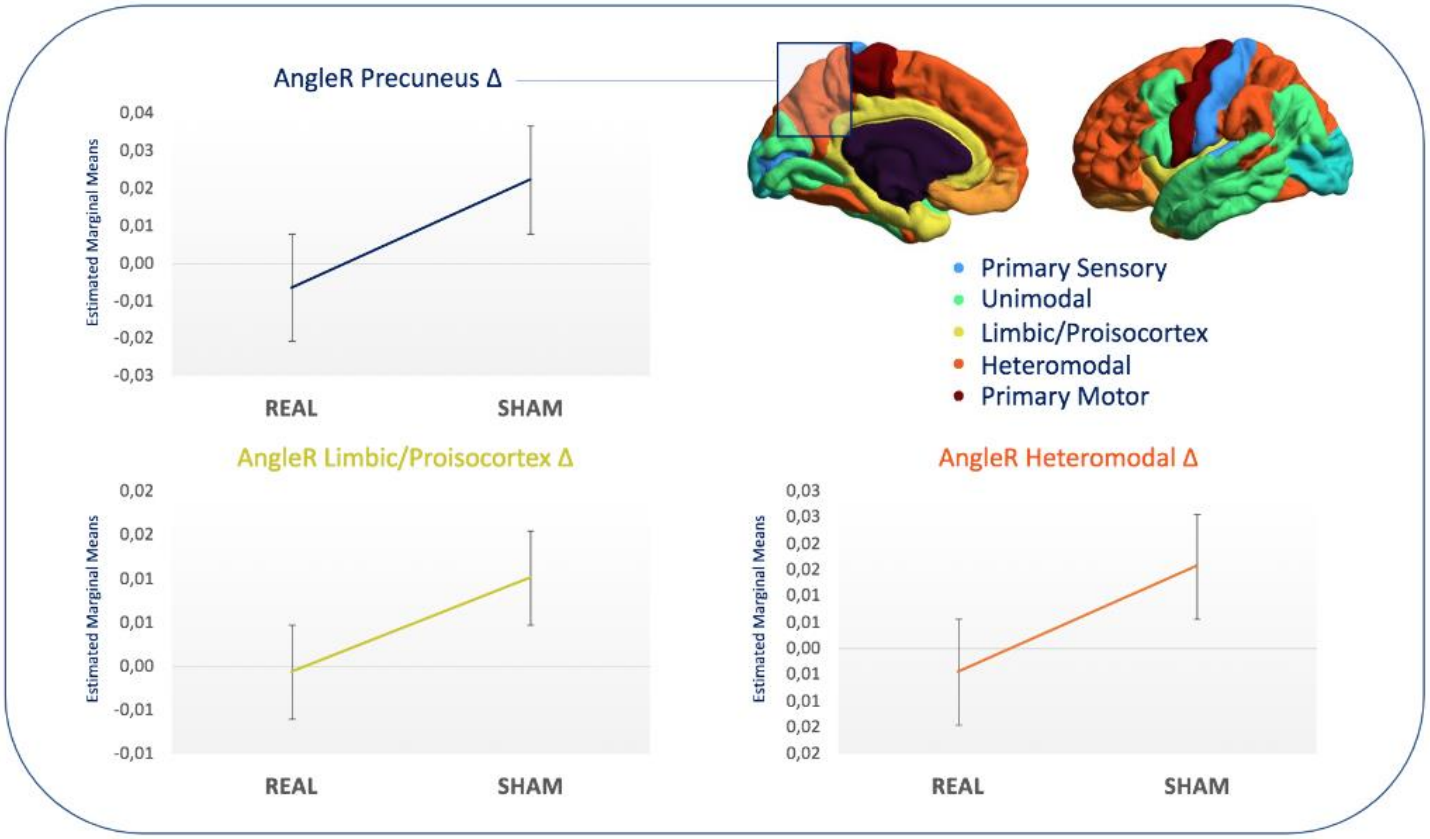
Aims: To investigate the effect of precuneus (PC) repetitive Transcranial Magnetic Stimulation (rTMS) on cortical microstructure of PC and five hierarchically grouped macroregions (primary sensory, unimodal, limbic/proisocortex, heteromodal and primary motor).
Methods: Fourteen Alzheimer's Disease (AD) patients were randomly assigned to treatment with rTMS (Real, N=7) or placebo (Sham, N=7). All participants were Amyloid-Beta-42 and pTau-181 positive. Both groups received an intensive 2-weeks course with daily rTMS sessions, followed by a maintenance phase in which rTMS has been applied once a week for 6 months. Each rTMS session consisted of forty 2-second trains delivered at 20 Hz that were spaced out by 28 seconds, for a total of 1600 stimuli in 20 minutes. Before and after the treatment structural and diffusion MRI were collected and used to calculate a novel cortical diffusivity measure [PMID:31355989] the angle between the radial minicolumnar direction and the principal diffusion direction (AngleR) in the precuneus and macroregions. Clinical, cognitive data (MMSE, ADAS-COG, CDR-SB, ADCS-ADL, NPI and FAP) and standard macrostructural measures (cortical volume fraction, cortical thickness) pre and post stimulation, were used to characterize the groups. The annualised percentage change pre/post treatment in each metric was computed as Δ = 100 x (post — pre) / (pre x time-interval). All results reported survive FDR correction.
Results: AngleR PC Δ showed a significantly greater ($F_{1,13}=13.150$, $p=0.004$, $\eta p2=0.545$) decline in sham (mean=0.185) than real rTMS (mean= -0.0026). Macroregions exhibited significant differences in limbic/proisocortex ($F_{1,13}=7.348$, $p=0.020$, $\eta p2=0.400$) and heteromodal ($F_{1,13}=7.948$, $p=0.017$, $\eta p2=0.419$) AngleR Δ. ADAS-COG Δ was significantly associated with PC AngleR Δ (Pearson's r= 0.735, $p=0.006$).



Conclusions: These findings suggest that PC rTMS can slow neurodegenerative changes in the microstructure of cortical grey matter, indicating cortical microstructural preservation and potential slowing of AD.

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P0321 / #1682

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

EFFECT OF THE ASSOCIATION OF THE CHOLINESTERASE INHIBITOR DONEPEZIL AND THE CHOLINERGIC PRECURSOR, CHOLINE ALPHOSCERATE, ON BRAIN ATROPHY IN ALZHEIMER'S DISEASE.

Enea Traini, Anna Carotenuto, Angiola Fasanaro, Francesco Amenta
University of Camerino, School Of Medicinal And Health Sciences Products, Camerino, Italy

Aims: Cerebral atrophy is a common feature of several neurodegenerative disorders, including Alzheimer's disease (AD). In AD brain atrophy is associated with loss of gyri and sulci in the temporal and parietal lobes, in parts of the frontal cortex and cingulate gyrus as well as in the hippocampus.
Methods: The ASCOMALVA trial recruited AD patients with concurrent cerebrovascular damage, that represent a population with major cholinergic hypofunction. Patients were treated for 48 months with donepezil + choline alphoscerate [donepezil (D,10 mg/day) + choline alphoscerate (CA 1,200 mg/day)] or donepezil + placebo [reference group, D (10 mg/day) + placebo]. Patients were examined by cognitive, functional and behavioral tests. Among patients who underwent annual MRIs, 56 patients who had resonances obtained with similar and new generation equipment, to ensure data comparability, were selected (27 treated with D+P; 29 treated with D+CA). Data from magnetic resonance were used for the cerebral volume analysis.
Results: The volume analysis of total grey matter and that of hippocampus and amygdala has shown a progressive reduction in the volume of these two areas noticeable along the course of the study. These reductions were more pronounced in the D+P group than in the D+CA group. The reduction of the volumes of grey and white matter was compensated by a significant increase in cerebrospinal fluid volume. Morphometric findings found confirm in the outcomes of the neuropsychological tests.
Conclusions: Our findings indicate that the addition of choline alphoscerate to standard treatment with the ChE-I donepezil counters to some extent the loss in volume occurring in some brain areas of AD patients. The observation of results in cognitive, functional and behavioral tests suggests that morphological changes observed may have clinical relevance.

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P0322 / #2130

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

INTRACEREBROVENTRICULAR (ICV) ADMINISTRATION OF MTOR INHIBITORS IN EARLY AD PATIENTS: A PHASE 1-2 CLINICAL TRIAL.

Diego Dolcetta[1], Stefano Giovagnoli[2], Roberto Dominici[3]
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Aims: Objectives. We aim to exploit the pro-autophagic activity of mTOR inhibitors and replicate, in 10 patients with initial AD, what was observed in mice. All mouse models of AD, starting from 2010 (Caccamo et al, JBC) have been treated with oral rapamycin: complete recovery of pathological and cognitive deficits has always been recorded. After a decade, two clinical trials with the same oral drug are now underway (NCT04200911 & NCT04629495). Given the systemic immunosuppressive effect, they will be necessarily very limited in dosage and lengthened in duration, reducing the chances of success. The AD 3xTg-AD model was treated ICV with high doses of everolimus for 10 days (Cassano, Exp Neurol 2019), obtaining a complete and lasting cognitive recovery (Fig. 1). Although invasive, ICV administration with Ommaya reservoir is currently considered safe and never life-threatening (Peyrl, J Neurooncol 2014). However, the clinical translation required a stable liquid formulation of mTOR inhibitors, suitable for ICV administration, which was not available (Fig 2).
Methods: Methods. Everolimus was loaded in distearoylphosphatidylethanolamine-polyethyleneglycole 2000 (DSPE-PEG2000) micelles by the thin layer method. The compounds were dissolved in chloroform. The solvent was evaporated at r.t. under nitrogen stream and vacuum dried for 1 hour. Micelle formation was obtained by hydration of the thin layer with an Everolimus physiologic solution.

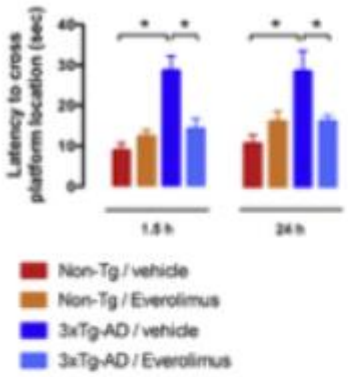

Fig. 1: The Morris Water Maze is a test that evaluates the memory performance of mice. Above, the results displayed after a 10-days ICV administration of Everolimus in DMSO solution, which rapidly decays (see fig 2). We recorded a high improvement of Everolimus-treated 3xTg-AD mice (light blue), compared to 3xTg-AD mice treated with vehicle (dark blue).

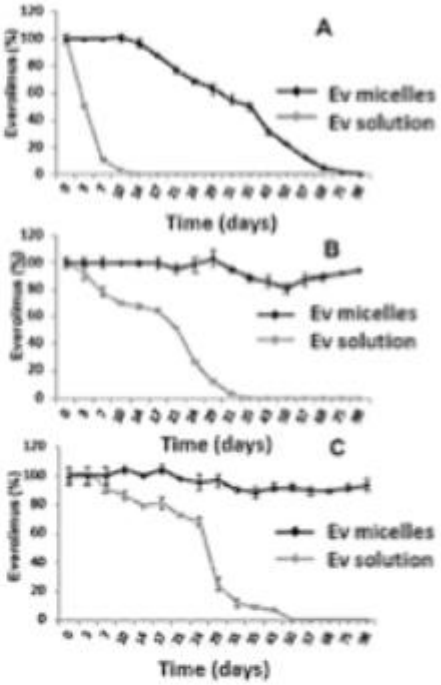

Fig. 2: **A.** Everolimus decay in DMSO solution (grey) and in micelles (black) at Body Temperature (37° C). **B.** At Room Temperature (25° C). **C.** Everolimus decay in DMSO solution (grey) and in micelles (black) at 4° C.

Results:

Results. We have developed a micellar formulation stable at body temperature (see Fig 2) (PCT: WO 2021205297A1). Moreover, the already known biocompatibility, its ease of production, storage, and preparation for use are also interesting features.

Conclusions: Conclusions. Despite the need of a further in vivo validation of the formulation, it has been bridged the missing step towards the clinical translation of the local administration of mTOR inhibitors strategy in neurodegenerative proteinopathies.

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P0323 / #2149

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

INTRACEREBROVENTRICULAR (ICV) ADMINISTRATION OF MTOR INHIBITORS IN "DRUG-RESISTANT" TUBEROUS SCLEROSIS COMPLEX (TSC) PATIENTS: PHASE 1-2 CLINICAL TRIAL

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Aims: TSC is characterized by often life-threatening intracerebral Giant Cell Astrocytomas (SEGAs), whose growth is tipically stopped and reverted by oral mTOR Inhibitors. We aim to propose a treatment suited to TSC patients unable to tolerate sufficient doses of drug. Such inoperable patients are usually a few months or years of age, or to be already adults who underwent too many brain surgeries. If treated intracerebroventricular (ICV), i.e. locally, these patients could take much higher doses of mTOR inhibitors, with minor systemic effects. This route is currently used for the administration of anticancer drugs in the treatment of primary cerebral lymphomas. Extensive studies have led to the conclusion that this route is safe (Peyrl, Neurooncol 2014). However, a tailored device should be made for TSC patients. Until now it could not be applied to TSC patients because a thermostable liquid formulation of mTOR inhibitors was not available.
Methods: Everolimus was loaded in distearoylphosphatidylethanolamine-polyethyleneglycole 2000 (DSPE-PEG2000) micelles by the thin layer method. The compounds were dissolved in chloroform. The solvent was evaporated at r.t. under nitrogen stream and vacuum dried for 1 hour. Micelle formation was obtained by hydration of the thin layer with an Everolimus physiologic solution.

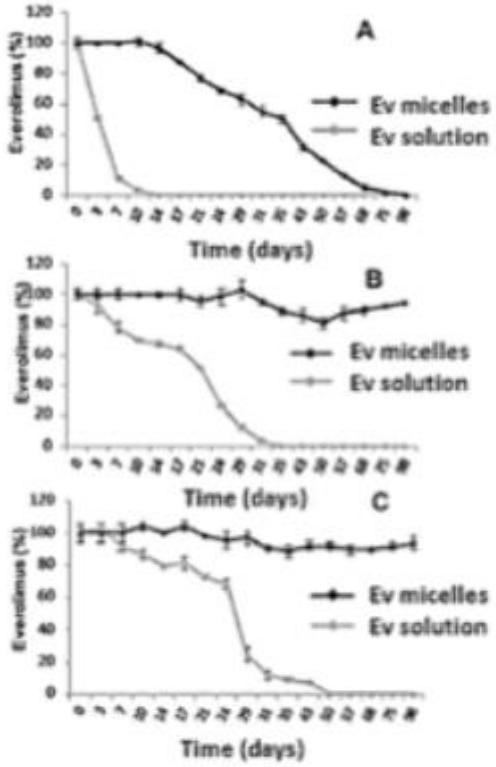

Fig. 2: **A**. Everolimus decay in DMSO solution (grey) and in micelles (black) at Body Temperature (37° C). **B**. At Room Temperature (25° C). **C**. At 4° C.

Results:
We have developed a micellar formulation stable at body temperature (see Fig 1) (PCT: WO 2021205297A1). Moreover, the already known biocompatibility, its ease of production, storage (in powder form), and preparation for use are also interesting features.
Conclusions: The availability of a thermostable formulation of mTOR inhibitors finally makes treatable TSC patients considered to date "drug-resistant". A short in vivo validation in mouse models is still necessary. **WE ARE LOOKING FOR PARTNERS AND INVESTORS**

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POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

REDUCED PREVALENCE OF DEMENTIA IN PATIENTS TREATED WITH A BRAIN PENETRANT CALCINEURIN INHIBITOR

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Aims: Evidence suggests patients treated with calcineurin inhibitors (CNIs) have a lower prevalence of dementia, including Alzheimer's disease (AD), compared to the general population. While plausible, whether the observed effects are related to brain penetrance remains unresolved. To address this question, we interrogated electronic medical records comparing dementia prevalence in patients treated with the brain penetrant CNI tacrolimus to patients treated with the non-brain penetrant CNI cyclosporine.
Methods: We conducted a retrospective cohort study using the TriNetX global health research network. Patients currently over age 65 were included based on prescription of tacrolimus or cyclosporine. Patients who were prescribed both drugs were excluded. Cohorts were propensity-score matched by age, race, sex, and a range of other covariates. The outcomes examined were diagnosis of dementia, including AD, at least thirty days following earliest recorded drug treatment.
Results: Of the 65,868 patients in each cohort, 2,506 (3.90%) of those prescribed tacrolimus and 3,040 (4.77%) of those prescribed cyclosporine were later diagnosed with dementia. Tacrolimus treatment was associated with a 18% risk reduction of developing dementia (relative risk of 0.82 of dementia in tacrolimus vs. cyclosporine, $p<0.0001$). Similar results were achieved when examining AD diagnoses separately (relative risk of 0.67 of AD in tacrolimus vs. cyclosporine, $p<0.0001$).
Conclusions: The results suggest the brain penetrant CNI is associated with a lower prevalence of dementia, including AD, relative to the non-brain penetrant CNI. These data encourage clinical evaluation of localized delivery of tacrolimus to the brain as a viable therapeutic for prevention and treatment of dementia, including AD, with localized delivery potentially reducing systemic side effects.

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P0325 / #231

POSTERS: A03.N. DRUG DEVELOPMENT, CLINICAL TRIALS: REGULATORY ASPECTS

ACCELERATING DRUG DEVELOPMENT THROUGH PRECOMPETITIVE DATA SHARING AND COLLABORATION IN THE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM

Sudhir Sivakumaran[1], Yashmin Karten[1], Nicholas Cullen[1], Corissa Lau[1], Eileen Priest[1], Hazel White[1], Klaus Romero[1], Michael Irizarry[2]
[1]Critical Path Institute, Critical Path For Alzheimer's Disease, Tucson, United States of America, [2]Eisai, Inc., Alzheimer Disease And Brain Health, Nutley, United States of America

Aims: The Critical Path for Alzheimer's Disease (CPAD) consortium serves as a pre-competitive, neutral convenor to generate novel, regulatory endorsed quantitative drug development tools (DDTs) and solutions that are made freely available to the public to accelerate drug development.
Methods: Patient-level data from contemporary Phase II and III Alzheimer's disease (AD) clinical trials and observational studies make up the CPAD integrated database. CPAD's existing clinical trial simulation (CTS) tool for pre-dementia (CDR-SB as endpoint) is being expanded with additional information (other cognitive scales, fluid and imaging biomarkers, subjects in earlier disease states). To overcome sources of variability between tau tracers, a standardized method is needed to ensure consistent and reproducible quantitation of tau deposition; therefore, in Q3 2022 CPAD launched a precompetitive effort with leading academic and industry experts, to share data and neuroimages for the purpose of harmonizing tau-PET quantification across tracers and cohorts.
Results: As of May 2022, CPAD's data repository contains 61 studies with 41,541 individual anonymized patient records, with a rich source of key AD biomarkers (biofluids and imaging). Different linear and non-linear mixed effects models were fit based on relevant biomarker combinations and evaluated using traditional regression metrics, while confidence intervals were evaluated using bootstrapping. Harmonization of cross-sectional and longitudinal tau PET results and their impact on cognition along the Alzheimer's disease continuum were evaluated.
Conclusions: The precompetitive collaboration, data acquisition and analysis pioneered by CPAD is fundamental to the generation of actionable quantitative DDTs for accelerating and advancing AD drug development.

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P0326 / #2783

POSTERS: A03.O. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

A PHASE 3 CLINICAL TRIAL PROTOCOL TO EVALUATE THE EFFICACY AND SAFETY OF NA-831 IN SUBJECTS WITH EARLY ONSET OF ALZHEIMER'S DISEASE

Lloyd Tran[1], Fern Vu[2]
[1]Biomed Industries, Inc., R&d, San Jose, United States of America, [2]Biomed Industries, Inc., Clinical Research, San Jose, United States of America

Aims: This phase 3 study consists of a Core and Open Label Extension (OLE) Phase in 465 participants with early onset of Alzheimer's Disease (EAD), and will be conducted to evaluate the efficacy and safety of NA- 831. The Core is a 52-week treatment, multicenters, double blind, placebo controlled parallel group study.
Methods: Core Study: Participants will receive one capsule of 30 milligram (mg) NA-831 orally once a day in the morning. The core study will be double blinded. Placebo Comparator: The core study will be double blinded. Experimental: Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31 capsule orally once a day in the morning.
Results: Key Outcome Measures: 1. Core Study: Change From Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score at 48 Weeks [Time Frame: Baseline, Week 52] 2. Open-Label Extension Phase: Number of Participants With Treatment-Emergent Adverse Events (AEs) [Time Frame: Up to Week 52 of Extension Phase] Secondary Outcome Measures: Cognition-13 (ADAS-Cog-13) at Weeks 24, 52 [Time Frame: Baseline, Week 24, Week 52 of Extension Phase] CORE STUDY: Mild cognitive impairment due to AD or mild AD dementia including 1. MMSE score equal to or greater than 24 2. CDR global score of 0.5 3. CDR Memory Box score of 0.5 or greater
Conclusions: The Phase 3 clinical trial are being conducted in 25 sites in the US and several countries. The details of the Phase 3 methodology and protocol will be presented and discussed.

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P0327 / #2052

POSTERS: A03.O. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

IMPACT OF CONTINUOUS SITE ENGAGEMENT ON STUDY CONDUCT: INSIGHTS FROM THE "BRAIN SHUTTLE AD" STUDY AND THE CONTINUOUS SCREENING MODEL

Fabien Alcaraz[1], David Agnew[2], Ruth Croney[2], Luka Kulic[1], Dolly Niles[3], Annamarie Vogt[1], Hanno Svoboda[4]
[1]Roche Innovation Center Basel, Pharmaceutical Sciences - Clinical Pharmacology, Basel, Switzerland, [2]Roche Pharma Research and Early Development, Roche Products Limited, Welwyn Garden City, United Kingdom, [3]Executive Director, Quest Research Institute, Farmington Hills, United States of America, [4]Roche Diagnostics GmBH, Neuroscience & Rare Diseases, Mannheim, Germany

Aims: During regular site engagement meetings with investigators of the trontinemab (previously known as RO7126209) Phase Ib/IIa study (NCT04639050), the fixed screening window was identified as a hurdle for both sites and participants. Following collaborative discussions with site investigators, a continuous screening model was implemented. The impact of site engagement, using the change from a fixed to continuous screening, was assessed.
Methods: Continuous screening was introduced through a protocol amendment between cohort 1 and 2, allowing for an indefinite period to complete screening. Recruitment metrics were compared in cohort 1 (fixed screening) versus cohorts 2 and 3 (continuous screening) for time for first participant randomisation, time to complete the cohort (10 participants), and average time in screening.
Results: Preliminary results suggest that while participants in all cohorts remained in screening for a similar amount of time (cohort 1: 70, cohort 2: 78, and cohort 3: 80 days), the time to enroll the first participant was shorter in cohorts 2 (3 days) and 3 (0 days) compared to cohort 1 (81 days), as well as the time to complete the cohorts (cohort 1: 182, cohort 2: 95, cohort 3: 99 days). This suggests continuous screening allowed clinical sites to line up participants while waiting for the opening of the next cohort, leading to a significant reduction in recruitment timelines.
Conclusions: Ongoing site-partnering activities, led to an early change in trial design, which ensured that feedback from both the sites and participants were successfully addressed, while safety and data integrity were maintained. Continual site partnership yields mutual benefit to all parties, as demonstrated in this study. Results of a planned survey that aims to validate the impact of this approach will be presented.

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P0328 / #2007

POSTERS: A03.O. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

POWER ANALYSIS FOR A HYPOTHETICAL TRIAL WITH AD COURSE MAP ENRICHMENT, A SIMULATION STUDY FROM RETROSPECTIVE OBSERVATIONAL DATA

Etienne Maheux[1,2], Igor Koval[1,2], Juliette Ortholand[2], Colin Birkenbihl[3,4], Stanley Durrleman[1,2]
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Aims: We evaluate a new trial enrichment method, based on a prognostic score automatically computed from a disease progression model and participant's multimodal screening data.
Methods: We trained a disease progression model called **AD COURSE MAP** using longitudinal data from ADNI amyloid positive subjects (N=866), thanks to open-source software **Leaspy** (https://gitlab.com/icm-institute/aramislab/leaspy). The model summarizes the distribution of trajectories for several endpoints from asymptomatic to symptomatic stages of AD: cognitive and functional assessments, CSF and vMRI biomarkers, Amyloid and Tau PET SUVR. From held-out ADNI participants and four external observational cohorts (AIBL, J-ADNI, MEMENTO, PHARMACOG), we selected participants matching EMERGE/ENGAGE inclusion criteria (N=895). For each participant, we computed with **AD COURSE MAP** his prognostic score, namely his predicted change from baseline of MMSE after 18 months. We simulated a hypothetical 25% treatment effect and computed the sample size required to adequately power the trial (two-sided t-test with 5% significance, 80% power, no drop-out) on either the whole population or an enriched population with high prognostic scores (i.e. participants likely to decline during the trial).
Results: The Pearson correlation between the prognosis score and the primary outcome is 38.9% (95% CI=[36.5%, 41.9%]). The sample size for **AD COURSE MAP** enriched population is reduced by 45.4% (95% CI=[41.3%, 49.3%]) as compared to no enrichment, while targeting 49.6% of initial participants.
Conclusions: From a pool of trial candidates, **AD COURSE MAP** is able to identify the ones at risk of declining in the short-term and enables to design more powered trials. This demonstrates the benefits of such a companion software tool for patient recruitment in trials and, in the future, for supporting clinicians in prescribing the right treatment to the right patient at the right time.

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P0329 / #2018

POSTERS: A03.O. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

MITIGATING LOSS OF STATISTICAL POWER DUE TO OUTCOME IMBALANCE IN ALZHEIMER'S DISEASE CLINICAL TRIALS

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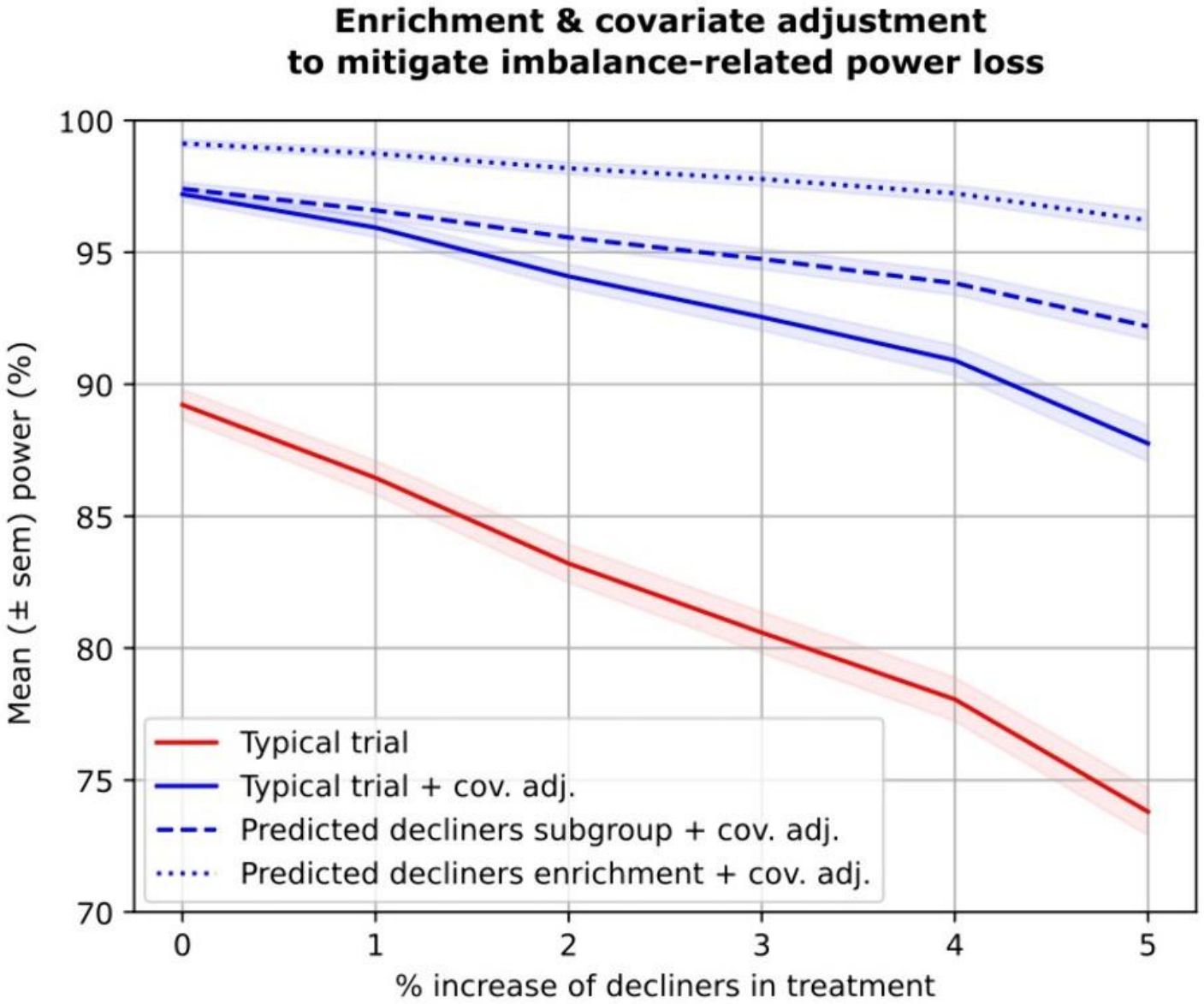
Aims: Unequal rates of decline between placebo and treatment arms reduce a trial's power. We aimed to demonstrate that we can mitigate the impact of outcome imbalance with a machine learning model that predicts decliners and non-decliners.
Methods: We trained a model to classify decliners (i.e. individuals who had increased CDR-SB scores at 24 months of follow-up) and non-decliners on 1329 individuals with mild cognitive impairment or Alzheimer's dementia from ADNI (adni.loni.usc.edu) and NACC (naccdata.org). We 1) simulated 100,000 trials by randomly assigning individuals to placebo and treatment (n=250 per arm) and measured the differences in prevalence of decliners across the arms to assess the probability of imbalance, 2) measured the power to detect a 25% effect across 1000 simulated trials when the arms were balanced and when the treatment arm had up to 5% more decliners compared to placebo, 3) and studied whether covariate adjustment and enrichment with decliners predicted by the model mitigate the imbalance-related loss in power.
Results: The probability of observing at least 5% imbalance across arms was 22.4%. A typical trial with an imbalance of 5% more decliners in treatment experienced 15% less power compared to a balanced trial. Covariate adjustment on prognostic factors (e.g. APOE4, diagnosis, baseline outcome score) increased power irrespective of imbalance. A subgroup analysis of the predicted decliners (excluding the predicted non-decliners) also increased power, despite the reduction in sample size. Using an enriched sample with 250 predicted decliners per arm obtained the greatest power and constrained the power loss to 3% at 5%
imbalance.



Conclusions: Covariate adjustment and enrichment of likely decliners substantially mitigate imbalance-related power loss, and they can be combined for greatest effect.

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P0330 / #2555

POSTERS: A03.P. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

EFFECTS OF MULTIDOMAIN INTERVENTIONS WITH NUTRITIONAL SUPPLEMENTS ON COGNITION AND GUT MICROBIOME IN EARLY-STAGE ALZHEIMER'S DISEASE: A RANDOMIZED CONTROL TRIAL

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Aims: This study evaluated effects of the SUPERBRAIN (SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention in elderly people at risk) program with nutritional supplements in alzheimer's pathology proven early-stage Alzheimer's disease patients.
Methods: Methods: Forty-six participants who were positive in the amyloid PET study and diagnosed with mild cognitive impairment or early-stage of dementia were randomized into three groups: group A, multidomain intervention with nutritional supplements; group B, nutritional supplements only; and a control group. The primary outcome was a change in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score after an 8-week intervention. Secondary outcomes, including gut microbiome data were also analyzed.
Results: Results: The Pre-Post Evaluation of Trial showed a significant difference in changes in RBANS total scale index score among the three groups, [group A: 9.02 (5.12, 12.92), group B: 1.75 (-2.18, 5.67), control group: -4.53 (-8.31, -0.75), $p<0.001$]. The change of MMSE was significantly higher in group A compared to that of the control group ($p=0.003$). The SPPB score improved significantly in group A compared to that of group B ($p=0.005$) and the control group ($p<0.001$). The gut microbiome data analysis showed that the changes in alpha diversity were not different among the three groups. PERMANOVA analysis for beta diversity showed no differences among the three groups ($p=0.453$). Comparison of the LEfSE between group A and the control group after the intervention showed that group A was more enriched with *Faecalibacterium* and *Bifidobacterium* than that of the control group.
Conclusions: The multidomain intervention with nutritional supplements improved cognition, physical and gut microbiome, thus may provide supportive evidence regarding a multidomain intervention with nutritional supplements in early AD.

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P0331 / #1847

POSTERS: A03.P. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

FEASIBILITY OF PREVENTING ALZHEIMER'S DISEASE WITH GAMMA ENTRAINMENT USING SENSORY (GENUS) STIMULATION IN PEOPLE WITH DOWN SYNDROME

Diane Chan[1,2], Brennan Jackson[1], Gabrielle De Weck[1], Erin Kitchener[3], Vanesa Fernandez[1], Ute Geigenmuller[1], David Lewis[1], Megan Colburn[1], Brian Skotko[4], Li-Huei Tsai[5,6]
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Aims: People with Down syndrome (DS) are uniquely at risk for developing Alzheimer's disease (AD) due to the triplication of the APP gene, which increases the risk of cerebral amyloid accumulation. Our lab previously showed in AD mouse models that non-invasive sensory stimulation using light and sound to induce 40Hz entrainment resulted in reduced AD pathology such as cerebral amyloid and tau levels. Preliminary studies in the Ts65Dn mouse model of DS showed that gamma stimulation can ameliorate neuropathological signs of DS. Our objective is to determine whether non-invasive sensory stimulation can be used to modulate gamma power and synchronization in people with DS as a potential therapeutic to prevent AD in this population.
Methods: In a Phase 1/2 study, we treated people with DS (n=17) and age-matched, neurotypical controls (n=7) with our GENUS light and sound device while using electroencephalography (EEG) to evaluate induced entrainment and effects on neural circuitry (NCT05196984). Participants were blindly randomized to receive 1-hour of either sham or active, 40Hz light and sound stimulation. Cognitive testing was performed before and after the stimulation session.
Results: GENUS light and sound stimulation was found to be safe and tolerable in both the neurotypical and DS groups. Both groups showed 40Hz entrainment in response to active light and sound stimulation, but entrainment was reduced in people with DS compared to neurotypical controls. We report findings relating gamma entrainment and neural circuitry with cognitive level of functioning in people with DS.
Conclusions: Our non-invasive GENUS device safely induces gamma entrainment in people with DS. Based on this result, we are planning a trial to explore the potential of repeated GENUS treatment to prevent dementia in people with DS.

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P0332 / #1243

POSTERS: A03.P. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

GAMMA-FREQUENCY SENSORY STIMULATION DIMINISHES BRAIN ATROPHY IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: Evaluating Cognito Therapeutics' medical device, a non-invasive sensory stimulation device that evokes steady-state gamma oscillation, on brain volumetric changes and amyloid plaque load in patients with Alzheimer's disease (AD).
Methods: Neuroimaging data were collected during the clinical trial which assessed safety, tolerance, and efficacy of Cognito Therapeutics medical device in patients with clinical presentation of AD spectrum. Patients were randomized 2:1 to receive daily, one-hour, EEG-assessed, 40Hz noninvasive audio-visual stimulation (active arm) or sham (placebo arm) stimulation over a 6-month period. In addition to assessments of cognitive and functional abilities, brain pathological changes were evaluated by neuroimaging methods, including MRI and [18F]florbetapir PET.
Results: The MRI results demonstrated a significant reduction in whole brain volume loss, found to be associated with a strong trend to reduced lateral ventricle expansion, in subjects who received gamma sensory stimulation when compared to the placebo arm. Active arm subjects also showed a significantly reduced loss in white matter volume, occipital lobe volume and cortical thickness when compared to placebo arm subjects. Changes in MMSE scores demonstrated significant cognitive benefits in active arm subjects, and positive correlation was noted between changes in MRI volumes and MMSE scores in active arm subjects. Neither the active nor the placebo arm participants showed a significant difference in amyloid plaque load, assessed by composite SUVr value, between baseline and end of trial.
Conclusions: Significant brain volume preservation and clinical benefits, independent from amyloid plaque loads were demonstrated by 40Hz sensory stimulation delivered by Cognito Therapeutics medical device in patients with AD.

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P0333 / #1973

POSTERS: A03.P. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

LONG-TERM SAFETY AND COMPLIANCE TO A MULTINUTRIENT INTERVENTION FOR UP TO 8 YEARS IN PRODROMAL AD/MCIAD: THE LIPIDIDIET TRIAL

Tobias Hartmann[1,2], Alina Solomon[3,4,5], Pieter J Visser[6,7], Kaj Blennow[8,9], Miia Kivipelto[10,11], Hillka Soininen[12]
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Aims: Objectives: Interventions aiming to slow disease progression may require long-term compliance to achieve clinically meaningful results. The LipiDiDiet study is a unique long-running randomised, double-blind, placebo-controlled trial, investigating the effects of Fortasyn Connect (Souvenaid) in individuals with prodromal AD/MCI$_{AD}$ over up to 6 years of double-blind, placebo-controlled and additional 2 years of open-label intervention. Here we report on long-term safety and compliance to the intervention over a maximum of 8 years.
Methods: Methods: 311 individuals with prodromal AD (IWG-1) were randomized to active (125ml once-a-day drink; Fortasyn Connect) or a calorie-matched control. Following the first 2 years of intervention, participants could opt in for annual extensions up to a maximum of 6-year double-blind and 2-year open-label intervention. Safety assessments included (serious) adverse events ([S]AEs), concomitant medications, and vital signs. Product compliance was assessed by participants' recording in a daily dairy.
Results: Results: The frequency, severity and types of recorded AEs were consistent with the studied population, the overall incidences were comparable between groups, and none of the SAEs was related to the study product as assessed by the investigators. Self-reported study product compliance was 85% to 98% across the different intervention years.
Conclusions: Conclusion: Safety and feasibility of long-term use are relevant prerequisite factors for compliance to interventions aimed at slowing disease progression. Results show that compliance to the study product remains high over a long-term intervention period and there was no indication of health concerns related to the use of Fortasyn Connect for up to 8 years in a prodromal AD/MCI$_{AD}$ population.

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P0334 / #379

POSTERS: A03.P. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

IMPROVING THE ADHERENCE TO LIFESTYLE INTERVENTIONS FOR PREVENTING COGNITIVE DECLINE: STRATEGIES FROM THE PENSA STUDY TO PROMOTE PATIENT ENGAGEMENT

Thais Lorenzo[1], Laura Forcano[1], Aida Cuenca-Royo[1], Iris Piera[1], Anna Boronat[1], Natàlia Soldevila-Domènech[1], Carolina Minguillón[2], Karine Fauria[2], Oriol Grau-Rivera[2], Juan Domingo Gispert[2], José Luis Molinuevo[2], Rafael De La Torre[1]
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Aims: Lifestyle interventions have provided promising results to maintain cognitive function in late/middle-aged individuals at high risk of developing Alzheimer's disease. Participant's involvement (PI) and engagement are highly related to the intervention's success. However, they are often unattended issues within these interventions. The PENSA study is a 12-month lifestyle intervention focused on preventing cognitive impairment in *APOE*ε4 carriers experiencing subjective cognitive decline. We aim to present the activities that have been implemented to improve the adherence of PENSA study participants.
Methods: Several resources have been implemented that may promote PI: co-creation group, personalised intervention, face-to-face and phone meetings with reference professionals, monthly adherence reports, satisfaction questionnaires, continuous technological monitoring, informative sessions, user guides, and psychoeducational sessions (PS) promoting participants expertise on the intervention, and giving them psychological support, as well as strategies to confront their lifestyle changes.
Results: 104 participants were included, from which 6% dropped out. Activities were attended by an average of 85% of the participants. 90% responded to the Ecological-Momentary-Assessment and achieved a 75% of cognitive training compliance. Regarding the PS satisfaction questionnaires, 69% responded to at least one of them. Overall, 98,9% were satisfied with the sessions' content. 98,6% thought that it may have a positive impact on their health, that may contribute to dealing with difficulties and relapses (97,2%), and may help getting over themselves (96,1%).
Conclusions: PI is a critical aspect of lifestyle interventions. Our results suggest that an early participant's involvement helped to improve adherence, enhanced satisfaction and helped attaining a very low attrition rate. PI and engagement initiatives should be included within clinical trials for preventing cognitive decline, offering participants psychological support to make them feel safe and comfortable, thus achieving higher retention and engagement.

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P0335 / #2605

POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

EYE-TRACKING METRICS FOR FIGURE-COPYING IN AMYLOID-NEGATIVE VERSUS AMYLOID–POSITIVE MILD COGNITIVE IMPAIRMENT: A PILOT STUDY

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Aims: We conceptually split the copying processes into three stages: visuoperceptual function, visuoconstructional function, and working memory function. To evaluate subtle differences, we measured eye-tracking metrics while participants performed the simplified Rey Complex Figure (RCFT).
Methods: We recruited 23 participants with MCI who had amyloid positron emission tomography (PET) results. To focus on copying and drawing processes, we conceptually split the area of interest (AOI). We defined perceptual and working spaces AOIs to investigate the different stages of copying. We used Tobii Glasses Pro 2, which records binocular eye movements. Eye-tracking was recorded during the copying. After standard gaze mapping, we quantified the number of fixations on each AOI. These quantified metrics were compared between amyloid-negative versus amyloid–positive MCI groups using Mann-Whitney U test.
Results: This study group comprised 14 patients with amyloid-negative MCI and 9 patients with amyloid-positive MCI. Amyloid PET positivity was interpreted according to the guidelines of each PET ligand. Statistical analyses only showed that the total number of fixations on the perception AOI was higher in the patients with amyloid-positive MCI than among the patients with amyloid-negative MCI ($p = 0.03$).
Conclusions: Patients with amyloid-positive MCI showed a greater number of fixations compared amyloid-negative MCI on the perceptual AOI. Consistently, our previous study showed that patients with AD also showed a longer fixation duration and greater number of fixations on the perceptual AOI than the NC participants. An increased number of fixations and fixation duration on the perceptual AOI indicate an increase in target processing times. Therefore, the results indicated that a greater number of fixations on perceptual AOI are required while visually encoding complex figures, a neurobehavior that might be related to visuoperceptual dysfunctions in patients with AD.

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POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

PRELIMINARY DEVELOPMENT OF A MULTI-ORGAN-ON-A-CHIP PLATFORM FOR ALZHEIMER'S DISEASE IN VITRO DRUG DEVELOPMENT

Francesca Fanizza[1], Gianluigi Forloni[2], Carmen Giordano[1], Diego Albani[2]
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Aims: Our project (PEGASO, http://www.minerva.polimi.it/?page_id=1459) aims to contribute to innovative in vitro solutions suitable for Alzheimer's disease (AD) drug development. Its goal is to deliver a multi-organ-on-a-chip platform composed of six millifuidic bioreactors connected in series and loaded with induced pluripotent stem cells (iPSCs) models representing the main tissues and systems involved in oral drug administration: the microbiota, gut, immune cells, liver, blood-brain-barrier (BBB) and brain. Here we focus on the validation of the liver-on-a-chip.
Methods: Thanks to software-based simulations we evaluated different medium flow rates to obtain suitable oxygenation and shear stress values in our organ-on-a-chip featuring a Transwell system hosting human iPSC-derived hepatocytes encapsulated in a 3D configuration thanks to a collagen-poly(ethylene)glycol hydrogel. Endothelial cells were also seeded in the Transwell to model the vascular compartment. After 7 days of perfusion the cells features were characterized by ELISA, Real Time PCR and immunofluorescence. The approved AD drug Donepezil was then added to the model. The drug diffusion and partition coefficient were determined, experimentally basing on a quantitative spectroscopy assay.
Results: From the software simulation a medium flow rate of 30µL/min was set to guarantee oxygen supply and suitable shear stress. Hepatocytes were viable after 7 days of dynamic culture and exhibited significantly higher liver-specific functions with respect to the static condition, for instance urea and albumin production and CYP3A4 expression. Measurement data and model predictions revealed that the 5% of Donepezil diffused through the hydrogel in the liver-on-a-chip 72h after drug administration.
Conclusions: We developed a human iPSC-based liver-on-a-chip suitable for AD drug screening as key step to deliver a multi-organ platform for drug pharmacokinetics and pharmacodynamics.

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POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

VALIDATION OF A COGNITIVE SAFETY MONITORING SYSTEM FOR REAL TIME DETECTION OF ADVERSE EVENTS IN CLINICAL TRIALS

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Aims: In clinical trials of patients with neurodegenerative disease it is possible that individual subjects show an adverse reaction to the investigational drug manifesting as an encephalopathy, delirium, or exacerbation of dementia. In many cases such adverse events are indicated by a new and substantial decline in cognition. Where diseases under investigation are characterized by cognitive decline, new onset cognitive deterioration can be difficult to detect clinically. We aimed to establish the sensitivity and specificity of a cognitive safety monitoring system (SMS) for automatic detection of new clinically important cognitive decline in symptomatic Alzheimer's disease.
Methods: The cognitive SMS was based on repeated application of the Cogstate Detection and Identification tests and the International Shopping List Test (ISLT). Reliable change indices for performance on each test was developed from the symptomatic AD subjects enrolled in the AIBL ROCS cohort, where assessments had occurred monthly for 12 months and where there had been no adverse events or new illness reported. From this sample a decision rule for classification of clinically important cognitive decline was determined. This rule was then applied to the placebo data from an 18-month clinical trial of a putative disease modifying therapy and a trial where adults with preclinical AD receive an acute dose of 0.2mg scopolamine.
Results: Across 456 repeated assessments from AIBL ROCS, a rule requiring RCI of </=-1.65 on 2/3 tests provided a specificity of 98%. Application of this rule to 1085 repeated assessments identified clinically important cognitive decline in 3 (0.3%) cases from the clinical trial and 100% of adults after acute scopolamine.
Conclusions: The cognitive SMS has strong specificity and sensitivity to the appearance of new clinically important cognitive decline in adults with AD.

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POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

EXPLORATORY DELAYED-START ANALYSIS OF PASADENA PART 3 52-WEEK OLE EVALUATING PRASINEZUMAB EFICACY ON MOTOR PROGRESSION AND COMPLICATIONS IN EARLY-STAGE PD

Gennaro Pagano[1,2], Annabelle Monnet[3], Kirsten Taylor[1], Emma Moore[4], Andrea Hahn[5], Tanya Simuni[6], Ken Marek[7,8], Ron Postuma[9], Nicola Pavese[10], Fabrizio Stocchi[11], Hanno Svoboda[1], Paulo Fontoura[3], Rachelle Doody[3], Geoffrey Kerchner[1], Azad Bonni[1], Tania Nikolcheva[3]
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Aims: Prasinezumab is a humanised monoclonal antibody designed to target aggregated α-synuclein and slow disease progression in Parkinson's disease (PD). PASADENA is a multicentre, randomised, double-blind, placebo-controlled study evaluating efficacy of prasinezumab in participants with early-stage PD. Here, we describe the results from the first 3 years of PASADENA up to 1 year into Part 3 open-label extension (OLE).
Methods: Participants with early-stage PD (diagnosis ≤2 years at screening; Hoehn & Yahr Stages I–II) were randomised to receive intravenous prasinezumab every 4 weeks (1500 mg or 4500 mg) for 104 weeks, or placebo for 52 weeks followed by prasinezumab (1500 mg or 4500 mg) for 52 weeks. All participants have a 12-week treatment-free follow-up period before entering a 5-year OLE receiving prasinezumab 1500mg every 4 weeks. All 316 PASADENA participants were considered in the analysis regardless of change in symptomatic therapy. Motor progression and motor complications were defined, respectively, as a ≥5-point increase on MDS-UPDRS Part III and reaching a score ≥1 point on MDS-UPDRS Part IV and analysed using Cox proportional hazards models.
Results: Baseline characteristics were balanced between individuals in the early- and delayed-start groups. At the end of Year 1 of Part 3, fewer participants in the early-start (3-year prasinezumab) group showed motor progression (84.4%) or developed motor complications (58.8%) compared with the delayed-start (2-year prasinezumab) group (92.4% and 68.6%; hazard ratio: 0.78 [80% CI 0.66–0.92] and 0.79 [80% CI 0.65–0.96]).
Conclusions: The PASADENA Part 3 OLE is currently ongoing, and we aim to describe long-term safety and efficacy on a yearly basis.

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P0339 / #884

POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

ADVERSE EVENTS REPORTED IN ASSOCIATION WITH APOE-E4 ALLELE(S) FROM PLACEBO ARM OF CLINICAL TRIALS FOR ALZHEIMER'S DISEASE

Kenichiro Sato[1,2], Yoshiki Niimi[2], Ryoko Ihara[3], Kazushi Suzuki[4], Atsushi Iwata[3], Takeshi Iwatsubo[1,2]
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Aims: Having *APOE*-ε4 allele[s] is strongly associated with the development of Alzheimer's disease (AD), and so with the vascular risk factors to a fewer extent. In this point, during clinical trials, participants with *APOE*-ε4 allele[s] may experience additional vascular-related adverse events (AEs) via the increased vascular risk due to *APOE*-ε4 allele[s] in addition to the baseline risk of events, which may require investigators to consider in the safety monitoring. In this study, we aim to investigate the degree of contribution of *APOE*-ε4 allele[s] to the reporting of AEs during clinical trials for AD participants, using randomized controlled trials (RCT) data of placebo arm.
Methods: We used Critical Path for Alzheimer's disease (CPAD) data which collects thousands of AD participants of placebo arm of RCT of AD treatment. As in the case of conventional pharmacovigilance analysis, we evaluated whether each reported AE is more likely to be reported in participants with *APOE*-ε4 allele[s] than in those without. This was quantified with reporting odds ratio (ROR) using a mixed effect model in which study project was appointed as random intercept.
Results: There were 1,860 participant cases who reported any of the 165 AEs; convulsion, muscle spasms, atrial fibrillation, hypercholesterolaemia, and tremor were significantly highly reported in AE-reporting cases with *APOE*-ε4 allele[s] than those without (lower 95% ROR > 1), as well as were significantly highly developed in cases with *APOE*-ε4 allele[s] than those without (lower 95% OR > 1).
Conclusions: Although their causal relationship remain uncertain at all, some AEs may be more likely to be reported from AD individuals with *APOE*-ε4 allele[s] during RCTs regardless of the effects actual drugs. This may be helpful for investigators in monitoring drug safety during clinical trials concentrating ε4-positive AD participants.

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P0340 / #706

POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

DEVELOPMENT OF DRUG CANDIDATES FOR A SPECIFIC ELIMINATION OF TOXIC IAPP OLIGOMERS

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Aims: Type 2 Diabetes Mellitus is a progressive, chronic and incurable disease characterized by insulin resistance, insufficient insulin secretion, loss of β-cell number and function, and accumulation of amyloid deposits in the islets of Langerhans. The major component of these deposits consists of islet amyloid polypeptide (IAPP, aka amylin), a peptide hormone consisting of 37 amino acid residues, which is secreted by the β-cells of the pancreas. Under physiological conditions, IAPP exists as a soluble, monomeric peptide and controls gastric emptying and glucose homeostasis, among other functions. Under so far unknown circumstances, natively occurring monomeric IAPP aggregates into smaller soluble aggregates and amyloid deposits. During this process, cytotoxic intermediates called oligomers are formed. Here, we hypothesize that these toxic IAPP oligomers are the cause of T2DM.
Methods: By use of mirror image phage display, we have selected d-peptides for the direct elimination of toxic IAPP oligomers. Those d-peptides were analyzed in various in vitro assays (binding assays, aggregations assays and oligomer elimination assay).
Results: We demonstrate that the selected d-peptides were able to specifically bind to monomeric IAPP, are able to reduce (or inhibit) the IAPP fibril formation and to eliminate toxic IAPP oligomers in vitro. Further steps will be to challenge the d-peptides pharmacokinetic properties (in vitro and in vivo) and the efficacy in vivo in the so-called RIPHAT diabetes mouse model.
Conclusions: Approximately 450 million people worldwide are suffering from diabetes mellitus, 95% of whom have T2DM. It is estimated that this number will continue to rise as the world's population grows and prosperity increases. Since the treatment of T2DM is only symptomatic, we are describing here a possible approach for a causal treatment by the specific elimination of toxic IAPP oligomers.

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P0341 / #383

POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

TRANSCRANIAL PULSE STIMULATION IN ALZHEIMER´S PATIENTS: WHOM, HOW AND WHERE TO STIMULATE?

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Aims: Transcranial Pulse Stimulation (TPS) uses shockwaves for the treatment of Alzheimer´s patients. Recently, our group published short-term clinical results after the first treatment cycle (Cont et al. 2022). However, many aspects remain unclear concerning patient selection and treatment protocols.
Methods: A consecutive series patients received TPS using the Neurolith System (Storz Medical). After the initial treatment cycle over 2 weeks patients were scheduled for monthly booster sessions. Safety data and different cognitive scores were assessed over 5-12 months. Individual symptomology, MRI- and CSF biomarker, disease stages, inclusion / exclusion criteria and treatment protocols where registered.
Results: The initial treatment was well tolerable with low number of only transient and not severe side effects even in selective patients with minor vascular lesions and platelet aggregation inhibitors. Cognitive and affective scores improved significantly after the first treatment cycle regardless of symptom severity at baseline and CSF biomarker. Standard protocol was 6000 pulses with 4 Hz stimulation of precuneus, bilateral frontal and parietal cortex but was extended to bitemporal cortex and / or motor areas such as SMA, M1, PMC to treat concomitant tremor or hypokinesia. Preliminary long-term data showed stable effects over months with the selected booster interval.
Conclusions: TPS might be an option for Alzheimer´s not only in mild cases and regardless of the biomarker constellation und thus maybe for other dementia types. Minor vascular pathology and platelet aggregation inhibitors is generally acceptable. Treatment protocols can extend standard patterns and include e.g. motor areas to address concomitant hypokinesia or tremor. Imaging and electrophysiology biomarkers need to established. Systematic treatment protocols should be tested with a translational approach including basic neuroscience techniques and in comparison to other methods such as ultrasound and electric / magnetic stimulation.

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P0342 / #1610

POSTERS: A03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

EXPLORING THE ROLE OF NEUROINFLAMMATION AND RELATED PATHWAYS ON THE EFFECTS OF SEMAGLUTIDE IN ALZHEIMER'S DISEASE: BIOMARKER ANALYSES IN EVOKE/EVOKE+

Henrik Zetterberg[1,2,3,4,5], Jeffrey Cummings[6], Charlotte Hansen[7], Peter Johannsen[8], Filip Knop[9,10,11,12], Lars Raket[13], Mary Sano[14], Hillka Soininen[15], Christian Wichmann[16], Alireza Atri[17,18]
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Aims: Glucagon-like peptide-1 receptor agonists (GLP-1RA) have been reported to reduce neuroinflammation, provide neuroprotection and improve cognition in animal models. Moreover, post-hoc analyses of randomized clinical trials in type 2 diabetes suggest that GLP-1RAs may reduce cognitive impairment and dementia risk. Studies are required to understand the role of neuroinflammation in Alzheimer's disease (AD) and elucidate the mechanism of action of GLP-1RAs and provide evidence of disease modification.
Methods: Plasma biomarkers will be measured in all participants (except those in China) of the phase III randomized, placebo-controlled evoke/evoke+ trials (N=1840 per trial) (NCT04777396 and NCT04777409) studying oral semaglutide 14 mg once daily in early AD. Cerebrospinal fluid (CSF) biomarkers will also be measured in a sub-set of ~210 participants. Blood samples will be collected at baseline (week 0) and weeks 52, 104, and 156 and CSF samples will be collected before randomization and at week 78 for assessment of biomarkers (Figure). Participants will be stratified by participation in the CSF sub-study to ensure 1:1 randomization in the sub-study population. The biomarkers analyzed will focus on markers of neuroinflammation (e.g. glial fibrillary acidic protein [GFAP], chitinase-3-like protein [YKL-40], soluble triggering receptor expressed on myeloid cells [sTREM-2], interleukin-1b, etc) as well as neurodegeneration (e.g. neurofilament light chain [NfL] and neurogranin), blood–brain barrier integrity (e.g. albumin ratio in CSF and plasma), and oxidative stress (e.g. isoprostanes)
(Figure).

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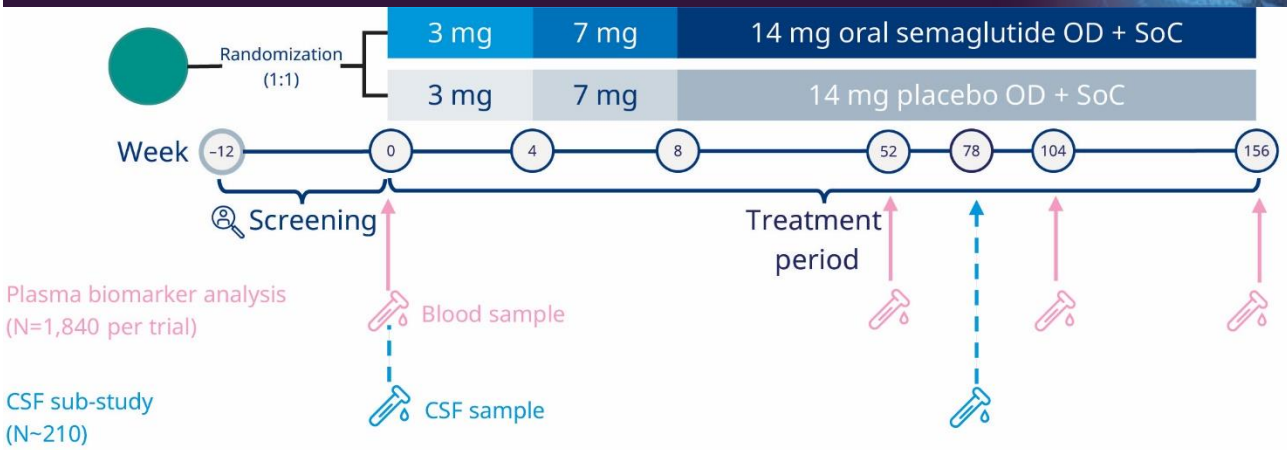

Sample	Neuroinflammation		Neurodegeneration	Oxidative stress	Amyloid	Tau	BBB integrity	
Blood		GFAP	NfL			p-tau-181		
CSF	YKL-40 sTREM2 GFAP MCP1/CCL2 SMOC1 IL-6 Osteopontin	IL-1b IL-10/CXCL10 IL-18 IL-1RA Complement factor 3 & 4	NfL t-tau Neurogranin	Isoprostanes 8-OHdG	Aβ 42/40 ratio	p-tau-181	sPDGFRβ	Albumin ratio (CSF/serum)

8-OHdG, 8-oxo-2'-deoxyguanosine; Aβ, amyloid beta; CCL, C–C motif chemokine ligand; CSF, cerebrospinal fluid; CXCL, C–X–C motif chemokine ligand; GFAP, glial fibrillary acidic protein; IL, interleukin; MCP1, monocyte chemoattractant protein; NfL, neurofilament light chain; OD, once daily; p-tau, phosphorylated tau; SMOC1, secreted modular calcium-binding protein 1; SoC, standard of care; sPDGFRB, soluble platelet-derived growth factor receptor b; sTREM2, soluble triggering receptor expressed on myeloid cells 2; t-tau, total tau; YKL-40, chitinase-3-like protein 1.

Results: of the biomarker analyses of the evoke/evoke+ trials are expected in 2025.

Conclusions: The evoke/evoke+ program is collecting a large repertoire of biomarkers to document the biological impact of semaglutide, provide evidence of disease modification, and aid understanding of the relationship between neuroinflammation and neurodegeneration in early AD.

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P0343 / #1249

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

EVALUATION OF TRANSFER LEARNING METHODS FOR CLASSIFYING AMYLOID POSITIVITY FROM BRAIN MRI SCANS

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Aims: A key biomarker of Alzheimer's disease (AD) is abnormal accumulation of beta-amyloid plaques in the brain, typically assessed using PET or CSF samples. Inferring β-amyloid positivity (Aβ+) from brain MRI is extremely challenging, but even if accuracy were only moderate, it could be used to pre-screen patients prior to more invasive, expensive tests. As paired MRI-PET training data is limited, here we assessed the potential of transfer learning to learn to predict Aβ+ from ADNI data. Transfer learning is a type of artificial intelligence/deep learning method that has been found to boost MRI-based AD classification performance [1].
Methods: To pre-train our predictive model, we used 3D T1-weighted brain MRIs from 19,839 subjects (age: 64.6+/- 7.6 y; 10,294 F/9,545 M) from the UK Biobank. The 3D convolutional neural network (CNN) architecture was first pre-trained for the (unrelated) task of sex classification, and the weights were stored.
Results: Aβ+ prediction was around 70% accurate for models either trained from scratch or pre-trained on sex classification. Perhaps surprisingly, the pretraining - and the amount of data used for pre-training- did not affect the downstream Aβ+ prediction task accuracy.
Conclusions: This may be because UKBB primarily consists of healthy subjects, whose MRIs may not provide ideal predictive features for amyloid detection in ADNI. Future work with more paired training data, and with other modalities of data such as diffusion MRI, may boost performance on this challenging task. [1] Dhinagar et al., (2022). Evaluation of Transfer Learning Methods for Detecting Alzheimer's Disease with Brain MRI, in press, SIPAIM
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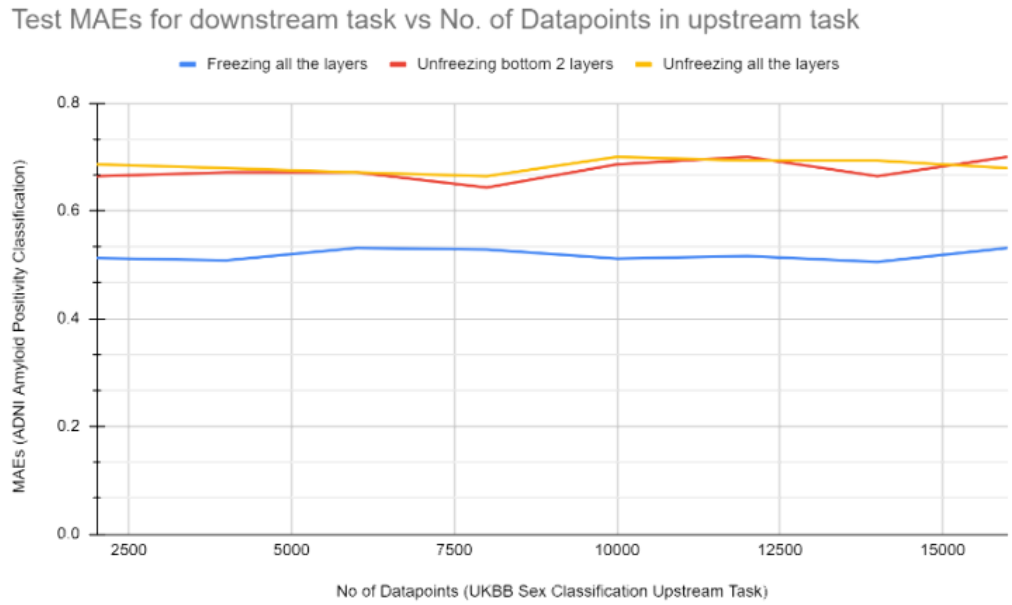

Fig 1. For the downstream task of Aβ+ prediction, we analyzed 3D T1w MRI from 765 subjects (age: 75.1 +/- 7.6; 397 F/368 M; 459 CN/67 MCI/236 AD/3 Pending) from the ADNI dataset. The cut-off for amyloid levels used was based on PET cortical SUVR uptake (denoted as Aβ_1 by ADNI) determined by either mean 18F-florbetapir (Aβ+ defined as >1.11 for cutoff) or florbetaben (Aβ+ defined as >1.20 for cutoff), normalized by using a whole cerebellum reference region. The model was trained using both frozen and unfrozen layers, and test performance was assessed using independent data not used to train the model.

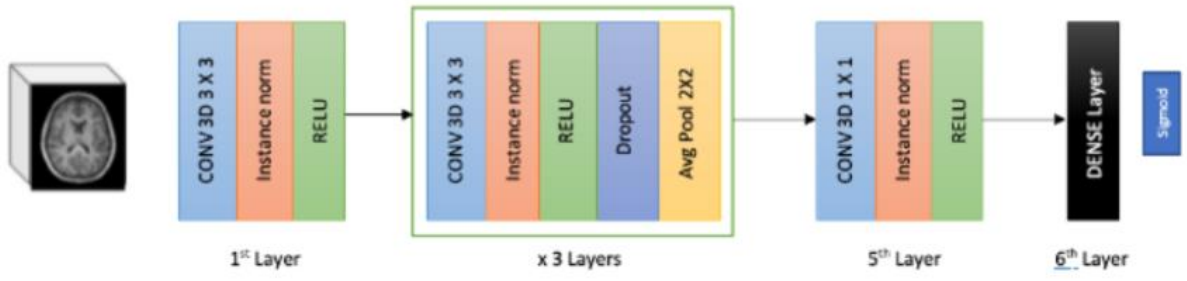

Fig 2. 3D CNN Architecture

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P0344 / #711

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

INCREASING THE RESOLUTION OF T1W MRI IMPROVES SUBJECT-LEVEL ESTIMATION OF CORTICAL DEGENERATION IN DEMENTIAS

Amir Fazlollahi[1,2], Soohyun Lee[1], Felicia Coleman[1], Martijn Cloos[3,4], Pierrick Bourgeat[5], Peter Nestor[1,6]
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Aims: We aimed to demonstrate that increasing the resolution of MRI scans would improve sensitivity of cortical atrophy detection for individual patients.
Methods: 7 semantic-variant primary progressive aphasia (svPPA), six posterior cortical atrophy (PCA) and 28 cognitively unimpaired participants underwent 3.0T MRI (**Table 1**). Two sets of T1W images with 0.8 mm^3 (HighRes) and conventional 1.0 mm^3 (ConvRes) resolution were acquired and surface-based cortical thickness maps were calculated using Freesurfer.

Table 1. Patient Demographics. MMSE: Mini-Mental State Examination (/30); ACE-III: Addenbrooke's cognitive examination III (/100)

	Control	svPPA	PCA
#n	28	7	6
Age (mean ± SD)	66.6 ± 7.5	63.4 ± 3.8	66.2 ± 5.3
Sex (female/male)	16/12	3/4	2/4
MMSE (mean ± SD)	28.6 ± 1.9	24 ± 2.7	15.2 ± 5.9
ACE-III (mean ± SD)	95.0 ± 3.3	61.7 ± 11.2	48.7 ± 17.2

Results: The HighRes scans produced higher image quality scores (signal- and contrast- to noise-ratio) at a cost of 90 seconds extra scan time (**Table 2**). HighRes scans showed more robust patterns of atrophy in expected regions in all individual patients (Examples are shown in **Figure 1**). The effect size of cortical thickness differences between patients and cognitively unimpaired participants was 15-20% larger for HighRes scans (**Figure 2**).

	ConvRes	***HighRes***	***ConvRes***	***HighRes***
Brain structures	SNR	SNR	CNR	CNR
Whole Cortex	49.6	73.8	34.0	47.1
Frontal Lobe	37.2	54.9	26.8	36.5
Parietal Lobe	76.0	114.0	46.7	62.7
Temporal Lobe	54.6	82.5	37.0	50.1
Occipital Lobe	89.1	130.9	50.9	68.9

Figure 1. Patients' z-score maps comparing 1.0x1.0x1.0 mm^3 (ConvRes) and 0.8x0.8x0.8 mm^3 (HighRes) MPRAGE scans (left and right hemispheres, along with an inferior view for svPPA and posterior view for PCA patients).

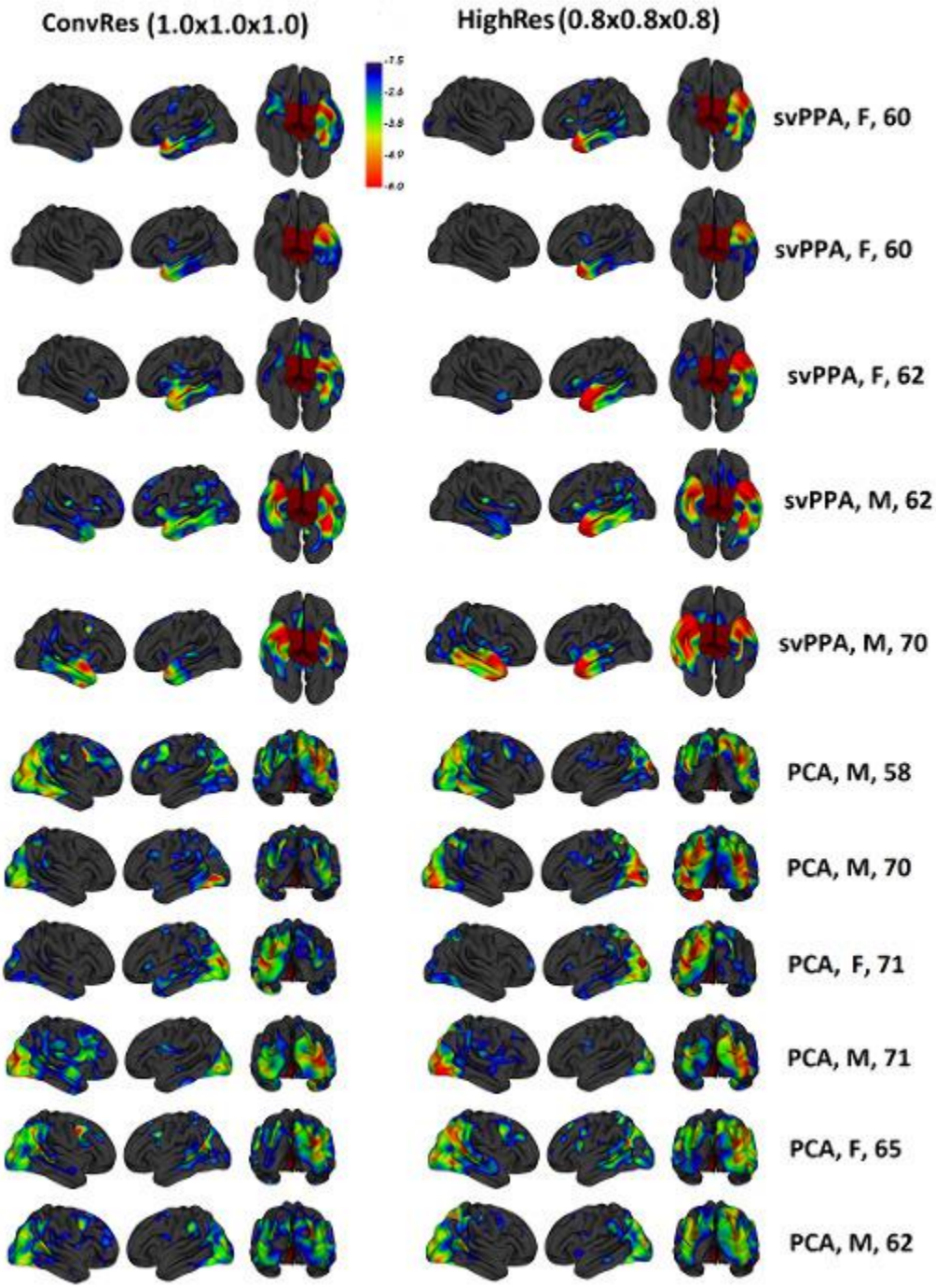
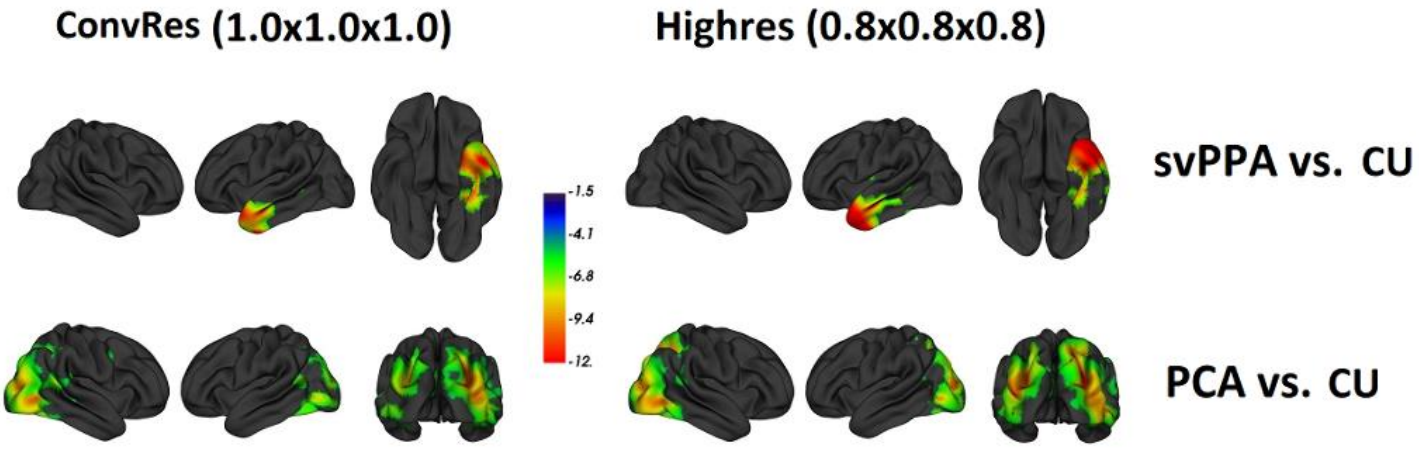


Figure 2. The t-map of thickness differences between patient and cognitively unimpaired (CU) groups. The t-values are obtained from a general linear model comparing the cortical thickness of the svPPA group with the CU group (top row) and the PCA group with the CU group (bottom row). The significance level for this analysis was set to $P = 0.001$ FDR corrected.



Conclusions: HighRes T1-weighted scans showed superior precision for identifying the severity of cortical atrophy in individual patients, offering a proof-of-concept for clinical translation. Studying svPPA and PCA, two syndromes with well-defined focal atrophy patterns, offers a method to clinically validate and contrast automated algorithms.

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P0345 / #1570

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

DIFFERENT PATTERNS OF LOCUS COERULEUS INVOLVEMENT IN ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA

Alessandro Galgani[1], Giovanani Palermo[1], Francesco Lombardo[2], Nicola Martini[3], Filippo Baldacci[1], Sara De Cori[2], Daniela Frosini[1], Luca Tommasini[1], Filippo Cademartiri[2], Francesco Fornai[4], Gabriele Siciliano[1], Nicola Pavese[5], Roberto Ceravolo[1], Filippo Giorgi[4]
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Aims: To assess Locus Coeruleus (LC) integrity in patients suffering from Alzheimer's Disease Dementia (ADD) or Lewy Body Dementia (LBD), and to explore whether LC alterations differ between the two groups of patients.
Methods: Eleven LBD and 35 ADD patients, and 53 cognitively intact subjects (HC) were submitted to a detailed neurological and neuropsychological assessment and then underwent a high field Brain MRI scan with LC-sensitive sequence. LC images were processed using a standardized template-based approach and LC integrity was expressed using the LC_{CR} (contrast-ratio) parameter.
Results: Patients belonging either to the LBD or ADD group showed lower LC_{CR} when compared to HC. ADD patients showed a main involvement of the rostral part of the left LC, while LBD subjects were characterized by a global degeneration of LC, also involving the right LC and the caudal subregions. These results survived also test adjustment for the effect of sex and age. No significant LC_{CR} differences were found when comparing ADD and LBD.
Conclusions: Our *in vivo* findings are in line with existing neuropathological *post-mortem* data, showing LC degeneration both in AD and LBD, although with two different underlying degenerative pathologies (secondary tauopathy and synucleinopathy, respectively). Moreover, the different spatial patterns we found may suggest a potential use of LC-MRI as a helpful tool, together with other ones, to distinguish these two dementing disorders, even though further studies on preclinical and mild stage diseases are warranted. **Funding:** Funded by Italian Ministry of Health [code: Ricerca Finalizzata 2013,# PE2013-02359574 "*In vivo assessment of the role of Locus Coeruleus in the development of Alzheimer's Disease and other types of Dementia*" (P.I.: F. Giorgi.)].

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P0346 / #2162

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

CORRELATION BETWEEN HIPPOCAMPAL SUBFIELDS AND CEREBROSPINAL FLUID PATHOLOGICAL MARKERS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: Hippocampal atrophy is common in Alzheimer's patients, but the relationship between the total volume of the hippocampus , the volume of the hippocampus subarea and the cerebrospinal fluid markers of AD is rarely studied. Therefore, this study mainly observed the relationship between the volume changes of the hippocampus subarea and the cerebrospinal fluid biomarkers of AD patients
Methods: Methods A total of 53 individuals were recruited, including AD and Non-AD subjects. All subjects went through a 3.0 T magnetic resonance (MR) scan and a neuropsychological assessment. Hippocampal subfield volumes were processed using the FreeSurfer 6.0.0, and using the IBM SPSS Statistics 24 for correlation analysis. To estimate the possible correlation between the volume changes of hippocampus subfields and cerebrospinal fluid(CSF) pathological markers.
Results: There was significant positive correlation in the cortical thickness of inferiorparietal and precuneus and rostralmiddlefront in left hippocampus, and postcentral in right hippocampus with Aβ($p<0.01$). The cortical thickness of superiorfrontal in right hippocampus was negatively correlated with T-tau ($p<0.01$). In addition, the cortical thickness of caudalmiddlefront in right hippocampus have a significant positive correlation with Aβ and a significant negative correlation with T-tau ($p<0.01$).
Conclusions: This study provides provisional evidence that the volume changes of hippocampus subfields was closely associated with CSF pathological characteristics, and these exploratory results support new research ideas for the early diagnosis of AD.

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P0347 / #1855

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

MEDIAL TEMPORAL LOBE ATROPHY IN PREDEMENTIA ALZHEIMER'S DISEASE: A LONGITUDINAL STUDY COMPARING CLINICAL AND A/T/N STAGES IN A CLINICAL COHORT.

Jonas Jarholm[1,2], Bjørn-Eivind Kirsebom[3,4], Lene Pålhaugen[1,2], Kaja Nordengen[1,2], Arne Nakling[5], Sandra Tecelão[6], Tormod Fladby[1,2], Per Selnes[2,7]
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Aims: Automated magnetic resonance imaging segmentation methods can detect subregional medial temporal lobe (MTL) volume loss in early-stage AD, but the clinical utility needs to be further explored in the context of new frameworks of cognitive staging and biomarker classification.
Methods: We used mixed linear regression to determine baseline and longitudinal morphometric group differences. 422 subjects were included from the Dementia Disease Initiation cohort, and longitudinal data was available for 239 (ASHS) and 190 (FreeSurfer). Subjects were classified as amyloid-β positive or negative (A+/-), healthy controls (HC A-), subjective cognitive decline (SCD A+/-) or mild cognitive impairment (MCI A+/-), and according to the A/T/N-system.
Results: Compared to A-/T-/N- at baseline, all hippocampal subfields (anterior and posterior hippocampus, presubiculum, subiculum, cornu amonis (CA1, CA3 and CA4) and entorhinal cortex (ERC) were smaller in A+/T+ or N+. Compared to HC A- at baseline, all hippocampal subfields, ERC and Brodman area (BA) 35 were smaller in MCI A+. Compared to A-/T-/N-, A+/T-/N- and A+/T+ or N+ had significantly greater longitudinal volume-loss in all subregions except BA36. Compared to HC A-, SCD A+ had significantly greater longitudinal volume-loss in all hippocampal regions except CA3, and MCI A+ subjects had significantly greater atrophy in all cortical and hippocampal subregions.
Conclusions: We found widespread cortical- and hippocampal longitudinal volume-loss in A+ with both normal and abnormal CSF total- or phosphorylated-tau irrespective of cognitive staging. We also found hippocampal atrophy before atrophy of the remaining MTL cortex in SCD A+, with additional cortical involvement in MCI A+, compared to controls. These results demonstrate the clinical value of staging by amyloid status and A/T/N classification in predicting early amyloid-β-linked MTL neurodegeneration within a relatively short follow-up period.

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P0348 / #1283

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

MULTI-RACIAL NORMATIVE VOLUMES OF LOBAR AND SUBCORTICAL BRAIN STRUCTURES IN NORMAL AGING MEASURED BY 'NEURO I': ITS APPLICATION TO AD DIAGNOSIS

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Aims: Previously, we demonstrated the validity of a regression model that included ethnicity as a novel predictor for predicting normative brain volumes in old age. The model was optimized using brain volumes measured with a standard tool FreeSurfer. Here we further verified the prediction model using newly estimated brain volumes from Neuro I, a quantitative brain analysis system developed for Asian populations.
Methods: Lobar and subcortical volumes were estimated from MRI images of 1,629 normal Korean and 786 Caucasian subjects (age range 59-89) and were predicted in linear regression from ethnicity, age, sex, intracranial volume, magnetic field strength, and scanner manufacturers. In the regression model predicting the new volumes, ethnicity was again a substantial predictor in most regions. Additionally, the model-based z-scores of regions were calculated for 428 AD patients and the matched controls, and then employed for diagnostic classification. The volumes of cortical and subcortical structures were measured by processing T1 brain images of all subjects using Neuro I which is a commercial software package for quantitative neuroimaging analysis.
Results: We analyzed to what extent the ethnicity adjustment improved the diagnostic power of the logistic regression models that were built using the z-scores of 6 regions only: bilateral temporal cortices, hippocampi, and amygdalae. The performance of the classifier after ethnicity adjustment was significantly improved compared to the classifier before ethnicity adjustment. When the AD classifier adopted the z-scores adjusted for ethnicity, the diagnostic accuracy has substantially improved (AUC = 0.85, ΔAUC = +0.04, D =4.10, $p < 0.001$).
Conclusions: Our results confirmed that the prediction model is valid regardless of the measurement tool, and ethnicity is an indispensable factor in establishing norms for brain volumes and a diagnostic system for neurodegenerative diseases.

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P0349 / #2247

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

IDENTIFICATION OF ALZHEIMER'S DISEASE USING KERNEL DENSITY ESTIMATION-BASED TEXTURE ANALYSIS ON SAGITTAL MR BRAIN IMAGES

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Aims: Brain atrophy is one of the most notable signs of neurodegenerative disorders like Alzheimer's Disease (AD). Texture alterations occur in grey and white matter tissues as a result of neuronal degeneration due to amyloid plaque deposition and tau protein aggregation. These changes are reflected in T1-weighted structural Magnetic Resonance (MR) images and are associated with clinical impairment in AD. This study aims to detect AD from sagittal MR brain images using novel kernel density-based textural features.
Methods: The 2D MR sagittal brain images for 92 normal and 92 AD participants in this investigation are acquired from Open Access Series of Imaging Studies database. In order to identify the local variations across brain tissues, images are subjected to the spatial multivariate kernel density estimation technique. First-order features indicating the distribution of estimated densities are evaluated from images. The validity of these texture features extracted from sagittal brain slices is analysed by employing Linear Discriminant Analysis (LDA).
Results: Textural variations captured by KDE attributes from MR brain sagittal images can differentiate between normal and AD individuals. The derived KDE textural parameters, including mean, kurtosis, skewness, and entropy, differ significantly between normal and AD individuals ($p < 0.05$). In classifying normal and pathological subjects, the LDA classifier achieves an accuracy of 70.2% and an F-score of 72.0%.
Conclusions: The atrophy patterns in the sagittal anatomical plane are thus found to be relevant in distinguishing AD with aid of KDE textural features. The proposed method enables automated detection of AD from single sagittal whole brain images without the need for complicated segmentation algorithms to localize and study specific brain structures.

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P0350 / #2264

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

BASAL GANGLIA COMPENSATORY WHITE MATTER CHANGES ON DTI IN ALZHEIMER DISEASE

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Aims: The volume reduction of gray matter structures in patients with Alzheimer's disease is often accompanied by an asymmetric increase in the number of white matter fibers located in the vicinity of these structures. This study aims to investigate changes in the white matter structure in motor basal ganglia in Alzheimer's disease patients compared to healthy controls by further utilizing white matter diffusion tensor imaging.
Methods: Twenty patients' brains (10 with a confirmed Alzheimer's disease diagnosis and 10 healthy controls) were analyzed by diffusion tensor imaging-based tractography for number of tracts, tract length, tract volume, quantitative anisotropy as a marker of tract directionality and crossing and general fractional anisotropy as a marker of tract connectivity.
Results: Significant decrease in the number of tracts and general fractional anisotropy was found in the patients with Alzheimer's disease compared to controls in the right caudate nucleus. On the contrary, an increase in the number of tracts and general fractional anisotropy was found in patients with Alzheimer's disease in left and right putamen. At the same time, there was a significant decrease in structural volume of left and right putamen measured by FreeSurfer automated reconstruction software.
Conclusions: Increases in the white matter diffusion tensor imaging parameters in patients with Alzheimer's disease were observed only in left and right putamen while their volumes were compared to controls. The right caudate showed, as expected, decreases in both diffusion tensor imaging parameters and volumes in Alzheimer's disease patients compared to controls. Right pallidum showed similarly to putamen increase in diffusion tensor imaging parameters but decrease in volume in Alzheimer's disease patients compared to controls.

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P0351 / #1108

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

COGNITIVE IMPAIRMENT RESTING-STATE FMRI MARKERS IN ELDERLY

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Aims: Resting state fMRI functional connectivity (FC rs-fMRI) analysis is broadly used to detect brain network differences in neurodegenerative diseases such as Alzheimer Disease (AD). Here, we analysis data from three groups of elderlies: a cognitively normal group, other with amnesic mild cognitive impairment and another diagnosed with AD; to identify FC rs-fMRI patterns characteristic of cognitive impairment and dementia.
Methods: Forty-five subjects were included: 14 patients with dementia,17 patients with MCI and 14 controls. All patients received an neuropsychological battery and brain MRI scanning.Resting state functional scans consisted of 240 T2*-weighted echo planar imaging (EPI) volumes. Additionally, a high-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) image was acquired. Data analyses were performed using the Functional Connectivity Toolbox (CONN) to identify large-scale patterns of temporal signal-intensity coherence, interpreted as functional connectivity. Preprocessing consisted of motion correction and spatial smoothing using an 8 mm full-width-at-half-maximum Gaussian kernel. fMRI volumes were registered to the subjects high-resolution T1weighted scan. Subsequently, a roi to roi analysis was performed for each subjects and between subjects group. Spatial maps of the group independent component analysis (ICA) were used in a linear model t against each individual fMRI data set.
Results: Within the Default Mode Network (DMN), two regions of lower FC were found in dementia compared with controls within the precuneus and the PCC ($p < 0.001$ uncorrected). No regions of FC changes were found within the DMN when comparing MCI patients with controls or dementia patients.
Conclusions: In a nutshell, these results show clinically meaningful changes in FC rsfMRI in dementia patients, specifically related to regions of the DMN. More
studies in larger samples are necessary to further determine FC differences between dementia patients, MCI patients and normal elderly.

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P0352 / #2410

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

CENTRAL EXECUTIVE AND FRONTOPARIETAL NETWORK ABNORMALITIES ACCOUNT FOR COGNITIVE COMPLAINS OF PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE

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Aims: Subjective cognitive decline (SCD) is a condition defining individuals who perceive a decrease in their own cognitive functioning in the absence of any clear-cut deficits on neuropsychological testing. In the presence of positive Alzheimer's disease (AD)-related biomarkers, SCD may be regarded as an early clinical condition preceding mild cognitive impairment due to AD. Aim of this study was to investigate the patterns of grey matter (GM) volumetrics and functional brain connectivity in SCD individuals and possible association with their cognitive performance.
Methods: Twenty-three individuals with SCD and 33 healthy subjects (HS) underwent an extensive neuropsychological assessment and brain MR scanning at 3T including a T1-w volume and resting-state fMRI. Voxel-based morphometry was used to assess regional GM volumetrics. The independent component analysis was used to extract the Default Mode Network (DMN), the Fronto-parietal (FPN), Executive Central (ECN) and Salience networks (SN).
Results: At a group level, SCD individuals reported significantly lower scores than HS at the Corsi block tapping backward test (CBTBT). There were no significant between-group differences in regional GM volumes. SCD subjects compared to HS showed increased FC in the ECN and right-FPN, and decreased FC in the right-FPN at hippocampal level. Additionally, they showed an inverse association between CBTBT scores and ECN FC in the anterior cingulate cortex. HS showed associations between CBTBT scores and ECN FC (positive in the hippocampus and basal ganglia; negative in the posterior cingulate cortex [PCC]), and FPN FC (positive in the PCC).
Conclusions: Dysfunctions in executive-frontal networks may be responsible for the cognitive decline subjectively experienced by SCD individuals despite their normal scores on formal neuropsychological testing. The associations found in HS might may reflect individual heterogeneity likely due to cognitive reserve mechanisms.

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POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

SLEEP DISTURBANCE AND EVIDENCE OF FAILURE OF THE GLYMPHATIC SYSTEM IN PRODROMAL ALZHEIMER'S DISEASE. PRELIMINARY INTRATHECAL GADOBUTROL CLEARANCE DATA

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Aims: The glymphatic system is responsible for the clearance of brain metabolic waste molecules, mainly during sleep, and its failure seems key in the accumulation of beta-amyloid (Aβ) in Alzheimer's disease (AD). The aim of this study is to investigate the function of the glymphatic system in patients with prodromal AD with consecutive magnetic resonance imaging (MRI) before and after the administration of intrathecal gadobutrol. Polysomnography study was also conduced to investigate the sleep pattern in these patients.
Methods: For this study we analysed 4 participants with prodromal AD (Clinical Dementia Rating (CDR)=0.5; Repeatable Battery for Neuropsychological Status (RBANS) < 85, CSF p-tau >52.1; Ab42/40 <0.062). Patients are studied with clinical and neuropsychological tests, polysomnographic study and four cranial MRI studies, following an established protocol 1 at baseline and 1-3 hrs, 5-7 hrs and 48 hrs after intrathecal administration of gadobutrol.
Results: The first four patients showed a previously unknown sleep disorder, meeting criteria for obstructive sleep apnoea syndrome. Likewise, they showed difficulty in clearance of gadobutrol, accompanied by adverse events, mainly severe headache. One patient remained hospitalized for 6 days due to confusion, agitation, and seizures, showing persistent frontal cortical enhancement 6 days after the intrathecal administration of gadobutrol.
Conclusions: These results suggest severe impairment of the clearance capacity of the glymphatic system in patients with prodromal AD and sleep disturbance using gadobutrol as contrast. The adverse effects observed, probably linked to failure in the clearance of gadobutrol, are not those observed in younger and healthy participants. These results support the need to develop novel approaches to study the glymphatic system in the ageing population, to eliminate the use of contrast including intrathecal administration of gadobutrol.

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P0354 / #2163

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

CORRELATION BETWEEN ALTERATIONS IN RESTING-STATE FUNCTIONAL CONNECTIVITY OF BRAIN NETWORK AND CEREBROSPINAL FLUID PATHOLOGICAL MARKERS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: The brain network function changed in Alzheimer's disease, but the relationship between these changes and their pathological changes is still not clear, so in this study, we aimed to explore the correlation between brain functional network alterations and cerebrospinal fluid(CSF) pathological biomarkers in AD-spectrum patients.
Methods: A total of 39 individuals were recruited, including 23 AD patients and 16 Non-AD subjects. All subjects underwent both fMRI and neuropsychological examinations. fMRI data was analyzed by independent component analysis to investigate the differences of functional connectivity（FC）among the two groups. Then correlation analyses were used to estimate the potential relationship between functional network alterations and cerebrospinal fluid pathological biomarkers.
Results: Compared to Non-AD individuals, AD patients exhibited a significant increase in functional connectivity between the default mode network (DMN) and left-frontoparietal network (LFPN), visual network and posterior cingulate cortex (PCC), but decreased functional connectivity between the LFPN and the cerebellum network. Alterations in functional connectivity between LFPN and DMN ,the cerebellum network were found to be associated with the dynamic changes of CSF Aβ.
Conclusions: This study provides provisional evidence that the brain functional network alterations was closely associated with CSF pathological characteristics, and these exploratory results support new research ideas for the early diagnosis of AD.

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POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

FUNCTIONAL LOCUS COERULEUS IMAGING AS BIOMARKER FOR AN AGEING NORADRENERGIC SYSTEM

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Aims: The locus coeruleus (LC) is our main source of norepinephrine (NE) in the brain. As it declines with age and is a potential epicentre of protein pathologies in neurodegenerative diseases, in vivo measurements of LC integrity and function are important biomarkers for healthy ageing and early onset of ND.
Methods: A reversal learning task provoking the release of NE was completed by 50 subjects (28 younger, 22 older adults). LC structure and function were assessed using multi-parameter mapping (0.4 × 0.4 × 3 mm voxel size) and high-resolution fMRI (1.5 mm isotropic voxel size). Precise spatial alignment in post-processing was assured.
Results: In line with a stronger noradrenergic involvement in processing negative events, the LC was more activated during loss than during gain feedback (left LC: T = 3.40, p = 0.04; right LC: T = 3.14, p = 0.05 (Fig.1 (I)) as well as during later remembered scene stimuli associated with losses (right LC: T = 3.46, p = 0.05 (Fig.1 (II)). Unexpectedly, older adults generally showed higher LC
activations.

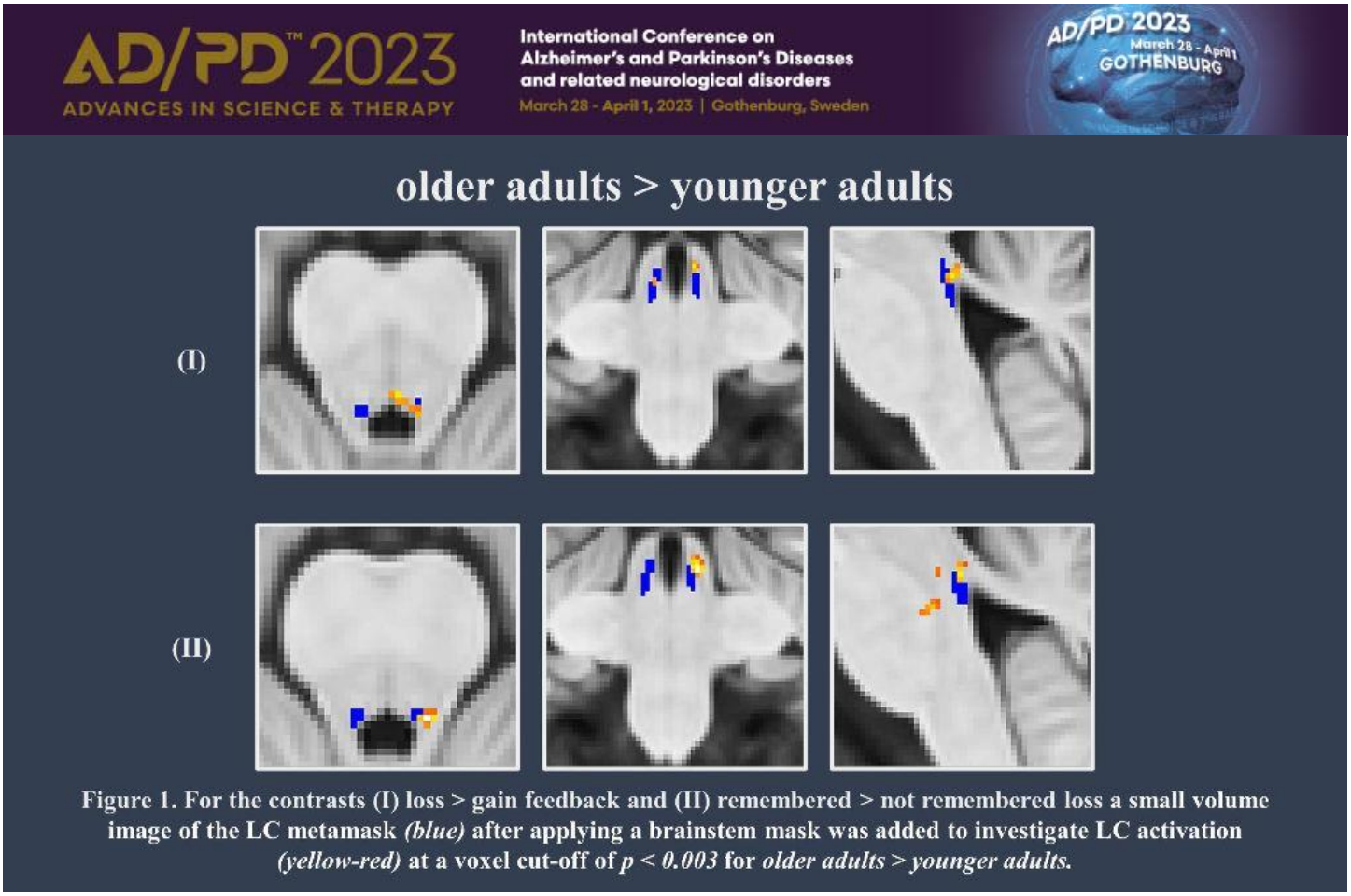

Figure 1. For the contrasts (I) loss > gain feedback and (II) remembered > not remembered loss a small volume image of the LC metamask *(blue)* after applying a brainstem mask was added to investigate LC activation *(yellow-red)* at a voxel cut-off of $p < 0.003$ for *older adults > younger adults.*

Conclusions: Especially in older adults, a stronger involvement of the LC in processing and remembering emotionally salient events was shown, possibly due to a stronger attentional modulation of salient events. We demonstrated the feasibility of investigating age differences in functional LC involvement, adding the possibility of a functional biomarker for NE decline in ageing.

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P0356 / #334

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

USING AMYLOID PET AS A BIOMARKER TO DETECT PROGRESSION OF EARLY ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD), the most common form of dementia, is a complex polygenic disease with genetic and clinical heterogeneity. Recently, significant attempts have been made for identifying AD biomarkers for reliably tracking disease progression. In the current study, we are aiming at identifying common and low-frequency variants associated with quantitative AD endophenotype from PET scans (Aβ) across different populations.
Methods: We systematically analyzed the largest collection of amyloid imaging data (N=11,406), across multiple ethnicities from multicenter cohorts as a quantitative trait to identify the functional variants and genes driving the association of AD. Furthermore, we have conducted gender- and APOE-stratified analyses to investigate the effect of these variables on brain amyloidosis.
Results: In the multi-ethnic meta-analysis, we found a strong APOE signal in the chromosome (Chr) 19 (min P = 4.1E-262). In the sex-stratified genome-wide association study (GWAS), two novel genome-wide significant signals were detected in Chr11 (P = 3.9e-08) and Chr5 (P = 1.5e-08). We observed a positive genetic covariance between amyloid PET endophenotype and neurodegenerative disorders (e.g. AD and Frontotemporal Dementia), stroke, and brain structure-related complex human traits. Moreover, we also detected suggestive and nominal hits in previously known AD-associated genes (e.g. *ABCA7, BIN1, CLU, and TREM2*).
Conclusions: In conclusion, we have performed the largest-to-date amyloid PET GWAS (N=11,406) for evaluating the association of genetic variants with brain amyloidosis. We are able to confirm the previously established association of the *APOE* locus with brain amyloidosis. Interestingly, we identified new hits in the sex-stratified analysis, suggesting the sex-specific effect of multiple genetic loci on amyloid deposition in the brain.

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P0357 / #433

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

A CENTILOID WINDOW TO HELP PREDICT TRUE AMYLOID ACCUMULATION

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Aims: Longitudinal PET-based imaging endpoints are often included in clinical trials, where they could provide critical evidence of disease modification. We assessed the longitudinal variability of the Centiloid (CL) scale and its ability to predict amyloid accumulation.
Methods: Longitudinal amyloid-PET (^{18}F-flutemetamol and ^{18}F-florbetaben) was conducted on 845 participants of the AMYPAD Prognostic and Natural History Study; 76 were identified as stable negative subjects, where no amyloid accumulation was expected. Quantification of scans was performed using an MR-based CL pipeline. Longitudinal change in CL was modelled using generalized estimating equations based on categorizing subjects with two different approaches. The first was based on visual read (VR), with subjects classified as Stable VR-, Converters or Stable VR+. The second classification was based on whether subjects showed evidence of amyloid accumulation, based on their annualised rates of change (ARC) being above the 95th percentile of the projected stable negative subjects.
Results: The 95th percentile of ARC in the stable negative group was 3.3CL/year. Baseline CL was higher in accumulators compared to 'non-accumulators' (31.7 versus 8.5 CL, p<.001) and in Stable VR+ and converters compared to Stable VR- (Table). Stable VR+ and Converters also had higher ARC than Stable VR-. When restricted to individuals with a baseline CL in the Grey-zone (12≤CL≤50), the patterns were similar ($\beta_{\text{Stable VR-}}$=0.3; $\beta_{\text{Converters}}$=4.9, p<.005). Results were robust across
tracers.

AMYPAD PNHS	All	Stable VR-	Converters	Stable VR+
N	845	281	43	78
Age (y (median (Q1-Q3)))	65 (60 - 70)	66 (60 - 70)	67 (62 – 72)	71 (67 - 75)
Gender (% female)	58	61	51	51
ApoE ε4 (% carriers)	41	32	56	75
Education (y)	14.9 ± 3.9	15.6 ± 4.2	15.3 ± 4.0	14.9 ± 4.1
***N* Timepoints**	2 (*N*=583) 3 (*N*=103)	2 (*N*=213) 3 (*N*=68)	2 (*N*=33) 3 (*N*=10)	2 (*N*=69) 3 (*N*=9)
Follow-up time (y)	FU1: 2.7 ± 1.1 FU2: 5.2 ± 0.6	FU1: 2.7 ± 1.1 FU2: 5.2 ± 0.7	FU1: 3.2 ± 1.3 FU2: 5.3 ± 0.1	FU1: 2.5 ± 1.1 FU2: 4.5 ± 1.3
CL at baseline	12.9 ± 23.4	4.9 ± 9.9	19.5 (17.4)	60.9 (30.1)
β	1.4	0.5	4.7	4.2
Standard error	0.2	0.2	0.3	0.7
% Accumulators	21.9	12.1	69.8	52.6

Table Demographics characteristics

Abbreviations - CL = Centiloid, y = years, ARC = annualised rate of change, PNHS = Prognostic and Natural History Study

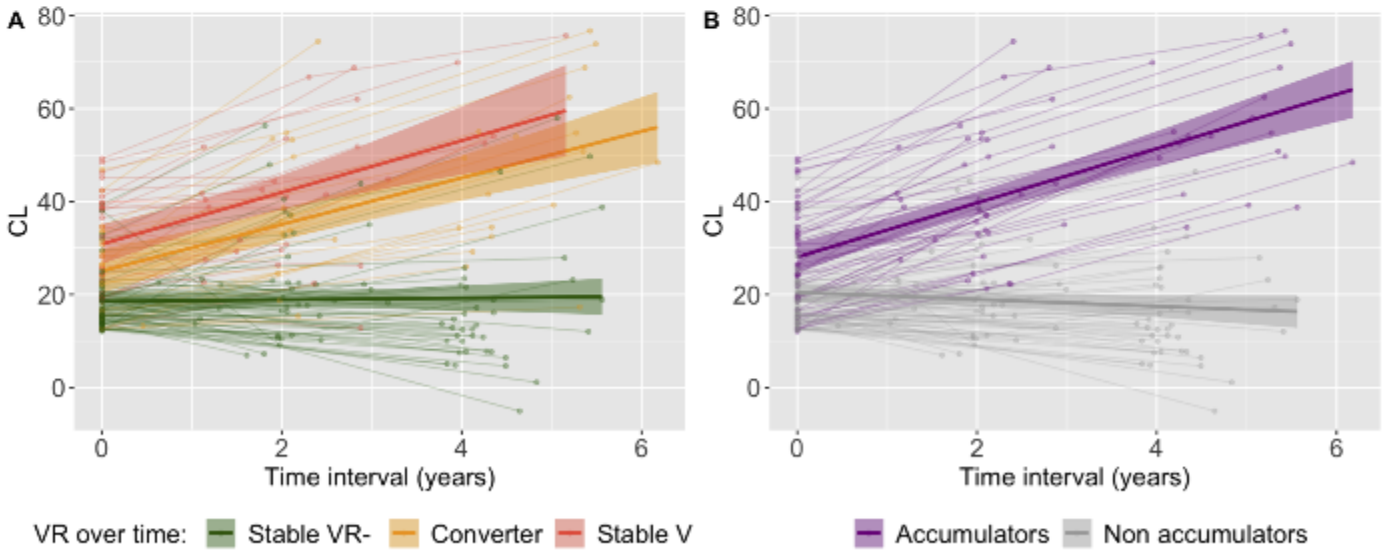

Figure Longitudinal trajectories of amyloid accumulation in subjects with baseline CL in the grey zone (12≤CL≤ 50)
(A) Trajectories based on visual reads; **(B)** Trajectories based on the annualised rate of change (ARC) above expected measurement variability, 'accumulators' are defined as individuals with an ARC >3.3 CL/year.

Conclusions: With a variability of ~3.3CL/year, an annual increase in CL above this threshold would be considered true amyloid accumulation. Baseline CL can help identify subjects more likely to accumulate pathology.

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P0358 / #2114

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

NAV-4694 AMYLOID-PET TARGETS 1-40 AND 1-42 FIBRILS

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Aims: WE WANTED TO ASSESS WHETHER [18F]NAV-4694 COULD DISCRIMINATE BETWEEN ABETA 1-40 AND 1-42 FIBRILS DERIVED FROM PATIENT SAMPLES..
Methods: 1-40 PURIFICATION METHOD: BRIEFLY, ABETA FIBRILS FROM VASCULAR AMYLOID DEPOSITS WERE PURIFIED USING 100 MG OF MENINGEAL TISSUE FROM AD PATIENT. TISSUE WAS HOMOGENIZED AS STATED IN KOLLMER ET AL., 2019. 1-42 PURIFICATION METHOD: MULTIPLE GREY MATTER REGIONS WERE USED FROM AD PATIENT BRAIN, AND HIPPOCAMPAL GM FROM PiD, FTD, CBD, AND PRIMARY MOTOR CORTEX FROM PSP, WAS HOMOGENIZED AS STATED IN YANG YANG ET AL., 2022 AUTORADIOGRAPHIC DOTBLOT: Briefly, 1:100 dilutions of each preparation were incubated with 82 fmol of mass (NAV-4694) in a 100uL total volume. Samples were incubated for 90 minutes. Reactions were terminated by pipetting the solution onto a glass fiber filter held within a 96-well dot-blot aspiration device. Unbound ligand was washed three times with ice cold PBS. The glass filters were transferred to a cassette for exposure to autoradiographic film and the activity in photostimulated luminescence units per mm2 was calculated using ImageJ software v.1.8.0.
Results: Disintegrations were corrected for decay and normalized to cerebellar GM extracts for both preparation types. We find that [18F]NAV-4694 shows retention in the sarkosyl insoluble fractions, enriched for abeta 1-42, from all cortical regions extracted from AD patient brain. We find that in 8 out of the 10 resuspension fractions from the abeta 1-40 purification protocol show [18F]NAV-4694 retention, which reflects the relative presence of abeta 1-40 fibrils as seen using EM and biochemically using anti-amyloid antibody.
Conclusions: This study suggests that [18F]NAV-4694 amyloid PET tracer can bind to both abeta 1-40 and 1-42 fibrils. Future studies will be required to better understand the contribution of this effect in human amyloid PET scans.

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P0359 / #314

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

IMPROVED SUVR CALCULATION FOR [18F]-AV45 AMYLOID PET IMAGING USING A NOVEL REFERENCE REGION APPROACH

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Aims: Utilization of a data-driven approach to find an optimal reference region (RR) for ^{18}F-AV45 PET imaging that differentiates the spectrum of Alzheimer's disease (AD) in both cross-sectional and longitudinal study designs.
Methods: Data from the ADNI database (http://adni.loni.usc.edu/) was used. In a detection analysis, voxel-wise group comparisons were performed between 75 amyloid(Aβ)-negative cognitively normal (CN) and 77 Aβ–positive ADs to identify a RR that is void off on-target tracer uptake. The identified RR was validated with a Receiver-Operating Characteristic (ROC) analysis in a separate dataset (60 Aβ-negative CNs, 70 Aβ-positive ADs). To assess longitudinal sensitivity of new and commonly used RRs, ROC analyses of global SUVR as a function of RRs were performed between Aβ-positive groups (19 CNs, 36 participants with mild cognitive impairment (MCI), and 24 ADs). To test tracer-specificity of all RRs, ^{18}F-FBB scans of Aβ-positive groups (47 CNs, 48 MCIs and 26 ADs) were used to perform ROC analyses with pairwise comparisons. Change in cognition was correlated with baseline global SUVR as a function of RR.
Results: Two new RRs were identified and produced similar results in an independent sample as commonly used RRs. The newly identified RRs showed similar longitudinal stability than commonly used RRs. Nevertheless, all RRs showed poor longitudinal discriminability rates between the Aβ-positive groups, which were at chance level. The identified ^{18}F-AV45 RRs were translatable to FBB scans but showed group-specific effects. All RRs were able to detect change in cognition, however, mostly in executive functions.
Conclusions: A data-driven approach to establish tracer-unspecific RRs proved valid. However, the selection of an appropriate RR for Aβ PET imaging should be considered carefully, depending on investigated groups.

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P0360 / #2362

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

QUANTIFIED AMYLOID BURDEN EVALUATION USING F-18 FLORBETABEN PET IN PATIENTS WITH ALZHEIMER'S DEMENTIA, MILD COGNITIVE IMPAIRMENT AND COGNITIVELY UNIMPAIRED

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Aims: The aim of the present study is to evaluate the performance characteristics of florbetaben F18 positron emission tomography (PET) in patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), subjective cognitive decline (SCD), and healthy control subjects (HCs).
Methods: Three hundred nineteen participants (146 AD, 100 MCI, 50 SCD and 23 HCs) were recruited and underwent a F-18 florbetaben PET scan. Amyloid burden was assessed visually and quantitatively, and was classified as positive or negative. The amyloid PET images were reviewed by two nuclear physicians according to the scoring system and classified as positive or negative. We simultaneously assessed quantitative analysis using a threshold for amyloid positivity of 1.26 for the mean cortical standard uptake value ratio.
Results: Florbetaben PET was rated visually amyloid positive in 88% of AD patients, 40% of MCI patients, and 26% of SCD and 4% HCs. Seventy-eight percent (114/146) of AD patients, 39% (39/100) of MCI patients, and 30% (15/50) of SCD and 9% (2/23) HCs were classified as amyloid positive using a quantitative threshold (mcSUVR > 1.26). Florbetaben cortical retention was highest in subjects with AD (mcSUVR = 1.35 ± 0.15) and lowest in cognitively normal subjects. Amyloid positivity and mean cortical amyloid burden were associated with age and apolipoprotein E ε4 carrier status
Conclusions: The current results are consistent with expected rates of amyloid positivity among individuals with clinical diagnoses of AD and MCI, and indicate the potential value of florbetaben F18 PET as an adjunct to clinical diagnosis and amyloid burden effect of progression of Alzheimer's disease spectrum.

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P0361 / #642

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

DEEP-LEARNING METHODS FOR ENRICHMENT OF ALZHEIMER'S DISEASE CLINICAL TRIALS USING MRI AND PET

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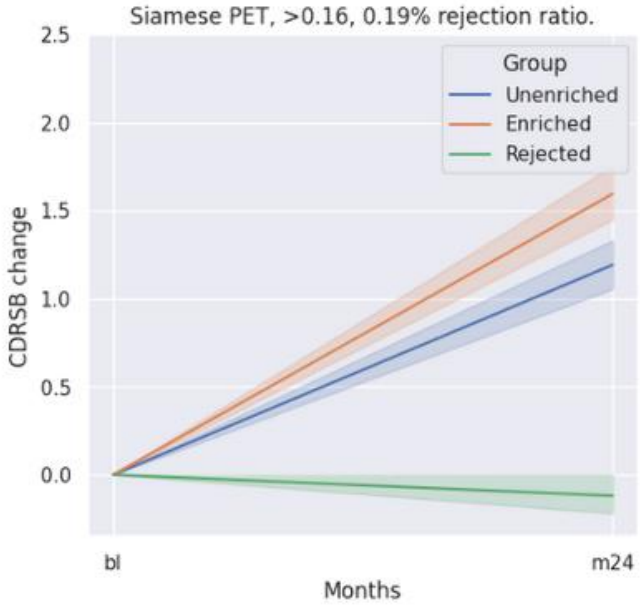
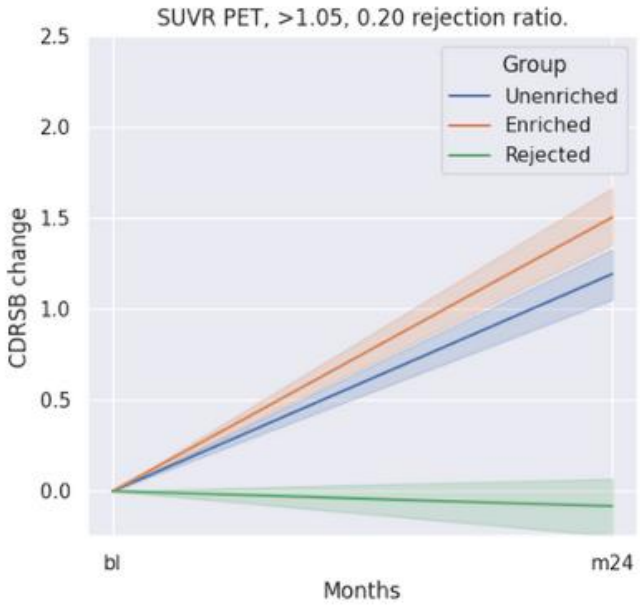
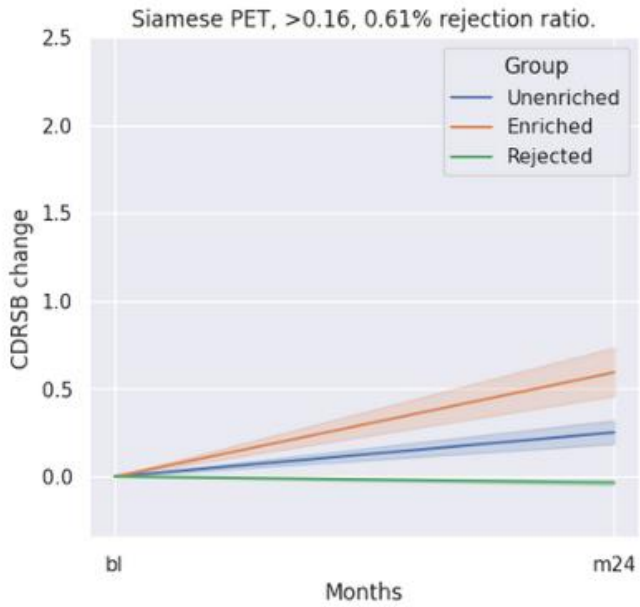
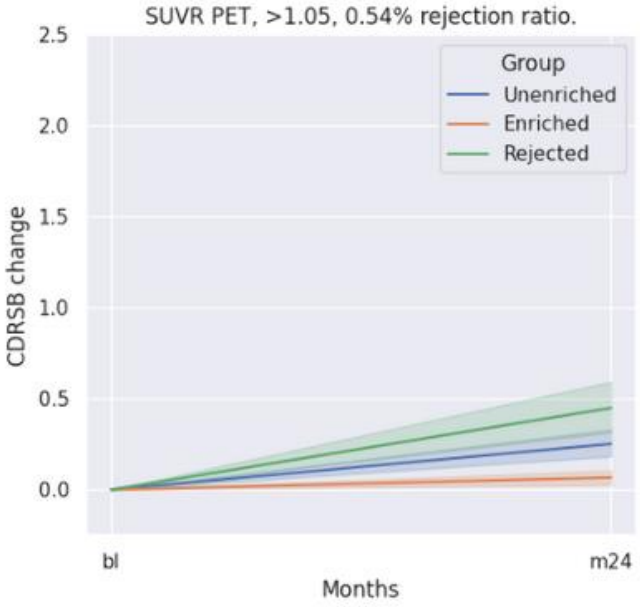
Aims: Drug development trials aimed to halt Alzheimer's disease (AD) progression favour recruitment of participants at early stages, preferably before symptomatic onset. In this investigation, we developed a deep-learning framework to differentiate participants with accelerated cognitive decline from those that remain cognitively stable within 24 months.
Methods: Siamese convolutional neural networks (CNNs) were trained using whole-brain PET (AV45, FBB) and MRI images from the ADNI longitudinal database. MCI and control participants were dichotomised into decliners and non-decliners if they were diagnosed with AD or not in future follow-ups. Cognitive decline was measured with the CDR-SB score. A sample of 206 participants (50% decliners) were randomly selected for training (70%) and evaluation (30%). Two CNNs were trained with PET and MRI data to obtain modality-specific embeddings and assess their classification performance: PET-only embeddings, as well as MRI and PET+MRI embeddings.
Results: PET embeddings showed an F1 score of 0.87 and 0.82 in the training and evaluation sets respectively when identifying decliners. Using MRI embeddings these scores were 0.70 and 0.69, and for PET+MRI combined the scores were 0.86 and 0.84. The combined embeddings resulted in a sample size reduction of approximately 20%. When predicting cognitive decline in MCI, the PET embeddings showed similar performance to a composite SUVR threshold >1.0, F1 score of 0.84. However, when predicting cognitive decline in controls, only the Siamese embeddings correctly identified decliners using either PET or MRI. The SUVR threshold showed no association with cognitive decline in healthy controls.



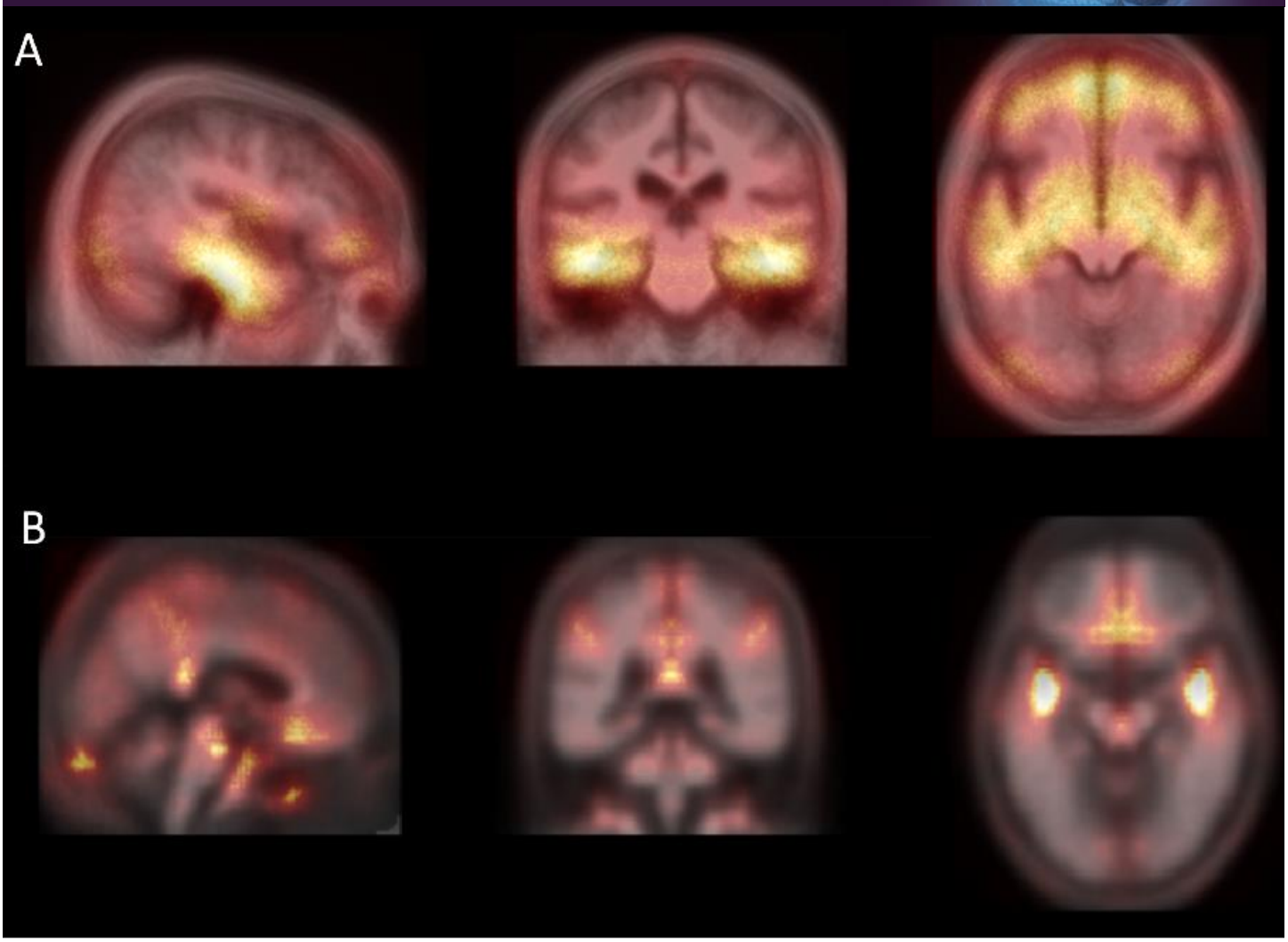


MCI





Healthy controls



Saliency maps with arbitrary threshold for A) structural MRI and B) amyloid PET

Conclusions: SUVR levels were associated with future cognitive decline in MCI but not in controls, while the CNN embeddings were able to identify both groups. Deep-learning algorithms offer a reliable framework to predict cognitive decline in MCI and control participants.

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P0362 / #1674

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

BISPECIFIC ABETA ANTIBODIES WITH OPTIMIZED BIOLOGICAL HALF-LIFE FOR IMMUNO-PET

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Aims: Bispecific antibodies, which pass the blood-brain barrier (BBB) via transferrin (TfR) receptor-mediated transcytosis, could be useful in molecular imaging of amyloid-beta. However, the long biological half-life of IgG antibodies, mediated by the neonatal Fc receptor (FcRn), makes radiolabelling with short-lived radioisotopes unsuitable. The aim of this study was to generate a bispecific antibody with impaired binding to FcRn, to shorten its biological half-life and perform same day immunoPET imaging.
Methods: Bispecific antibodies, based on Bapineuzumab (Bapi), either with or without a mutation in the FcRn binding domain, were recombinantly expressed in CHO cells. Biacore and ELISA analyses confirmed binding to Aβ and TfR. *In vivo* assessment of pharmacokinetics and brain uptake, was performed in wild-type (wt) mice or in the APP knock-in mouse model *App*$^{N\text{-}L\text{-}G\text{-}F}$. For PET-imaging, antibodies were functionalized with TCO-groups that were conjugated with a fluorine-18 ($t_{1/2}$ 110min) labelled tetrazine via inverse electron-demand Diels–Alder reaction.
Results: The antibody mutant with impaired FcRn binding showed a substantially reduced *in vivo* circulation time compared with the non-mutated antibody, displaying a 2-fold difference at 6 h after injection and 7-fold difference after 24 h. Further, *ex vivo* brain uptake of the FcRn impaired antibody was 24-fold higher in *App*$^{N\text{-}L\text{-}G\text{-}F}$ compared to wt mice 24 h after injection. The FcRn mutated antibody also displayed a 5-fold higher brain-to-blood ratio than the unmodified antibody in *App*$^{N\text{-}L\text{-}G\text{-}F}$ mice. *In vivo* PET imaging at different time points after injection will show how these differences translate to a same day imaging protocol.
Conclusions: The impairment of the FcRn is a promising method to shorten the biological half-life of antibodies to get one step closer towards the usage of biologicals as PET agents.

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P0363 / #2363

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

A MORE PRECISE DIAGNOSIS BY MEANS OF AMYLOID-PET CONTRIBUTES TO DELAYED INSTITUTIONALIZATION, LOWER MORTALITY AND REDUCED CARE COSTS IN A TERTIARY MEMORY CLINIC SETTING

Ingrid Van Maurik[1], Hana Broulikova[2], Arenda Mank[1], Els Bakker[1], Femke Bouwman[3], Arno De Wilde[4], Andrew Stephens[5], Bart Van Berckel[6], Philip Scheltens[7], Wiesje Van Der Flier[8]
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Aims: Previous studies demonstrated the diagnostic value of AD biomarkers in terms of clinicians' confidence in the clinical diagnosis and impact on patient management. A more precise diagnosis could have long term health benefits as a result of arranging more proper care, but such clinical utility not yet been demonstrated. We aimed to study the effects of a more precise diagnosis – by means of amyloid-PET – on institutionalization, mortality, and health-care costs.
Methods: Between October 27, 2014 and December 31, 2016, we offered amyloid-Positron Emission Tomography (PET) to all patients as part of their diagnostic work-up. Patients who accepted to undergo amyloid-PET (n=449) were propensity score matched with patients without amyloid-PET (n=571, i.e. no-PET). Matched groups (both n=444; 64±8yrs, 40%F, MMSE 25±4, 38% SCD, 19%MCI, 43%dementia) were compared on rate of institutionalization, mortality and health-care costs in the years after diagnosis.
Results: Amyloid-PET patients had a lower risk of institutionalization 10% (n=45) vs. 21% (n=92); HR=0.48 [0.33-0.70]) and mortality rate (11% (n=49) vs. 18% (n=81)); HR=0.51 [0.36-0.73]) over a four year period, and less health-care costs in the years after diagnosis compared to matched no-PET patients (β=-4573·49[-6524·76: -2523·74], p-value<0·001).Amyloid-PET patients had a lower risk of institutionalization 10% (n=45) vs. 21% (n=92); HR=0.48 [0.33-0.70]) and mortality rate (11% (n=49) vs. 18% (n=81)); HR=0.51 [0.36-0.73]) over a four year period, and less health-care costs in the years after diagnosis compared to matched no-PET patients (β=-4573·49[-6524·76: -2523·74], p-value<0·001).
Conclusions: We show that memory clinic patients with a more precise and better ifnormed diagnosis, had more beneficial long term outcomes in terms of institutionalization, death and health-care costs, which may translate into considerable cost savings on a macro-economic level. Randomized trials are required to validate these findings.

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P0364 / #1344

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

IS [11C]PIB PET INFLUENCED BY ANTIBODY TREATMENT?

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Aims: Amyloid PET ligand [^{11}C]PiB is used to diagnose Alzheimer's disease (AD) and to assess drug effects aiming at lowering brain amyloid-beta (Aβ) in clinical trials. In several studies of anti-Aβ antibodies, successful elimination of Aβ plaques after treatment was indicated by a substantially decreased [^{11}C]PiB binding in patients, even becoming "amyloid-negative" after treatment. However, this decrease in brain amyloid as measured by [^{11}C]PiB-PET has not been matched by a similar substantial effect on cognitive function. Thus, we aimed to evaluate if the decrease in [^{11}C]PiB signal is due to the removal of pathology or if repeated antibody administration blocks [^{11}C]PiB binding sites instead.
Methods: First, brain sections were prepared from 17-18 months of transgenic AD model ArcSwe mice (n=2) and wild type (wt) controls (n=2). Sections were pre-incubated with 3 µM mAb158 (murine version of lecanemab) overnight, while the consecutive sections were left untreated. All sections were then incubated in 0.5 mM thioflavin-S (ThS), which is structurally similar to PiB. Second, four ArcSwe mice were treated with 50 mg/kg mAb158 once per week for 3 weeks, while 4 ArcSwe mice were left untreated as controls. All mice were intravenously injected with [^{11}C]PiB (400 kBq/g), followed by *ex vivo* autoradiography. Aβ pathology was measured in all brains using immunohistochemistry and ELISA.
Results: The preliminary results from ThS staining showed that mAb158 pre-incubation did not decrease the ThS signal, suggesting that the antibody did not block binding sites for ThS *in vitro* (Figure 1).

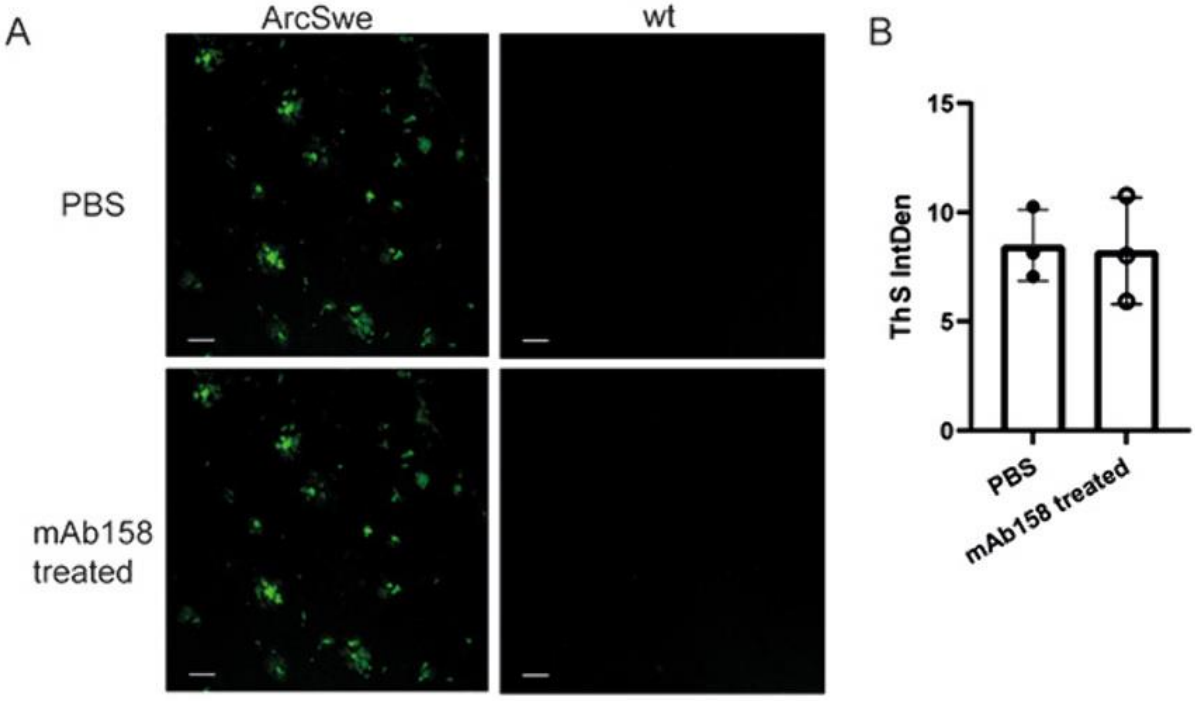

Figure 1. Representative thioflavin-S (ThS) images of amyloid deposits in the prefrontal cortex in ArcSwe and wild type (wt) mice with or without pre-incubation of mAb158. Scale bar: 100 µm.

Conclusions: *In vitro* results indicated that Aβ antibody mAb158 could not block ThS binding. Further analysis of data from the *in vivo* treatment study is ongoing.

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P0365 / #1493

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

IMPACT OF REDUCED INJECTED DOSE ON QUANTITATIVE AND QUALITATIVE ASSESSMENT OF [18F]FLUTEMETAMOL

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Aims: Positron emission tomography (PET) scans are regarded as expensive and are associated with relatively high radiation burden compared with other imaging modalities. Therefore, we aim to investigate the feasibility of reducing the recommended injected dose for the amyloid PET tracer [^{18}F]flutemetamol.
Methods: We included one hundred [^{18}F]flutemetamol PET scans (Table 1). Reduced injected doses were simulated by randomly extracting 75%, 50%, 40% 30% and 25% of the total events from list-mode data. SUVRs were computed for a cortical composite region-of-interest using the cerebellum as a reference region. The ability to quantitatively separate amyloid-positive (Aβ+) from amyloid-negative (Aβ-) SUVR images was assessed using Cohen's D. Furthermore, the effect of reduced injected doses on visual assessment was investigated by having two trained readers assess the same 25 images at 100% injected dose. In addition, one reader assessed images corresponding to three reduced injected dose levels. k-statistics were used to assess agreement between original visual reads and those at reduced injected doses.
Results: Differences in cortical SUVRs between the highest (100%) and lowest (25%) injected dose were less than 3% (Figure 1). Furthermore, effect sizes for quantitatively separating between Aβ groups showed negligible differences (<1%) across injected doses (Table 2). Visual assessment demonstrates excellent agreement for injected doses as low as 50% of the originally injected dose (Table 3, Figure
2).

Table 1 – Demographics and acquisition parameters for subject cohort

Tracer	Flutemetamol
Cohort	AMYPAD (100)
Amyloid Status (+/-)	56/44
Age (y)	73
Sex (M/F)	52/48
Diagnosis	SCI=10 MCI=55 Dementia=18 Other=7
Scanner	Siemens Biograph mCT flow
Scan length	20 minutes (90 minutes p.i.)
Mean Injected Dose	~170MBq
Acquisition Type	List-mode
Reconstruction	OSEM, ToF

Table 2 – Application of simulation results to the clinical cohort

Injected Dose (%)	Aβ-		Aβ+		Cohen's D
	Mean SUVR	SD	Mean SUVR	SD	
100	1.03	0.09	1.66	0.26	4.67
75	1.03	0.09	1.65	0.25	4.70
50	1.03	0.09	1.65	0.25	4.68
40	1.03	0.09	1.65	0.25	4.67
30	1.03	0.09	1.66	0.25	4.67
25	1.03	0.09	1.66	0.25	4.68

Table 3 -Visual assessment agreement between 100% and reduced injected doses

Injected Dose (%)	Total Agreement (N)	Cohen's Kappa	Standard Error	95% CI
100	24/25	0.915	0.083	0.75-1.00
75	23/25	0.834	0.111	0.62-1.00
50	23/25	0.826	0.118	0.60-1.00
25	19/25	0.525	0.160	0.21-0.84

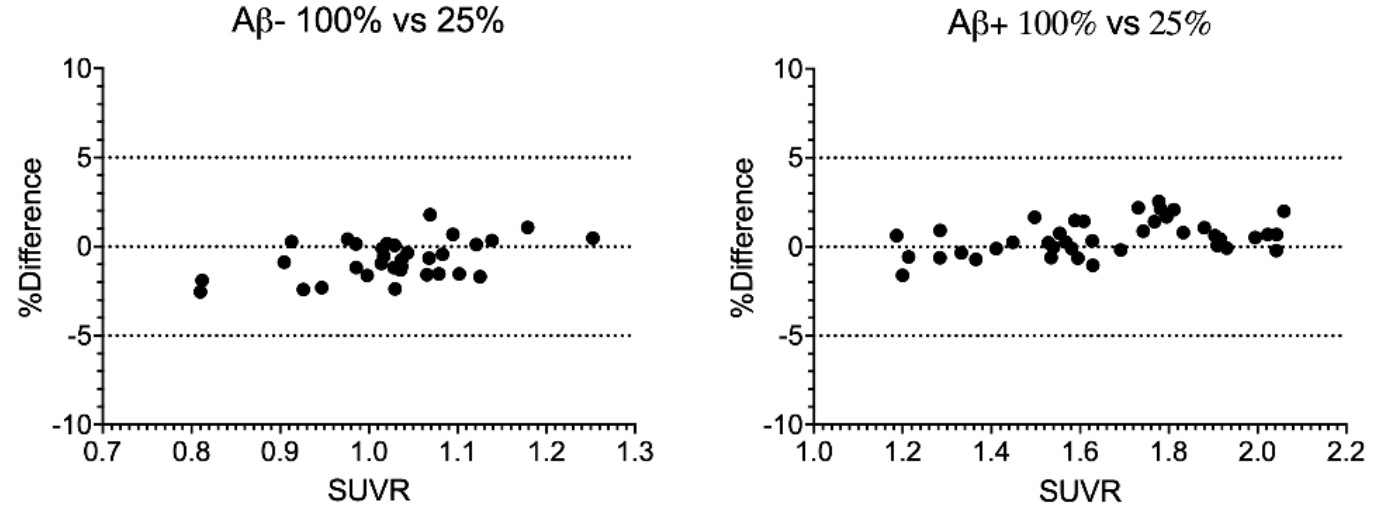

Figure 1 - Bland-Altman plots of Aβ+ and Aβ- subjects comparing SUVRs in whole cortical ROI at the original injected dose and at 25% of original injected dose

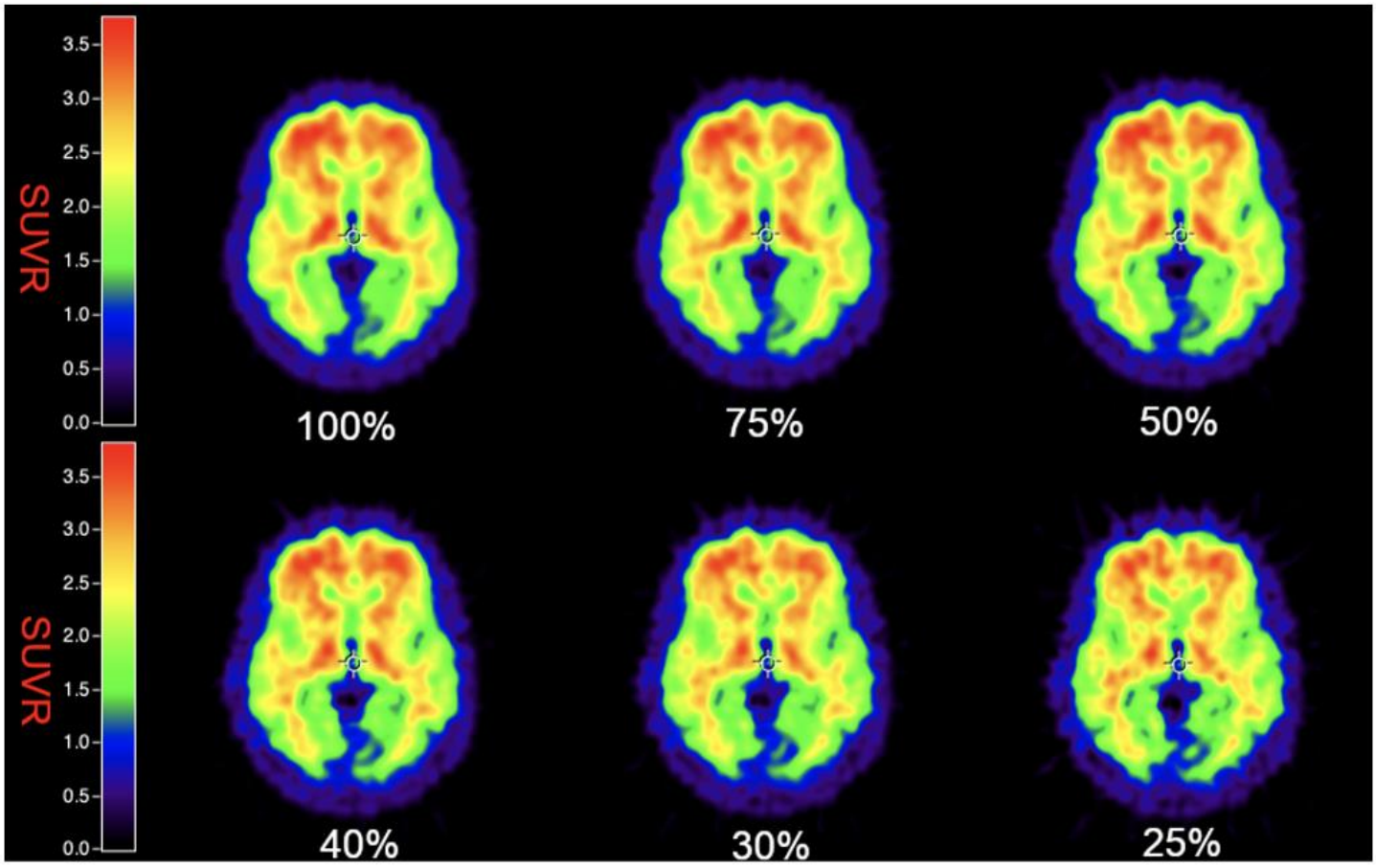

Figure 2 – Generated reduced injected dose in an amyloid-positive individual

Conclusions: Our findings suggest that a reduction of injected dose of 50% of [^{18}F]flutemetamol allows for robust visual assessments. The injected dose could potentially be further reduced to 25% for purely quantitative assessments. Future work will include cohorts examined with [^{18}F]florbetaben and [^{18}F]florbetapir PET.

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P0366 / #1425

POSTERS: A04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - GLUCOSE

NEURONAL NETWORK DIASCHISIS IN PARKINSON'S PATIENTS: DIAGNOSTIC IMPLICATIONS

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Aims: The idea that Parkinson's patients exhibit diagnostic signs of neural network diaschisis was put to the test.
Methods: Ten patients receiving transcranial low voltage pulsed electromagnetic fields (T-PEMF) treatment for Parkinson's disease (PD criteria were included. PD was diagnosed in these patients according to ICD-10 criteria. They ranged in age from 61 to 75 and had three females. Ten controls (HIs) with normal neurological function (mean age 62.5 years, range 43-75, females) were used. The cerebellum (Cb) and cerebrum's (Ce) total hemisphere glucose metabolism ratios (THGr) were calculated by specialized 3D-segmentation software (ROVER, ABX, Germany). The network diaschisis test was previously created using data from individuals with mild cognitive impairment and Alzheimer's disease. The Parkinson's patient data was subjected to this network diaschisis test.
Results: When HI and PD were compared, the forebrain THG ratios were substantially different (p = 0.028), with median THGr(Ce) values of 0.97 (min 0.65-max 0.99) and 0.91 (0.38-0.97), respectively. A statistically significant difference in the THGr of the hindbrain between PD and HI was observed, with a median THGr(Cb) of 0.84 (0.75-0.96) and a median of 0.77. (0.33-0.99). The network diaschisis test had an 80% negative predictive value for a neurologically healthy brain and a 100% and 86% positive predictive value for the PD brain, respectively.
Conclusions: The human brain's neural network of Parkinson's sufferers may show disconnection, which may be easily investigated with THGr.

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P0368 / #583

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

VASCULAR RISK FACTORS AND CSF CLEARANCE MEASURES

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Aims: Hypertension and vascular disease have been implicated as risk factors for Alzheimer's Disease and cognitive impairment. Prior studies point to a mechanism in which vascular comorbidities result in a chronic reduction of cerebral blood flow and perfusion, which in turn may impair cerebrospinal fluid (CSF) clearance. Our group developed a PET-based technology using [18F]-tau and [11C]-cocaine tracers to quantify brain/ventricular –CSF efflux. Here, we assessed whether hypertension affects this clearance measure.
Methods: We performed a retrospective analysis of data collected from cognitively unimpaired research participants enrolled in studies between 2020 and 2022 at the Brain Health Imaging Institute at Weill Cornell Medicine. All participants underwent standardized clinical interviews to assess their medical history and cognition, blood draws to assess metabolic and lipid panel, and blood pressure (BP) measurements. Imaging consisted of 3T MRI scans and 18F-MK6240 PET/CT to estimate brain clearance.
Results: Based on medical history and in- office BP levels, subjects were classified as normotensive (n=34, systolic BP<140mmHg, no antihypertensive treatment), controlled hypertension (n=21, systolic BP<140mmHg with antihypertensive treatment), or uncontrolled HTN (n=16, systolic BP>140 mmHg irrespective of treatment). The mean age of the entire sample was 66.7±10.8 years, 41 (58%) were women. The groups did not differ in age, sex distribution, measures of insulin resistance, total, high- or low-density cholesterol, triglycerides, but differed in BMI. After adjusting for BMI, clearance estimates differed between groups (p=0.02) and showed a significant linear trend (p=0.006) such that normotensive subjects showed the highest clearance, and subjects with uncontrolled hypertension the lowest clearance estimate.
Conclusions: Our study provides preliminary support for the idea that hypertension impairs the efficiency of mechanisms possible participating in brain waste removal.

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P0369 / #2108

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

PET-BASED BRAAK STAGING PREDICTS FUNCTIONAL DECLINE IN THE ALZHEIMER'S DISEASE CONTINUUM

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Aims: We aim to investigate the association between functional impairment and PET-based Braak stages and assess whether PET-based Braak staging predicts a longitudinal decline in the performance of activities of daily living.
Methods: We evaluated 181 cognitively unimpaired individuals, 56 individuals with mild cognitive impairment, and 57 individuals with Alzheimer's disease (AD) dementia. Participants underwent [18F]MK6240 tau-PET, were assigned a PET-based Braak stage at baseline and were followed for 2.17 (0.43) years. Functional performance was evaluated with the Clinical Dementia Rating (CDR) functional domains ("community affairs", "home & hobbies" and "personal care"), Functional Activities Questionnaire (FAQ), and Everyday Cognition (ECog). Cross-sectionally, multiple linear regressions were performed to assess the association between functional measures and PET-based Braak stages. Linear mixed-effects models were used to investigate whether baseline PET-based Braak stages predict a longitudinal functional decline.
Results:

Table 1. Regression coefficients of PET-based Braak stages for different functional measures

	FAQ			ECog			CDR "community affairs"			CDR "home & hobbies"			CDR "personal care"		
	Beta (95% CI)	T-value	p-value	Beta (95% CI)	T-value	p-value	Beta (95% CI)	T-value	p-value	Beta (95% CI)	T-value	p-value	Beta (95% CI)	T-value	p-value
PET-based Braak stage I	0.33 (-1.83 – 2.50)	0.303	0.762	0.16 (-0.09 – 0.40)	1.270	0.205	0.02 (-0.14 – 0.19)	0.285	0.776	0.01 (-0.18 – 0.19)	0.061	0.951	0.02 (-0.14 – 0.17)	0.223	0.823
PET-based Braak stage II	1.04 (-0.67 – 2.75)	1.202	0.231	0.18 (-0.01 – 0.38)	1.847	0.066	0.10 (-0.03 – 0.23)	1.577	0.116	0.09 (-0.05 – 0.23)	1.223	0.222	0.07 (-0.05 – 0.18)	1.119	0.264
PET-based Braak stage III	1.18 (-1.63 – 3.99)	0.827	0.409	0.20 (-0.12 – 0.52)	1.229	0.220	0.04 (-0.17 - 0.26)	0.390	0.697	0.02 (-0.22 – 0.25)	0.130	0.897	0.001 (-0.19 – -0.19)	0.012	0.990
PET-based Braak stage IV	4.89 (2.51 – 7.26)	4.051	**<0.001**	0.65 (0.38 – 0.92)	4.768	**<0.001**	0.10 (-0.08 – 0.29)	1.140	0.255	0.13 (-0.07 – 0.33)	1.291	0.198	0.11 (-0.05 – 0.27)	1.326	0.186
PET-based Braak stage V	5.56 (3.08 – 8.04)	4.422	**<0.001**	0.81 (0.53 – 1.09)	5.664	**<0.001**	0.17 (-0.01 – 0.36)	1.872	0.062	0.15 (-0.05 – 0.35)	1.449	0.148	0.05 (-0.11 – 0.22)	0.652	0.515
PET-based Braak stage VI	12.00 (9.94 – 14.07)	11.445	**<0.001**	1.44 (1.20 – 1.67)	12.115	**<0.001**	0.92 (0.79 – 1.06)	13.547	**<0.001**	0.89 (0.74 – 1.04)	11.812	**<0.001**	0.47 (0.34 – 0.59)	7.536	**<0.001**
Age	-0.09 (-0.18 – -0.001)	-2.001	**0.047**	-0.01 (-0.02 – 0.001)	-1.720	0.087	-0.003 (-0.01 – 0.002)	-1.280	0.202	-0.005 (-0.011 – 0.001)	-1.500	0.135	-0.003 (-0.01 – 0.002)	-1.201	0.231
Sex (male)	0.60 (-0.67 – 1.87)	0.925	0.356	0.11 (-0.04 – 0.25)	1.449	0.149	0.03 (-0.07 – 0.12)	0.562	0.575	0.05 (-0.06 – 0.15)	0.898	0.370	0.04 (-0.05 – 0.12)	0.870	0.385

Adjusted R^2: 0.42, F stat=21.63 (FAQ); Adjusted R^2: 0.45, F stat=24.19 (ECog); Adjusted R^2: 0.42, F stat=26.68 (CDR community affairs); Adjusted R^2: 0.35, F stat=21.01 (CDR home & hobbies); Adjusted R^2: 0.17, F stat=8.65 (CDR home & hobbies). Beta coefficients were obtained with Legend: CDR: clinical dementia rating; ECog: everyday cognition; FAQ: functional activities questionnaire; PET: positron emission tomography.

Figure 1. Cross-sectional progression of functional decline across PET-based Braak stages

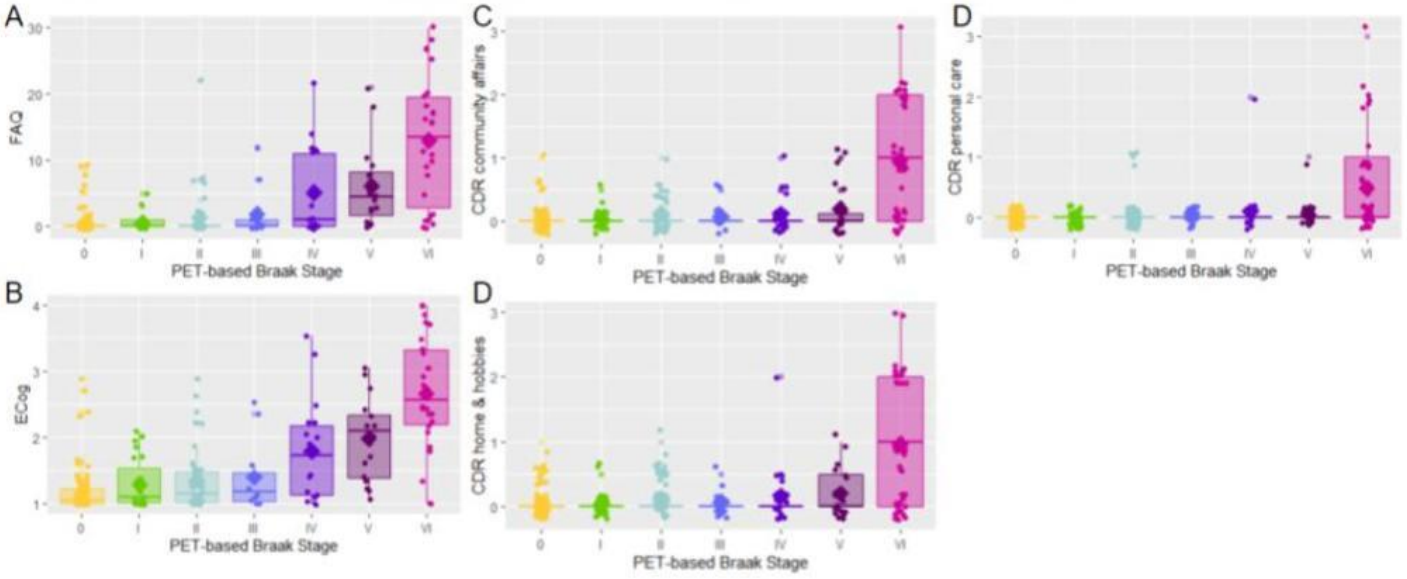
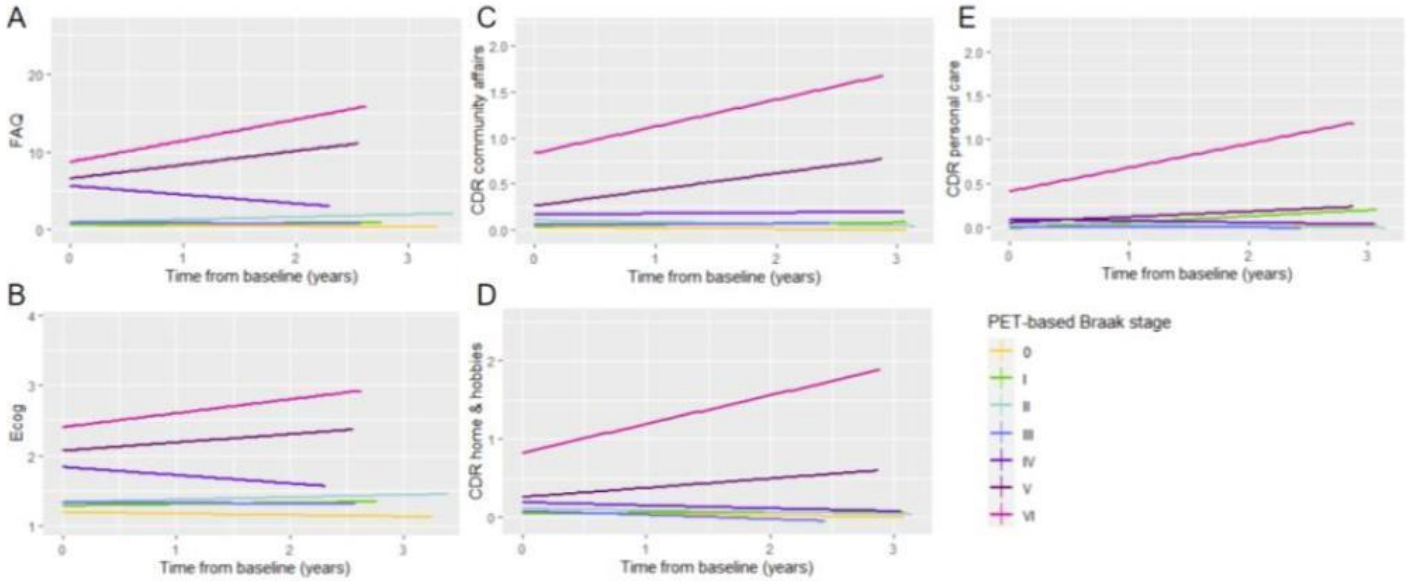


Figure 2. Longitudinal change in functional scores according to baseline PET-based Braak stage



Cross-sectionally, worse performances in the CDR functional domains were associated with PET-based Braak stage VI, while poorer scores in the FAQ and the ECog showed a significant association with stages IV and VI (Table 1; Figure1A-E). Furthermore, baseline PET-based Braak stages V and VI predicted significant longitudinal functional decline as assessed by the FAQ, the ECog, and the CDR "home & hobbies" and "community affairs" domains. For the CDR "personal care", only stage VI predicted a significant decline (Figure 2A-E).

Conclusions: Our results suggest that functional impairment increases with the severity of tau accumulation and is a late event in AD pathophysiology. These findings also indicate that PET-based Braak staging is a good predictor of functional impairment in the AD continuum. Finally, our study provides evidence for the clinical significance of the PET-based Braak staging framework.

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P0370 / #1957

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

SYNDECAN-3 AS A NOVEL BIOMARKER IN ALZHEIMER'S DISEASE

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Aims: Early diagnosis of Alzheimer's disease (AD) is of paramount importance in preserving the patient's mental and physical health in a fairly manageable condition for a longer period. Reliable AD detection requires novel biomarkers indicating central nervous system (CNS) degeneration in the periphery. Members of the syndecan family of transmembrane proteoglycans are emerging new targets in inflammatory and neurodegenerative disorders.
Methods: Reviewing the growing scientific evidence on the involvement of syndecans in the pathomechanism of AD, we analyzed the expression of the neuronal syndecan, syndecan-3 (SDC3), in experimental models of neurodegeneration.
Results: Initial in vitro studies showed that prolonged treatment of tumor necrosis factor-alpha (TNF-α) increases SDC3 expression in model neuronal and brain microvascular endothelial cell lines. In vivo studies revealed elevated concentrations of TNF-α in the blood and brain of APPSWE-Tau transgenic mice, along with increased SDC3 concentration in the brain and the liver. Primary brain endothelial cells and peripheral blood monocytes isolated from APPSWE-Tau mice exhibited increased SDC3 expression than wild-type controls. SDC3 expression of blood-derived monocytes showed a positive correlation with amyloid plaque load in the brain, demonstrating that SDC3 on monocytes is a good indicator of amyloid pathology in the brain.
Conclusions: Given the well-established role of blood tests, the SDC3 expression of monocytes could serve as a novel biomarker for early AD detection

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P0371 / #1602

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

MAPPING THE SYNAPTIC SUB-TYPE DISTRIBUTION OF THE PRE-SYNAPTIC PROTEIN SV2A

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Dementia Research Institute at Imperial College, Department Of Brain Sciences, LONDON, United Kingdom

Aims: Synapse loss and dysfunction is a key component of Alzheimer's Disease (AD) and is correlates with AD cognitive impairment. PET tracer, UCB-J, binds to a pre-synaptic protein SV2a and is a potential biomarker of synapse density. However, the exact location of SV2a has not been characterised and so the origin of the PET signal is unknown. The main objective of this study is to validate its use as a translatable biomarker by mapping the synaptic distribution of SV2a.
Methods: 1mm somatosensory sections from 6-month-old APP^{NL-G-F} (n=4) and age-matched wild-type (n=4) mouse brains were cleared using the X-CLARITY technique. Formalin-fixed non-diseased control (NDC; n=3, Braak 0-II) and AD (n=4, Braak III-IV) human post-mortem 1mm tissue sections (visual and entorhinal cortex) were cleared using a modified X-CLARITY protocol. Cleared tissue was stained with markers for SV2a, the excitatory pre-synaptic marker VGLUT1, and the inhibitory pre-synaptic marker VGAT and, after confocal imaging, the colocalisation of the synapse markers quantified.
Results: In the wild-type mouse tissue, 17% of SV2a puncta colocalised with VGLUT1 whereas 11% of SV2a puncta colocalised with VGAT. In the human NDC tissue, 20% and 22% of SV2a colocalised with VGLUT1 and VGAT respectively. In both cohorts, these proportions did not change significantly with AD pathology. Similarly, not all VGLUT1 and VGAT synaptic puncta (<50%) were SV2a-positive.
Conclusions: Our preliminary work has demonstrated that SV2a is not ubiquitously expressed at pre-synaptic terminals. This suggests that the origin of the PET signal comes from mixed synaptic and cellular populations yet to be characterised.

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P0372 / #309

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

DEVELOPMENT OF A BLOOD-BRAIN BARRIER PERMEABLE NEUROIMAGING BIOMARKER TO IDENTIFY THE PRO-COAGULANT STATE IN ALZHEIMER'S DISEASE

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Aims: Development of Alzheimer's disease (AD) therapies remain challenging, partially due to the multifactoriality of AD. A pro-thrombotic milieu – part of vascular components of AD - is present in AD favoring formation and persistence of fibrin clots. Long-term treatment with thrombin inhibitor dabigatran inhibits deposition of cerebral fibrin, preserves cognition, and reduces neuroinflammation and amyloid deposition. Anticoagulants might therefore be of therapeutic value in AD. However, this pro-coagulant state is not present in all AD patients. A biomarker is therefore highly needed to identify those AD patients that could benefit from such treatments. A peptide-based fibrin-binding probe (FBP) has been developed that shows binding to fibrin clots in the periphery and could therefore also be suitable for imaging of the pro-coagulant state of AD. This project aims to develop a BBB-permeable FBP for imaging of the pro-coagulant state of AD (Fig1).

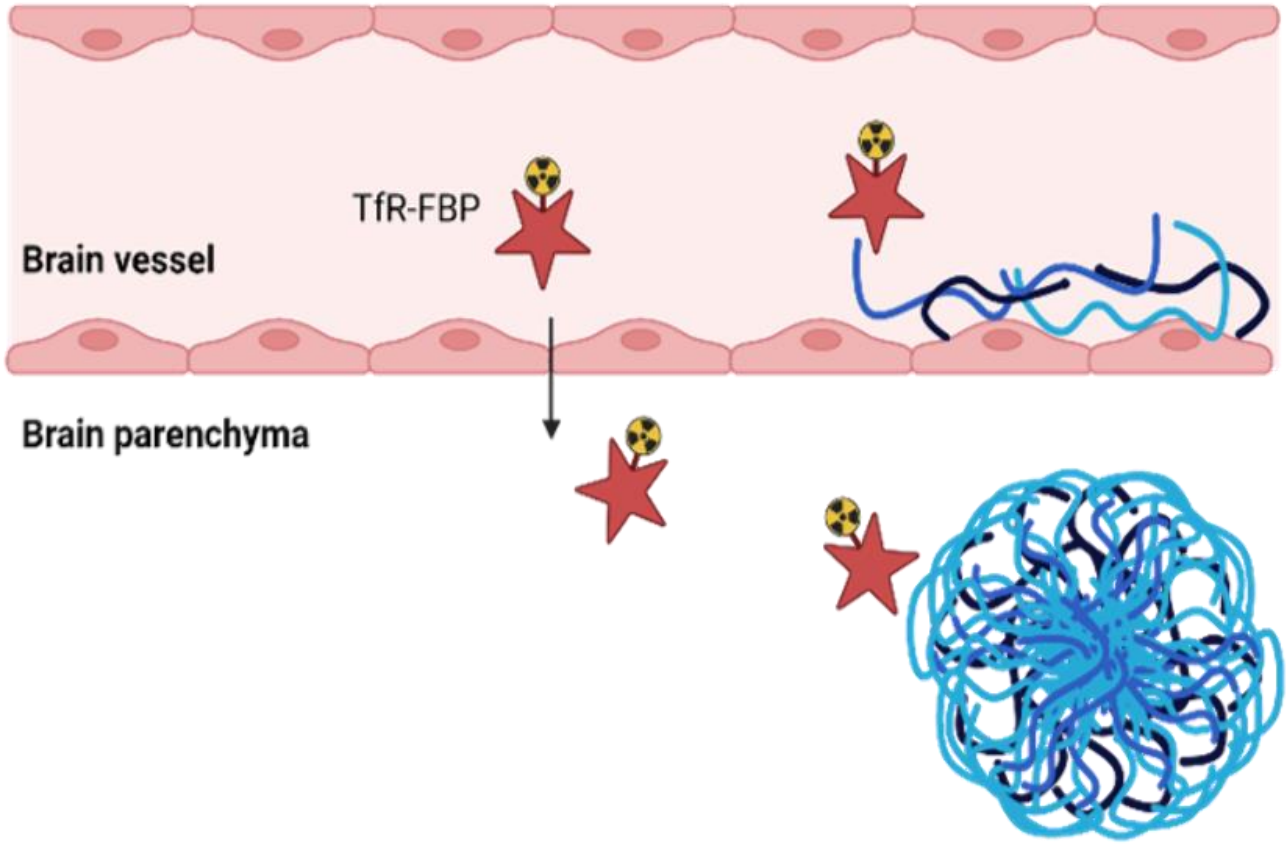

Figure 1: Overview of the project aim. Radiolabeled TfR-FBP will be developed which can bind to fibrin both in the brain vessels and in the brain parenchyma.

Methods: Our peptide does not cross the BBB passively, and therefore receptor-mediated transcytosis will be seeked by fusing it to a transferrin receptor (TfR) antibody fragment (scFv8D3). In vitro binding of the fused peptide (anti-TfR-FBP) to TfR and fibrin will be assessed and ex vivo brain uptake will be evaluated in wildtype mice. The anti-TfR-FBP will then be radiolabeled to image fibrin in the brains of transgenic AD mice.
Results: We synthesized FBP functionalized with an NHS ester for conjugation to scFv8D3, which consists of a lysine-rich tail. ScFv8D3 was produced, purified and tested in vivo for brain penetration. FBP has been successfully conjugated to scFv8D3 fragment while maintaining its binding capacity.
Conclusions: FBP has been conjugated to scFv8D3 to seek BBB uptake for imaging of the pro-coagulant state in AD. Future studies will aim to evaluate anti-TfR-FBP in vivo in mice.

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P0373 / #1165

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

ADDED VALUE OF [18F]RO948 TAU PET IN CLINICAL DIAGNOSIS OF DEMENTIA IN A MEMORY CLINIC SETTING.

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Aims: With tau PET coming closer to clinical use we aimed to assess the added value of [^{18}F]RO948 (tau) PET for diagnostic certainty in the diagnostic work-up of AD and its impact on patient management.
Methods: Participants (n=878) in the Swedish BioFINDER-2 study with subjective cognitive decline, mild cognitive impairment and dementia of all causes were included in the study. All participants underwent [^{18}F]RO948 PET after a thorough work-up including a neurological exam, cognitive testing, brain MRI, and blood and cerebrospinal fluid biomarkers (CSF), including $Ab_{42/40}$ ratio, $pTau_{181}$ and Neurofilament Light. The treating clinicians filled out a questionnaire before and after receiving the PET result, stating the most likely diagnosis, their certainty in the diagnosis (on a scale 0(low) to 10(high)) and whether the result led to a change in medication or patient management.
Results: Adding the [^{18}F]RO948 PET information resulted in an overall increase in diagnostic certainty in participants with a baseline diagnosis of AD (Figure 1a-d). Scans with a positive visual read, supporting AD, led to an increase in certainty ($p<0.0001$), whereas scans with a negative read led to a decrease in certainty ($p=0.01$). The results led to a change in diagnosis in 65 (7%) cases ($p=0.001$). Among participants with a baseline diagnosis of AD, 299/408 (73%) had medication to support memory functions at baseline and in 21 (5%) there was a change in medication ($p=0.03$).

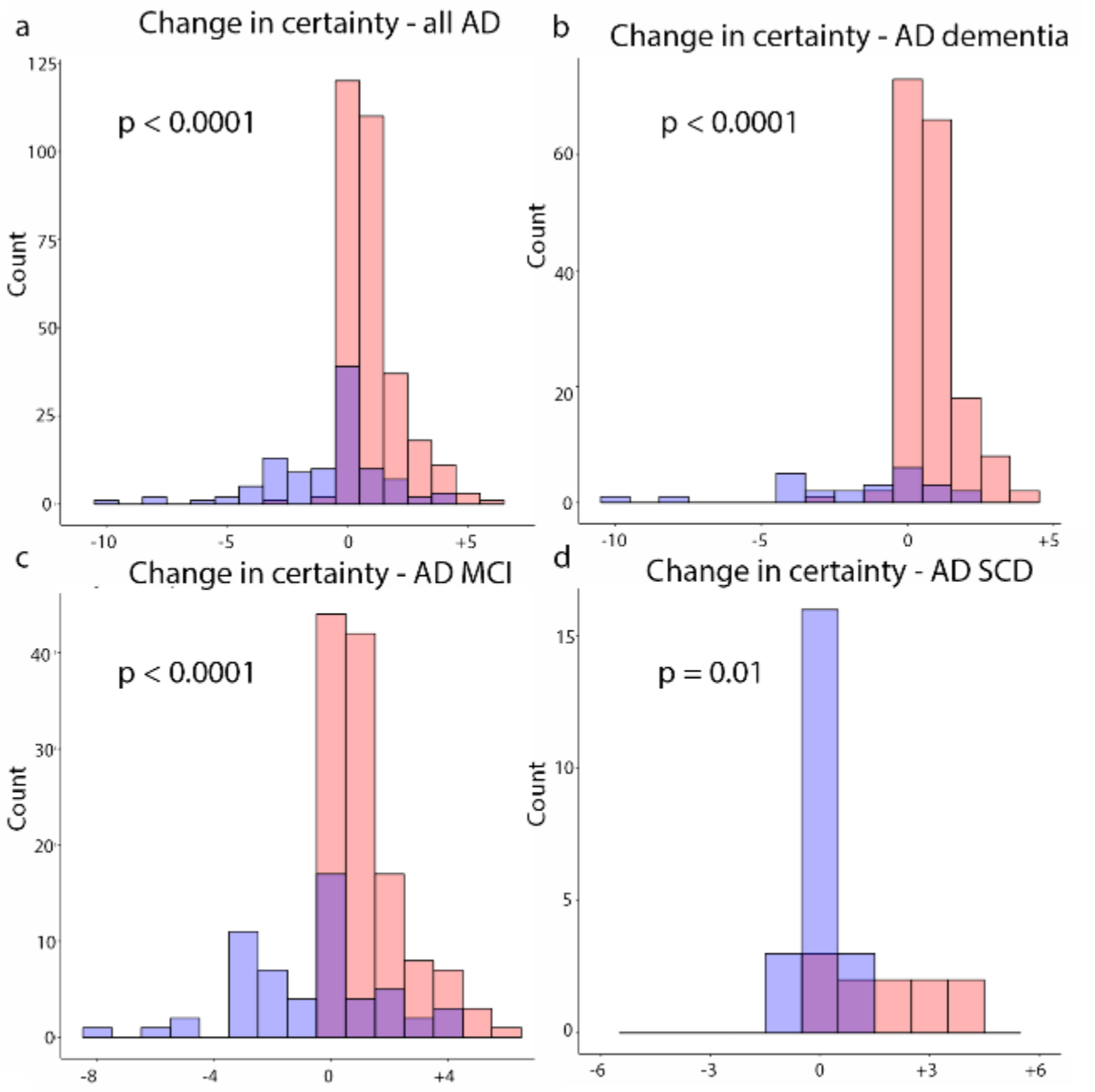

Figure 1. Change in certainty after [18F]RO948 results in participants with a baseline diagnosis of AD. Participants with positive scans are depicted in red, negative in blue. Change calculated as ($certainty_{after}$ - $certainty_{before}$). AD - Alzheimer's Disease; MCI - mild cognitive impairment; SCD - subjective cognitive decline.

Conclusions: We find an added value of [^{18}F]RO948 PET on top of an extensive baseline diagnostic work-up including CSF biomarkers. The added information leads to an increase in diagnostic certainty, and a significant change in diagnoses and medication.

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P0374 / #2761

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

APOE4 CARRIERSHIP AND AMYLOID-BETA POSITIVITY FOR THE POPULATIONAL ENRICHMENT OF CLINICAL TRIALS TESTING DRUG EFFECTS ON TAU TANGLES

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Aims: Investigate the implications of using apolipoprotein E ε4 (*APOE*ε4) carriership for population enrichment in clinical trials testing drug effects on tau tangle deposition in cognitively impaired (CI) individuals across the Alzheimer's disease (AD) continuum.
Methods: We studied 29 amyloid-β (Aβ) positive CI individuals (16 with mild cognitive impairment [MCI] and 13 with AD dementia) from the McGill Translational Biomarkers in Aging and Dementia (TRIAD) cohort. Study participants underwent clinical assessments, *APOE* genotyping, magnetic resonance imaging, positron emission tomography (PET) for Aβ ([^{18}F]AZD4694) and tau ([^{18}F]MK6240) at baseline, as well as a follow-up tau-PET scan (mean follow-up, 2.2 years). Aβ positivity was determined as global [^{18}F]AZD4694 SUVR ≥ 1.55.
Results: Demographics of the population are shown in **Table 1**. Regression analysis revealed that *APOE*ε4 carriers had higher tau-PET SUVR increase in temporal regions compared to *APOE*ε4 noncarriers (**Figure 1**). The use of Aβ positivity alone for population enrichment of a clinical trial focusing on CI individuals would require a sample size of 436 individuals per study arm to test a 25% drug effect on tau-PET accumulation (**Figure 2**). A similar clinical trial with a population enrichment strategy using Aβ positivity plus *APOE*ε4 carriership would require a sample size of as few as 158 individuals per study arm (reduction of 64% in relation to using only Aβ positivity) to test the same drug effect (**Figure 2**).

Table 1. Key characteristics of study participant.

	***APOEε4* noncarrier**	***APOEε4* carrier**	***P*-value**
No.	15	14	-
Age, years	70.0 (5.2)	71.2 (5.6)	0.564
Male, No. (%)	8 (53.3)	5 (35.7)	0.340
Clinical diagnosis, No. (%)			
MCI	8 (53.3)	8 (57.1)	0.837
AD dementia	7 (46.7)	6 (42.9)	
MMSE score	24.7 (6.1)	25.5 (4.5)	0.676
Global [^{18}F]AZD4694 SUVR	2.32 (0.52)	2.53 (0.39)	0.227
Temporal meta-ROI [^{18}F]MK-6240 SUVR	1.64 (0.90)	1.59 (0.49)	0.847
Follow-up, years	2.2 (0.3)	2.1 (0.3)	0.213

Continuous variables are presented as mean (SD). Student's t test (continuous variables) and contingency $\chi 2$ test (categorical variables) tested demographic differences. AD = Alzheimer's disease; *APOEε4* = Apolipoprotein E ε4; Aβ = amyloid-β; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PET = positron emission tomography; ROI = region of interest; SD = standard deviation; SUVR = standardized uptake value ratio.

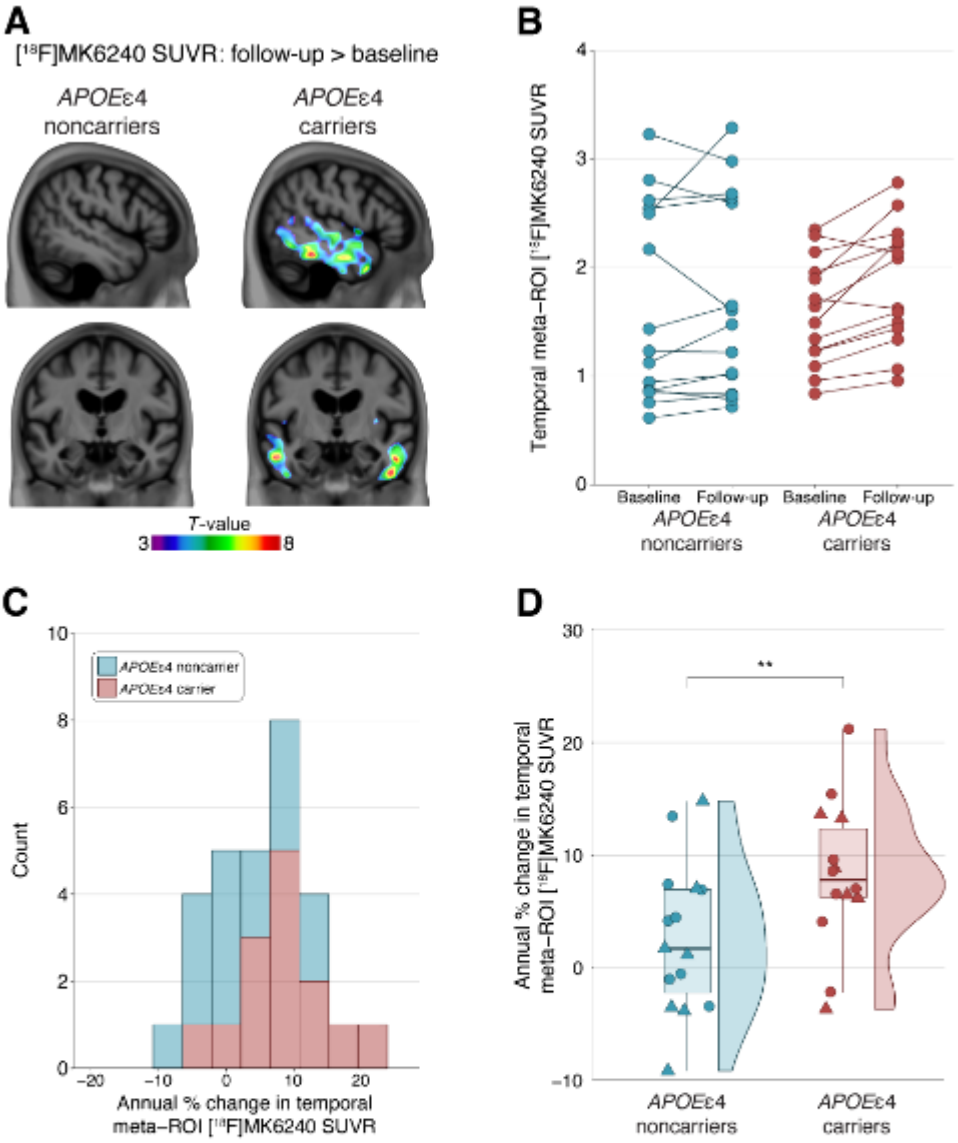

Figure 1. *APOE*ε4 carriership is associated with higher tau-PET accumulation. (**A**) Voxel-wise paired t-test comparison (random field theory corrected for multiple comparisons at $P<0.05$) between the baseline and follow-up [18F]MK6240 SUVR scans in *APOE*ε4 noncarriers (left) and *APOE*ε4 carriers (right). (**B**) Before-after plot for temporal meta-ROI [18F]MK6240 SUVR in APOEε4 noncarriers (blue) and *APOE*ε4 carriers (red). (**C**) The histogram shows the distribution of the annual percentage of change in temporal meta-ROI [18F]MK6240 SUVR in *APOE*ε4 noncarriers (blue) and *APOE*ε4 carriers (red). (**D**) Violin plot of temporal meta-ROI [18F]MK6240 SUVR percentage of change across groups defined at baseline based on *APOE*ε4 statuses. The horizontal line inside each box depicts the median, and box ends represent the 25th and 75th percentiles. Groups were compared using analysis of covariance (ANCOVA) with Tukey's multiple comparison test adjusting for age, sex, and diagnosis (** $P < 0.05$).

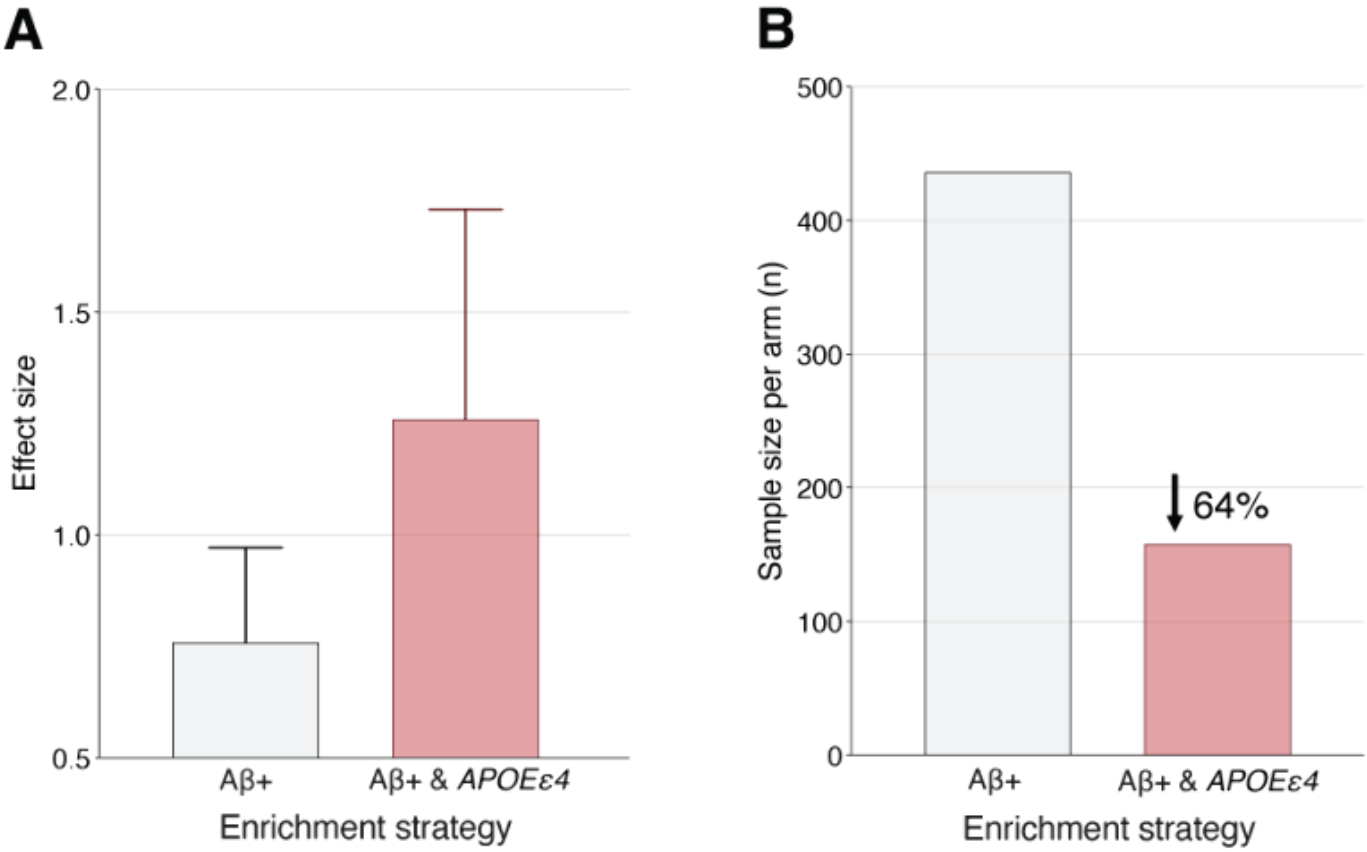

Figure 2. Enrollment based on *APOE*ε4 carriership and Aβ positivity reduces the sample size needed for trials testing drug effects on tau-PET. (*A*) The bar plot shows the effect size and standard error (SE) by using Aβ positivity alone (grey) or Aβ positivity in combination with *APOE*ε4 carriership (red) for participant selection. The effect size was calculated as the mean divided by the standard deviation of temporal meta-ROI [^{18}F]MK6240 SUVR percentage of change. The SE of the effect size was calculated with 10 000 bootstrap replicates. (**B**) Sample size estimation trials testing a 25% drug effect with 80% power at alpha level 0.05 on reducing tau-PET accumulation by using Aβ positivity alone (grey) or Aβ positivity in combination with *APOE*ε4 carriership (red) for participant selection.

Conclusions: Our results reveal that *APOE*ε4 carriership is associated with increased tau tangle accumulation in CI individuals who are Aβ positive. Clinical trials testing drug effects on tau tangle deposition may benefit from assessing both *APOE*ε4 carriership and Aβ positivity statuses as enrollment criteria to select individuals at higher risk of fast tau accumulation, resulting in a more cost-effective trial.

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P0375 / #366

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

WHOLE-BRAIN IMAGING AND ANALYSIS OF AMYLOID-BETA PLAQUE DYNAMICS IN PRE-CLINICAL ALZHEIMER'S DISEASE ANIMAL MODELS

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Aims: Brain regions are affected by amyloid-beta (Aβ) plaque deposition at varying time points throughout the progression of Alzheimer's Disease (AD). Current technology lacks the ability to quantitate region-specific targets on a heigh-yield whole-brain level. To address this gap, we developed a high-throughput whole-brain imaging and analysis pipeline of AD plaque dynamics, where resulting sections are indexed for Miralys™ MALDI-IHC secondary analysis.
Methods: 5XFAD mouse brains labeled with Methoxy-X04, an Aβ plaque-specific compound, were serially imaged and sectioned on the TissueCyte Serial Two-Photon Plus (STP[2]) imaging platform. Resulting volumetric 3D datasets were registered to the Allen Mouse Brain Common Coordinate Framework (CCFv3) and region-specific plaque analysis were conducted to determine plaque density throughout each brain. Select sections were evaluated with Miralys™ MALDI-IHC for Aβ42, pTau, MAP2, GAD67, GLUT1, NeuN, synapsin, myelin and neurogranin tags.
Results: The analysis of whole-brain STP[2] imaging, combined with CCFv3 mapping and MALDI-IHC revealed spatiotemporal changes within Aβ plaques of the 5XFAD mouse model.
Conclusions: The STP[2] imaging and analysis pathway can be applied to a variety of animal models to assess disease progression throughout the brain. Combining this technique with the high multiplexity of Miralys™ MALDI-IHC secondary analysis provides data-rich results to assess the difficult research questions surrounding AD disease progression.

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P0376 / #1629

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

LOCUS COERULEUS FEATURES ARE ASSOCIATED TO CORTICAL HYPOMETABOLISM IN ALZHEIMER'S DISEASE PATIENTS

Alessandro Galgani[1], Gayane Aghakhanyan[1], Andrea Vergallo[2], Francesco Lombardo[3], Nicola Martini[4], Filippo Baldacci[1], Gloria Tognoni[1], Gabriele Siciliano[1], Francesco Fornai[5], Nicola Pavese[6], Duccio Volterrani[1], Filippo Giorgi[5]
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Aims: To assess whether Locus Coeruleus (LC) integrity evaluated by high field MRI is associated to brain cortical metabolism measured through [^{18}F] Fluorodeoxyglucose (FDG) PET in cognitively impaired patients belonging to the Alzheimer's *continuum*.
Methods: Forty-three cognitively impaired subjects (30 individuals affected by Mild Cognitive Impairment and 13 patients suffering from Alzheimer's dementia) underwent 3.0T MRI scan with LC-sensitive sequence and [^{18}F]FDG Brain PET. LC images were processed through a standardized template-based method and LC integrity was expressed with the LC_{CR} (contrast-ratio) parameter. A voxel-wise regression analysis was performed to explore the association between FDG cortical uptake and LC_{CR}.
Results: LC_{CR} was directly associated to the [^{18}F]FDG uptake in frontoparietal cortical areas; this association was stronger in the left hemisphere than in the right one.
Conclusions: LC loss of integrity, assessed *in vivo* through MRI, is associated to cortical hypometabolism in cognitively impaired patients. This finding suggests that LC degeneration is related to the severity of AD cortical pathology and supports the hypothesis of the neuroprotective role exerted by LC itself. The association with frontoparietal areas is in line with previous functional and structural MRI studies and strengthens those observations, highlighting the occurrence of a specific LC-cortical network that may deserve further investigation for its possible clinical implications. **Funding:** Funded by Italian Ministry of Health [code: Ricerca Finalizzata 2013,# PE2013-02359574 "*In vivo assessment of the role of Locus Coeruleus in the development of Alzheimer's Disease and other types of Dementia*" (P.I.: F. Giorgi.)].

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P0377 / #2193

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

MULTIGRAPH AND DEEP LEARNING MULTIMODAL ANALYSIS OF SEX DIFFERENCES

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Aims: In the past few years, sex differences have become an important topic of research partially due to the fact that women have a higher vulnerability to develop Alzheimer's disease (AD), whereas men are more vulnerable to develop Parkinson's disease (PD). The aim of this study was to characterize the differences in network architecture between women and men using novel approaches based on multilayer networks and deep learning using the second version of our software: BRAPH 2.0.
Methods: We used resting-state functional magnetic resonance imaging (rs-fMRI) and diffusion-weighted imaging (DWI) data of 54 women and 46 men from the Human Connectome Project (HCP). For the multilayer network analysis, we used rs-fMRI to derive a functional connectivity layer and DWI to derive an anatomical connectivity layer. We then calculated the multilayer communities and the multilayer core-periphery for each group. Finally, we built a dense neural network using the functional and anatomical connections to distinguish men from women.
Results: Using both imaging modalities, we found 4 different multilayer communities in women, whereas men had 5 communities. There were several differences in the multilayer core-periphery between sexes mainly in the insula, frontal and temporal regions. The dense neural network distinguished men from women with an AUC of 0.83±0.04. Importantly, these results showed additional differences or a higher discrimination between sexes compared to analyses using the imaging modalities separately.
Conclusions: These results show advanced approaches combining both rs-fMRI and DWI reveal additional differences between men from women and can discriminate them to a greater extent compared to individual imaging modalities. Neuroimaging studies seeking to identify sex differences in healthy individuals or AD and PD patients should consider using them, which can be analyzed using our software BRAPH 2.0.

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P0378 / #1563

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

DELINEATING AMYLOID PEPTIDE SIGNATURES AMONG HETEROGENOUS PLAQUE POPULATION IN ALZHEIMER'S DISEASE

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University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden

Aims: Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting nearly 12% of individuals older than 65 years. The disease poses an immense societal challenge and personal suffering, particularly as there were still no curative treatments as the pathogenic mechanisms of AD remain elusive. One of the main challenge would be to understand the chemical basis of heterogeneity involved in the formation of variety of plaque polymorphs. These plaques are known to be extracellular deposits of amyloid beta (AB) peptide. In this study we aim to investigate the chemical nature of structuraly diverse plaque polymorphs in patient samples with sporadic AD, familial AD and Cognitively unimpaired pathological ageing.
Methods: We employed a novel chemical imaging strategy combining microscopy with matrix assisted laser desorption/ioninsation - mass spectrometry imaging (MALDI-MSI) to delineate AB signatures of heterogenous plaque polymorphs. These plaques are then grouped into sAD-diffused plaques (DP), sAD-cored plaques (CP), sAD coarse grain plaques (sAD-CG), CU-AP diffused plaques(DP of CU-AP), fAD cored plaques (fAD-CP) and fAD coarse grain plaques (fAD-CG) based on the high resolution hyperspectral microscopy images combined with multivariate image analysis performed on MALDI-MSI data. These plaques are then investigated for differences in the AB signatures.
Results: AB1-40 is more abundant in more compact plaques like CG and CP in comparison to DP and DP of CU-AP. ABx-38 in less aggregated diffused plaques of CU-AP than cored plaques of sAD, along with shorter, truncated peptides including AB1-31, AB4-25, AB4-33 and AB6-36.
Conclusions: Our results imply possible role of N-terminal and C-terminal truncations in driving the aggregation kinetics of AB peptides. This data would be helpful in understanding the possible regulatory mechanism involved in extra cellular AB deposition.

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P0379 / #898

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

PROBING THE MOLECULAR DIVERSITY AND CONFORMATIONAL POLYMORPHISM OF TAU PATHOLOGY IN ALZHEIMER'S DISEASE

Srinivas Koutarapu, Junyue Ge, Wojciech Michno, Jörg Hanrieder, Henrik Zetterberg, Kaj Blennow
University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden

Aims: The primary goal of this project is to combine hyperspectral confocal imaging and SIMOA to probe the chemical and structural aspects of neurofibrillary tau pathology in Alzheimer's Disease.
Methods: We employed hyperpsectral imaging of tau tangles with co staining of Luminescent Conjugated Oligothiophenes (LCOs) and pTau antobodies on AD brain sections to visualise various tau morphologies. This is achieved using laser-scanning microscopy LSM780 that allows for hyperspectral acquisition. Further, CSF and plasma samples from the same cohort can be further analyzed to examine the profiles of various phosphorylated antibodies like pTau-181 and pTau217: Microscopy data and SIMOA data are then correlated to understand dynamic nature of tangle maturation correlates with that of the expressionn of p-Tau181 and p-Tau 217.
Results: In this study we noticed differencec in the hyperspectral signatures of tau polymorphs. For further analysis , this data would be analysed in comparison with the p-Tau181 and p-Tau217 SIMOA data obtained from the CSF/plasma levels of the same
cohort.

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Hyperspectral Imaging on Tau isoforms

STAINING

Luminiscent Conjugated Oligothiophenes (LCOs)

Immunofluorescence (IF) with TAU antibodies

IMAGING

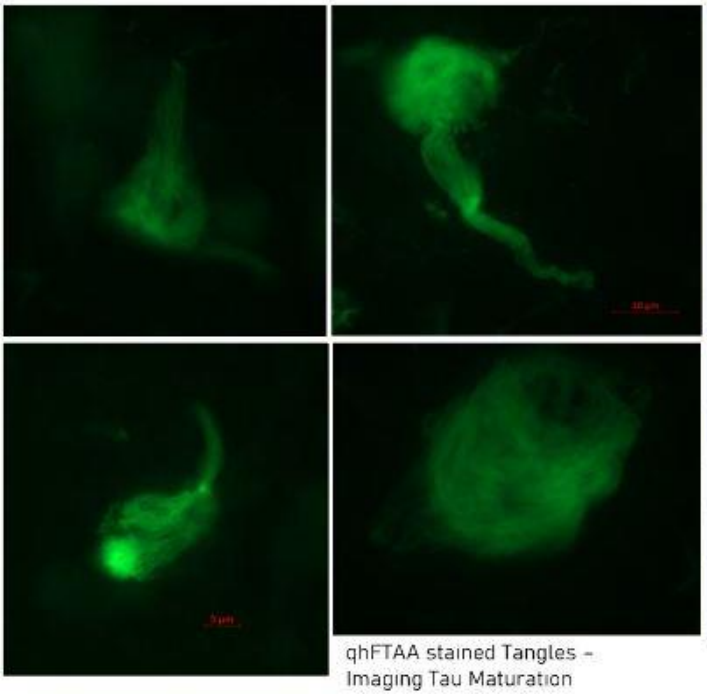
Confocal Microscopy

ANALYSIS

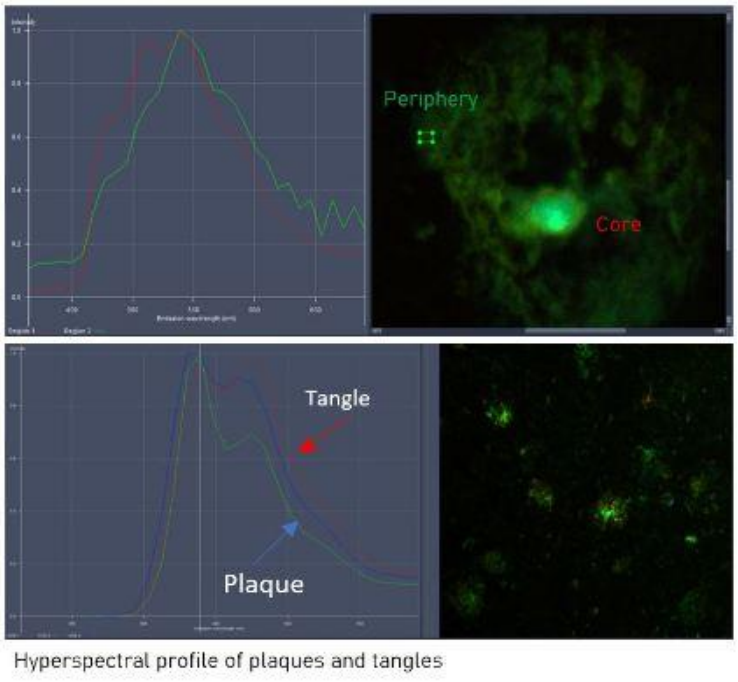
Hyperspectral analysis and structural imaging

IHC for Identification

Correlation of SIMOA and hyperspectral data



qhFTAA stained Tangles – Imaging Tau Maturation



Hyperspectral profile of plaques and tangles

Conclusions: The results obtained from this study aims in establishing the chain of molecular events that underlie tau pathology with a particular focus on the role of different polymorphs of tau and expression of different tau epitopes during the progression of disease

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P0380 / #965

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

ASSESSMENT OF WHITE MATTER MICROSTRUCTURAL CHANGES IN PATIENTS WITH COGNITIVE IMPAIRMENT USING DIFFUSION KURTOSIS IMAGING AT 7 TESLA

Tommaso Pavan[1], Federica Ribaldi[2], Michela Pievani[3], Sandra Da Costa[4], Jorge Jovicich[5], Giovanni Frisoni[2], Ileana Jelescu[1]
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Aims: Diffusion kurtosis imaging (DKI) is a clinically-feasible extension of diffusion tensor imaging (DTI) and represents a promising method to assess microstructural changes in neurodegenerative diseases. The aim of this study was to investigate white matter tract alterations in a memory population clinic using DKI.
Methods: Forty-six participants (n=18 cognitively impaired [CI] and n=28 cognitively unimpaired [CU] subjects) were recruited at the Geneva Memory Center. Multi-shell diffusion-weighted images (DWI) (b=0, b=1000 on 30 directions, b=2000 on 60 directions; TE/TR=60/7000ms; voxel size: 2x2x2mm3, 60 slices) and MP2RAGE scans were collected on a 7T Siemens MRI scanner at the EPFL. DWI pre-processing included MP-PCA denoising, Gibbs ringing, topup and eddy current corrections, followed by diffusion and kurtosis tensor estimation. White matter tract regions of interest (ROIs) from the Johns Hopkins University atlas were automatically segmented in each subject using atlas registration, and mean diffusion and kurtosis metrics were calculated for each ROI. Differences in kurtosis were tested using the Brunner-Munzel test.
Results: CI showed decreased axial and/or mean kurtosis in the cingulum, parahippocampal tract, superior longitudinal and fronto-occipital fasciculi, genu and splenium of the corpus callosum, corona radiata, internal and external capsule ($p<0.05$ corrected for multiple comparisons with FDR), while group differences based on the DTI metrics were much more limited.
Conclusions: These results indicate that DKI is more sensitive than DTI to microstructural changes in CI patients. Reduced kurtosis suggests a loss of tissue complexity and heterogeneity, and may represent an early marker of neurodegeneration. In addition to changes in associative and commissural tracts, our results indicate that projection tracts are also affected in CI. These results support the added value of DKI vs DTI alone, to study cognitive decline using ultra-high field MRI.

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P0381 / #304

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

DECODING AMYLOID BETA AND TAU PATHOLOGIES IMPACT ON NEURONAL ACTIVITY ACROSS THE ALZHEIMER'S SPECTRUM

Lazaro Sanchez-Rodriguez[1], Gleb Bezgin[1], Felix Carbonell[2], Pedro Rosa-Neto[1], Yasser Iturria-Medina[1]
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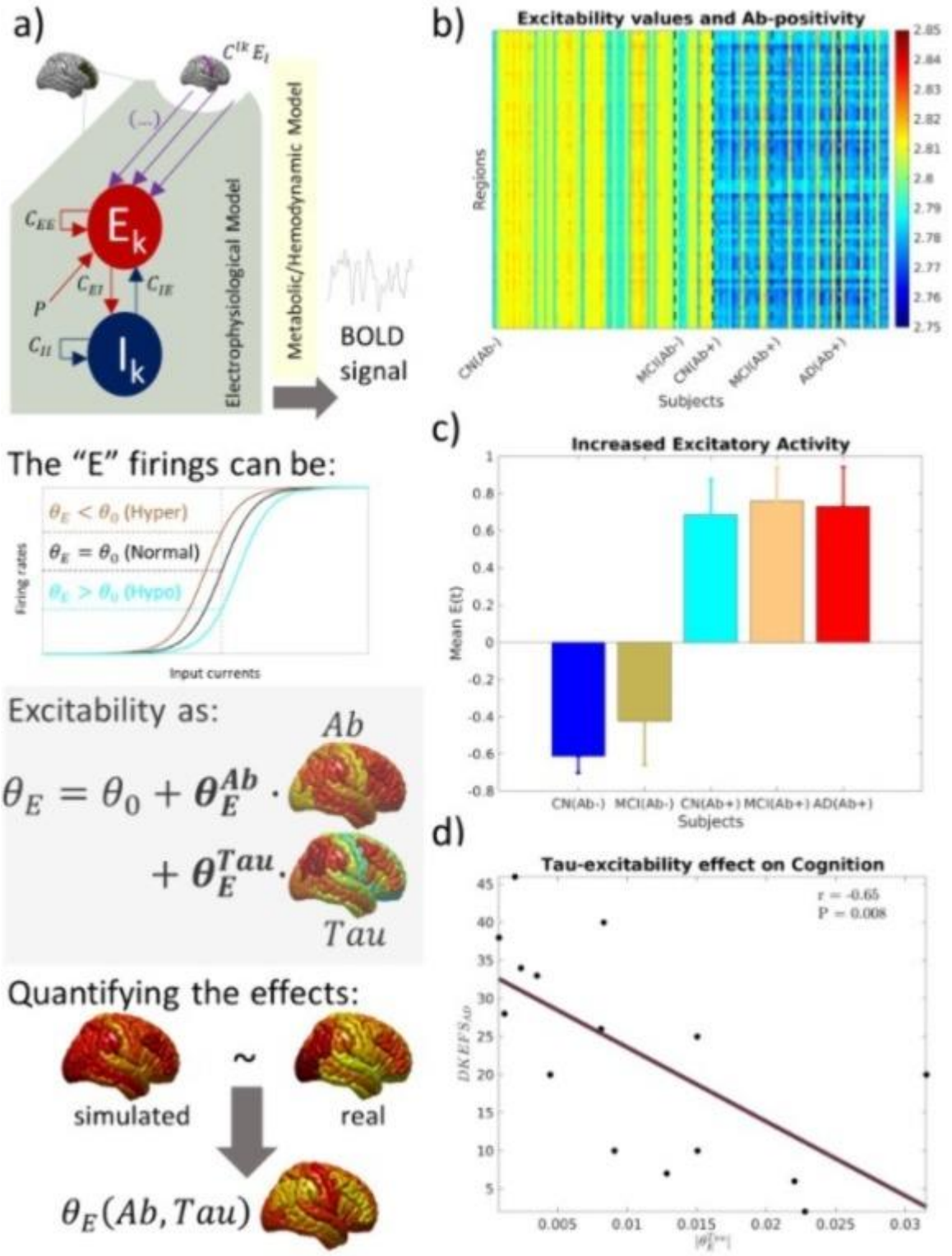
Aims: To better understand combined amyloid beta and tau effects on neuronal activity and cognitive integrity via a computational brain simulator informed by PET scans and fMRI.
Methods: We utilized 126 baseline evaluations from the TRIAD cohort, including 77 cognitively normal (CN), 33 mild cognitive impairment (MCI) and 16 Alzheimer's disease (AD) subjects. All participants underwent resting-state fMRI, amyloid beta (Ab) (^{18}F-NAV4694)- and tau (^{18}F-MK-6240)- PET and a cognitive assessment. The standardized uptake value ratios (PET-SUVR) and the fractional amplitude of low-frequency fluctuations (fMRI-fALFF) were calculated for regions in the DKT Atlas. Each subject's BOLD signal was simulated with an electrophysiological/metabolic-hemodynamic model. We assumed that the excitatory excitability can be associated with amyloid beta and tau PET-SUVRs and quantified these influences by minimizing the similarity between the simulated and real neuronal activity indicators (Fig. 1a).
Results: We mapped the individual excitatory excitability values from the estimated amyloid beta and tau effects (Fig. 1b). We observed lower neuronal firing thresholds in Ab+ than in Ab- participants across all clinical diagnoses, translating into higher firing rates with Ab accumulation (Fig. 1c). We also investigated the relationship between the obtained parameters and multiple indicators for cognitive integrity. For AD subjects, the higher the influence of tau on excitability was, the worse the cognitive performance was (Fig.



1d).

Conclusions: Amyloid beta-positivity shifts neuronal activity towards a higher firing rate. We observe a significant relationship between tau-excitability effects on neuronal activity and cognitive measurements. Taken together, these results support neuropathologies' direct role in brain activity dysregulation and cognitive deterioration.

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P0383 / #2539

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

THE CONSULTANT ANAESTHETIST DELIVERED LUMBAR PUNCTURE SERVICE FOR ALZHEIMER'S DISEASE RESEARCH: AN EVALUATION OF SUCCESS RATE AND PATIENT FEEDBACK.

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Aims: A lumbar puncture is often required when assessing novel AD therapies. The general public may perceive that a lumbar puncture is an unpleasant experience[1]. This may discourage participation in AD research trials. To improve patient experience, the Glasgow Memory Clinic provides a Consultant Anaesthetist delivered service. This service evaluation report describes our patient feedback.
Methods: All patients who receive a lumbar puncture at our clinic complete an evaluation survey. This is a 5-point satisfaction survey, with space for free-text comment. Patients are counselled regarding potential complications such as post-dural puncture headache. Patients who experience these complications are advised to get in touch with the clinic or seek urgent medical advice.
Results: The median satisfaction scores (1 = poor, 5 = very good) from 76 patients between February 2020 and August 2022 are described in the table below.

Table 1: Patient satisfaction following lumbar puncture at Glasgow Memory Clinic (n=76)

Question	Average Satisfaction Score
Q1: The staff making you feel at ease	5
Q2: Preparation of the procedure	5
Q3: The LP procedure	5
Q4: Immediate post LP care	5
Q5: Understanding the discharge instructions and post LP care	5

There were 58 free text comments describing the experience as positive with comments such as "painless", "professional team" and "felt at ease" being highly represented. There were no immediate complications such as post-dural puncture headache.
Conclusions: We have demonstrated this is a safe well tolerated procedure with positive feedback and high patient satisfaction following lumbar puncture performance at the Glasgow Memory Clinic. The provision of a lumbar puncture no longer has to be a barrier to AD diagnosis and research, providing it is performed by an experienced operator, in a comfortable environment with a supportive team.

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P0384 / #2375

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

EMERGING ROLE OF NOVEL SERUM AND RETINAL BIOMARKERS IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS (ADRD) IN THE INDIAN CONTEXT

Faheem Arshad[1], Suvarna Alladi[1], Paras Borse[1], Sarada Subramanian[2], Subasree Ramakrishnan[1], Pooja Mailankody[1], Rajani Bhattu[3]
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Aims: The aetiology of Alzheimer's Disease and Related Dementia (ADRD) is complex. The clinical methods lack sensitivity and specificity due to overlapping symptoms, especially in a diverse sociocultural Indian context. The use of methods to predict dementia years before its onset could play a vital role in early diagnosis and intervention. This underscores the need for novel biomarkers in the diagnosis of dementia. Serum glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) are non-amyloid blood-based biomarkers indicative of ongoing inflammatory and neurodegenerative process. In addition, retinal parameters were also measured. We aimed to assess and validate their diagnostic value in patients with ADRD in the Indian context.
Methods: Ninety-nine participants recruited in the study underwent detailed cognitive assessment along with basic brain imaging. Blood samples were collected from healthy controls (n=29), patients with AD (n=28) and FTD (n=43). Quantitative determination of serum GFAP and NfL was carried out with the Simoa platform. Participants also underwent retinal imaging using Optical Coherence Tomography (OCT) to study macular volume, thickness and retinal nerve fibre layer thickness.
Results: Serum GFAP and NfL were significantly higher in patients with dementia compared to healthy controls ($p<0.001$). Serum GFAP levels were higher in AD ($p<0.001$), while NfL levels were significantly elevated in AD and FTD compared to controls ($p< 0.05$). OCT showed that TMV (total macular volume) and retinal nerve fibre layer (RNFL) thickness in the naso-inferior (NI) quadrant in both eyes were significantly lower in patients with ADRD compared to healthy controls.
Conclusions: Our results suggest that, while serum GFAP and NfL, and retinal biomarkers seem to have an emerging role in differentiating AD and FTD from healthy controls, prospective cohort studies are required to confirm the findings.

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P0385 / #2714

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

RELATIONSHIP BETWEEN PLASMATIC PHOSPHORYLATED FORMS OF TAU IN DEMENTIA WITH LEWY BODIES, ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND HEALTHY CONTROLS.

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Aims: Studies in biofluids have shown that tau species could be promising biomarkers for AD neuropathology. We recently showed no statistically significant difference between plasma levels of p-tau181 and p-tau231 in DLB and PD patients; still, both phosphoforms were associated with cognitive impairment in DLB and AD but not in PD. Here, we aim to evaluate if there are differences in the relationship between these two phosphoforms, assessing their correlation in each diagnostic group.
Methods: This multicenter study included participants from the European-DLB Consortium cohort enrolled at ten centres with harmonized diagnostic procedures. Plasma p-tau181 and p-tau231 concentrations were measured using a clinically validated, in-house single-molecule array. Pearson's correlation coefficient was estimated for each group and compared by the Fisher's z-transformation test.
Results: Group demographics and clinical baseline characteristics are shown in table1. The correlation between the two Tau phosphoforms was highest in the PD group (r= 0.88), followed by HC (r= 0.84), AD (r= 0.70) and DLB (r= 0.69) (figure 1). The difference in the correlations observed between the DLB and PD groups using the Fisher's z transformation test was statistically significant (P value= <.001). On the contrary, no differences were observed in the correlations between DLB and AD (P value= 0.87).
Conclusions: These findings show that although the levels of p-tau181 and p-tau231 were increased in all diseases, the correlation between the two-tau phosphoforms was lower in DLB and AD when compared to PD and HC. These findings may be due to differences in the extent of amyloid-pathology in the different disease groups. It might be necessary to further stage PD patients as well as include PD related dementia cases to see if this trend is maintained in future studies.

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P0386 / #627

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

EFFECTS OF PRE-ANALYTICAL SAMPLE HANDLING ON THE PERFORMANCE OF PLASMA PHOSPHO-TAU217

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Aims: To investigate how pre-analytical factors affect the performance of one of the most promising plasma biomarkers of Alzheimer´s Disease, phosphorylated tau (p-tau)217.
Methods: We included 50 β-amyloid positive ($A\beta^+$) and 50 $A\beta^-$ participants from the Swedish BioFINDER-1 cohort. Plasma samples were either thawed at room temperature (RT) or on ice and centrifuged or not centrifuged. Plasma and CSF p-tau217 were measured using immunoassay developed by Lilly Research Laboratories. CSF Aβ42 and Aβ40 were measured using Elecsys® Roche immunoassays.
Results: In the whole cohort, we found significant correlations between plasma p-tau217 and CSF Aβ42/40 and p-tau217 for all tested conditions (Table 1). Correlations between plasma p-tau217 and CSF p-tau217 were also significant for all conditions in the $A\beta^+$ group (Table 1). However, in this group, correlations with CSF Aβ42/40 were only significant in the centrifuged samples (thawed at RT, Rs=-0.394, p=0.005; thawed on ice, Rs=-0.406; p=0.003). In $A\beta^-$ participants, significant correlations between plasma p-tau217 and CSF p-tau217 were found again only in the centrifuged samples (thawed at RT, Rs=0.394, p=0.005; thawed on ice, Rs=0.334; p=0.018, Table 1), with no significant correlations between plasma p-tau217 and CSF Aβ42/40 for any of the conditions. Even though the accuracy to identify individuals with abnormal CSF Aβ42/40 or CSF p-tau217 status was high for all conditions, the AUCs of samples that were thawed at RT without centrifugation were numerically lower than AUCs of other conditions (CSF Aβ42/40: 0.845 vs 0.872-0.884; CSF p-tau217: 0.866 vs 0.908-0.924, Table
2).

Table 1. Spearman correlations between plasma p-tau217 and CSF p-tau217 and Aβ42/40

	CSF p-tau217	CSF Aβ42/40
All (n = 100)		
Cond 1. EDTA, RT, NC	**0.614 (<0.001)**	**-0.515 (<0.001)**
Cond 2. EDTA, RT, C	**0.713 (<0.001)**	**-0.636 (<0.001)**
Cond 3. EDTA, on ice, NC	**0.666 (<0.001)**	**-0.607 (<0.001)**
Cond 4. EDTA, on ice, C	**0.717 (<0.001)**	**-0.652 (<0.001)**
Aβ $^{+}$ (n = 50)		
Cond 1. EDTA, RT, NC	**0.506 (<0.001)**	-0.215 (0.133)
Cond 2. EDTA, RT, C	**0.579 (<0.001)**	**-0.394 (0.005)**
Cond 3. EDTA, on ice, NC	**0.511 (<0.001)**	-0.284 (0.046)
Cond 4. EDTA, on ice, C	**0.550 (<0.001)**	**-0.406 (0.003)**
Aβ $^{-}$ (n = 50)		
Cond 1. EDTA, RT, NC	0.190 (0.186)	0.230 (0.108)
Cond 2. EDTA, RT, C	**0.394 (0.005)**	0.073 (0.615)
Cond 3. EDTA, on ice, NC	0.184 (0.202)	0.210 (0.143)
Cond 4. EDTA, on ice, C	**0.334 (0.018)**	0.105 (0.468)

Data are shown as Spearman correlation coefficients (p-value) with significant results highlighted in bold. Abbreviations: Aβ^{+}, Amyloid-β positive; Aβ^{-}, Amyloid-β negative; C, centrifugation; CSF, cerebrospinal fluid; NC, non-centrifugation; EDTA, Ethylenediaminetetraacetic acid; RT, room temperature.

Table 2. ROC analysis of plasma p-tau 217 for identifying abnormal CSF p-tau217 and Aβ42/40 status

	Area (95% CI)	Sensitivity %	Specificity %	Cut-off	Youden´s Index
CSF p-tau217					
Cond 1. EDTA, RT, NC	0.866 (0.797, 0.935)	95.1	67.8	0.282	0.629
Cond 2. EDTA, RT, C	0.917 (0.864, 0.970)	92.7	83.1	0.240	0.757
Cond 3. EDTA, on ice, NC	0.908 (0.853, 0.964)	95.1	71.2	0.232	0.663
Cond 4. EDTA, on ice, C	0.924 (0.875, 0.972)	87.8	81.4	0.242	0.692
CSF Aβ42/40					
Cond 1. EDTA, RT, NC	0.845 (0.769, 0.921)	88	72	0.282	.600
Cond 2. EDTA, RT, C	0.872 (0.799, 0.945)	80	90	0.247	.700
Cond 3. EDTA, on ice, NC	0.884 (0.818, 0.951)	86	82	0.252	.680
Cond 4. EDTA, on ice, C	0.883 (0.813, 0.953)	76	92	0.256	.680

Data are shown as (95% CI). Sensitivities and specificities are for cut points defined by the Youden index (maximizing the sum of sensitivity and specificity). Abbreviations: $A\beta^{+}$, Amyloid-β positive; $A\beta^{-}$, Amyloid-β negative; AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid; C, centrifugation; EDTA, Ethylenediaminetetraacetic acid; NC, non-centrifugation; ROC, receiver operating characteristic; RT, room temperature.

Conclusions: We found that while centrifugation improved the performance of plasma p-tau217 thawing temperatures did not have significant impact. These results might be of importance for future development of standard protocols for pre-analytical blood sample handling.

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POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ANALYTICAL AND CLINICAL PERFORMANCE OF THE LUMIPULSE G PTAU181 AND B-AMYLOID RATIO (1-42/1-40) PLASMA ASSAYS IN ALZHEIMER'S DISEASE

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Aims: Plasma tau phosphorylated at threonine-181 (pTau181) and β-Amyloid ratio(1-42/1-40) assays provide potential alternatives to tau and amyloid CSF or PET testing for Alzheimer's disease (AD). Here, we aimed to assess the analytical and clinical performance of novel plasma Lumipulse-G pTau181 and Aβ42/40 assays.
Methods: We examined the analytical (precision, parallelism, recovery, dilutional-linearity, sensitivity) and clinical (40 AD-dementia patients, 70%F, 64y±7y; 40 age-and sex-matched controls) performance of pTau181^{Lumipulse}, Aβ(1-42)^{Lumipulse} and Aβ(1-40)^{Lumipulse} (and Aβ42/40 ratio) in comparison to pTau181^{Simoa} from Quanterix.
Results: The average inter-assay precision of three quality controls over four runs was 10.4%CV for pTau181^{Lumipulse} (versus 19.0%CV for pTau181^{Simoa}), 5.6%CV for Aβ(1-42)^{Lumipulse}, and 8.1%CV for Aβ(1-40)^{Lumipulse}. All Lumipulse assays showed good parallelism, recovery, and dilutional-linearity (acceptance criteria: average 85-115%) (figure1). All clinical samples were measured above the functional LLOQs for both pTau181 and Aβ assays. With pTau181^{Lumipulse}, all clinical samples were measured with a CV of <20% between duplicate measurements, while with pTau181^{Simoa}, two samples had a CV>20%. The pTau181 measurements of both assays significantly correlated (*rho*=0.81), and the points showed strong agreement in a Bland-Altman plot (figure2B). The pTau181^{Lumipulse} demonstrated higher accuracy in identifying AD (AUC=0.91, 95%CI:0.83-0.98) than pTau181^{Simoa} (AUC=0.83, 95%CI:0.74-0.92; DeLong's *p*=0.004). Similarly, Aβ42/40^{Lumipulse} achieved an AUC of 0.78 (95%CI:0.66-0.89) (figure 3). Both pTau181^{Lumipulse} and Aβ42/40^{Lumipulse} contributed to the diagnostic accuracy of a logistic regression model. However, the resultant AUC remained similar *(*AUC=0.91, 95%CI:0.84-0.98).
Conclusions: The Lumipulse assays demonstrated robust analytical performance, as well as good clinical performance in our proof-of-concept cohort. The plasma pTau181^{Lumipulse} assay outperformed the pTau181^{Simoa} assay. Combining pTau181^{Lumipulse} and Aβ42/40^{Lumipulse} needs to be further investigated in larger cohorts and across the AD continuum.

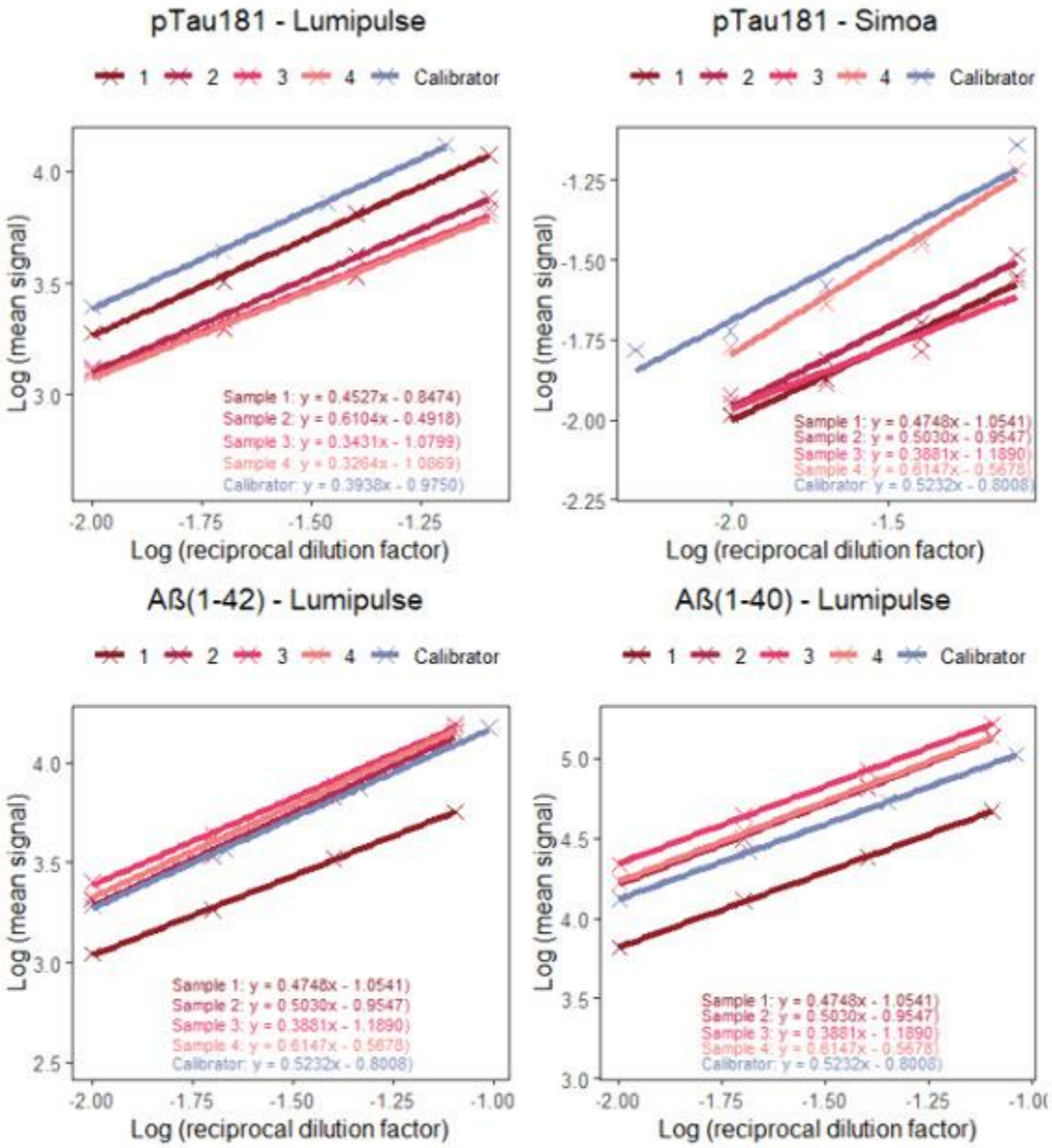

Figure 1. Parallelism of the assays. Serial dilution of four plasma samples (in red) and one calibrator (in purple) was performed for the pTau , Aβ(1-42)^{Lumipulse} and Aβ(1-40)^{Lumipulse} assays. Crosses represent the individual measurements. A linear slope was fitted for each sample and the calibrators. Equations of the slopes are presented in the figures. Parallelism results were acceptable when slopes were within the 80-120% comparability range.

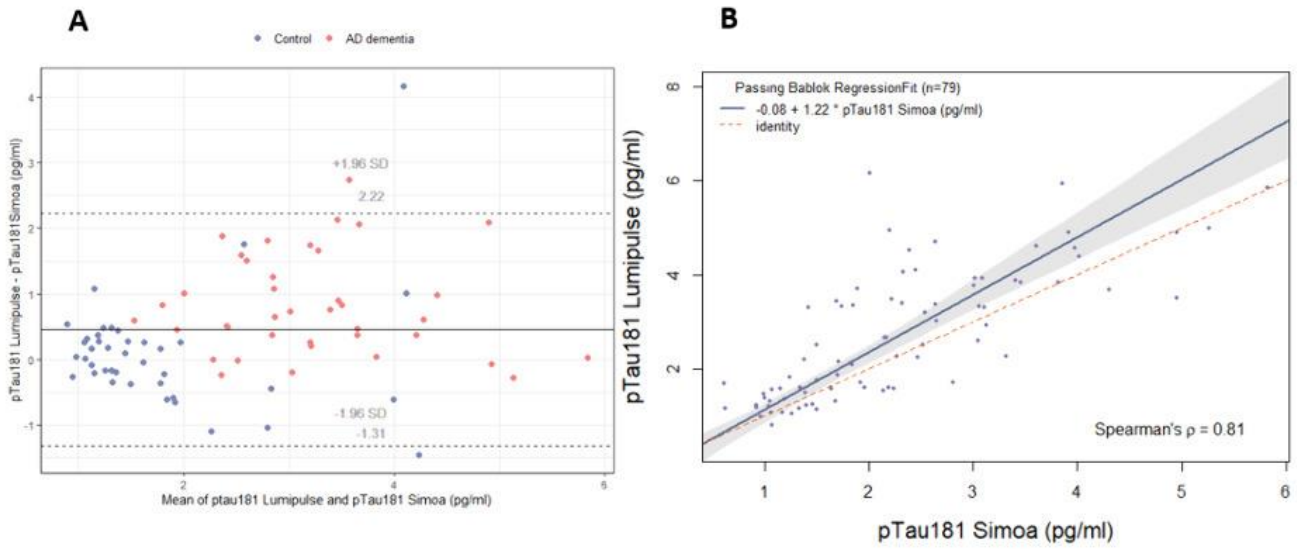

Figure 2. A) Comparison of the Lumipulse and Simoa methods using Bland–Altman plots in units. B) Passing Bablok regression for the agreement between pTau181 Lumipulse and pTau181 Simoa measurements. In Bland Altman's plot, the clinical samples were color-coded for diagnostic groups (AD dementia: red, control: purple).

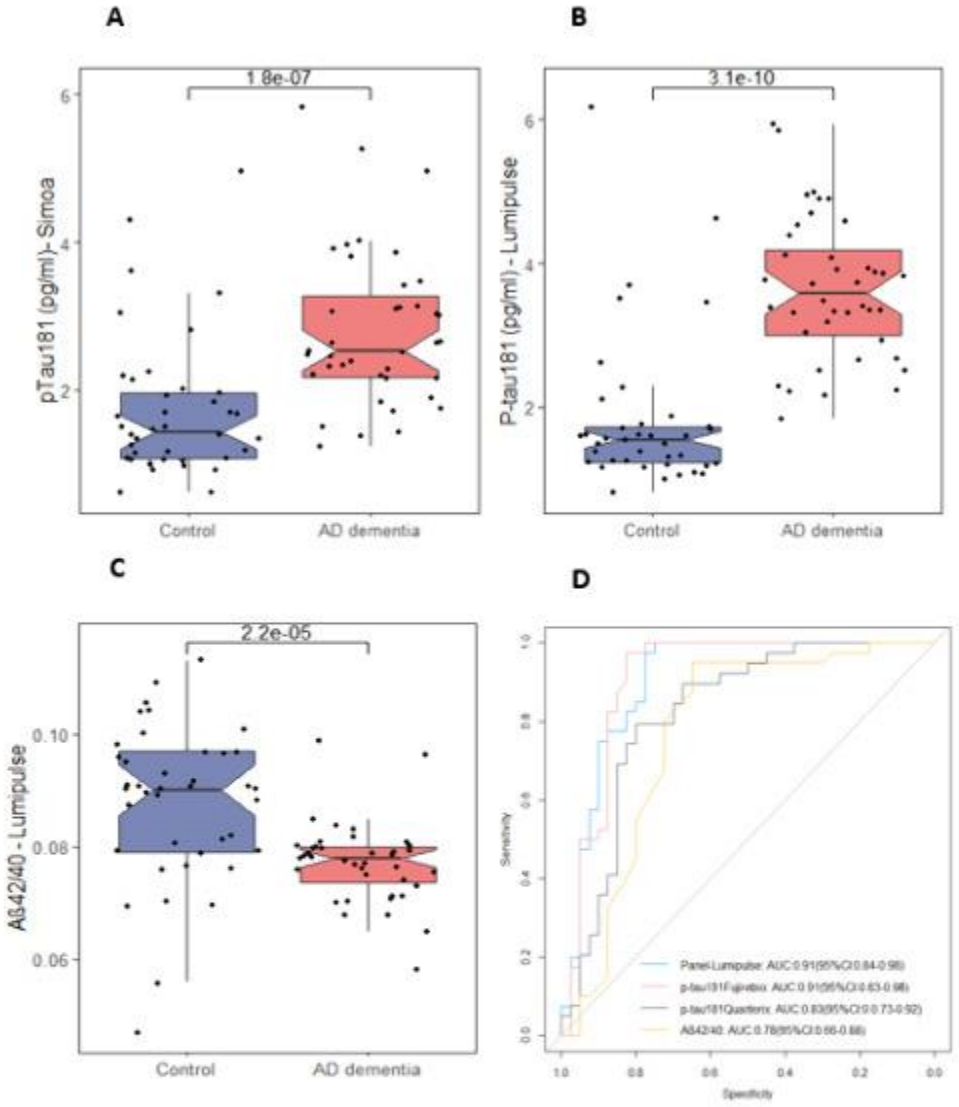

Figure 3. A-C) Boxplots to demonstrate pTau levels and Aβ42/40 measured in 40 AD dementia and 40 control samples. P-values for group differences were calculated using the non-parametric Mann-Whitney U Test. The pTau levels were higher in patients with AD-dementia compared to controls ($pTau181^{Lumipulse}$: 2.3-fold; $pTau181^{Simoa}$: 1.8-fold). **D) ROC curves of the discrimination between controls and AD dementia for the pTau181 and β-Amyloid assays**. The $pTau181^{Lumipulse}$ demonstrated higher accuracy in identifying AD (AUC=0.91, 95%CI:0.83-0.98) than $pTau181^{Simoa}$ (AUC=0.83, 95%CI:0.74-0.92; DeLong's p=0.004). Similarly, $Aβ42/40^{Lumipulse}$ achieved an AUC of 0.78 (95%CI:0.66-0.89) (figure 3). Both $pTau181^{Lumipulse}$ and $Aβ42/40^{Lumipulse}$ contributed to the diagnostic accuracy of a logistic regression model. However, the resultant AUC remained similar (AUC=0.91, 95%CI:0.84-0.98).We applied logistic regression with Wald's backward selection to assess a panel-Lumipulse. The correlation coefficient *rho* is calculated using Spearman's rank correlation analysis. P-tau: phosphorylated tau, AD: Alzheimer's Disease, SD: standard deviation. Group comparisons using the assays were significant, with p-values below 0.05.

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P0388 / #2731

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

A STRUCTURE-BASED FLUID BIOMARKER FOR THE DIFFERENTIAL DIAGNOSIS OF EARLY-STAGE NEURODEGENERATIVE DISEASES MEASURED BY THE IMMUNO-IR-SENSOR (IRS)

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Aims: We have developed an immuno-infrared sensor that determines the secondary structure distribution of protein biomarkers in body fluids, especially in blood, as read out. Its performance is shown exemplary for Aß misfolding in CSF and blood plasma for Alzheimer's disease (AD).
Methods: Up to now Fourier-transform infrared (FTIR) instruments have been used. Here we present a greatly improved miniaturized immuno-IR sensor system based on the newest generation of quantum cascade lasers. It has a 12-fold reduction in size to 25x25x10 cm^3 and also shows significantly improved S/N, especially beyond the large water absorbance band. It uses a QCL-light source instead of a globar and room temperature detectors in contrast to liquid nitrogen cooled MCT detectors used in FTIR instruments. The heart of the instrument is a patented silicon crystal which surface-is functionalized with Aß–specific antibodies. CSF and plasma samples are measured by a fully automated flow-through system. This prototype is currently being further developed into a soon-to-be commercially available device.
Results: The structure biomarker has been validated in three independent clinical studies and correlates nicely with CSF biomarkers and PET scans. Especially, very early preclinical AD can be identified in symptom-free individuals before plaque formation, 17 years before the clinical stage is diagnosed.
Conclusions: Its performance is clearly superior to the concentration biomarker at these early stages, e.g., compared to p-tau 181 biomarker. The structure biomarker also indicates Parkinson´s disease using misfolding of alpha-synuclein and ALS using TDP 43 misfolding. This provides a differential diagnosis at very early stages using fluid biomarkers.

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P0389 / #935

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

NEURONAL PENTRAXINS AS FLUID BIOMARKER FOR SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE – HUMAN & TAU TRANSGENIC MOUSE MODEL DATA

Stefan Barghorn, Petra Jakob, Janina Ried, Julian Sefrin, Philipp Secker
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Aims: We investigated neuronal pentraxins (NPTX-1, NPTX-2 and NPTX-R) as fluid biomarkers for synaptic dysfunction and as potential correlates for cognitive performance in Alzheimer's Disease (AD).
Methods: We successfully developed in-house immunoassays for NPTX-R and NPTX-2 on the Ella platform and utilized a commercial NPTX-1 assay (Meso Scale Diagnostics). All assays were cross-reactive for human and mouse analytes and were fit-for-purpose validated according to standard guidelines. This enabled us to measure all three neuronal pentraxins side-by-side in biofluids of two independent human cohorts (AD, MCI and control subjects) and Thy1-hTau.P301S transgenic mice of different age and pathology states.
Results: We detected significantly lower CSF NPTX-2 levels in AD subjects versus healthy controls in one of two human cohorts, while NPTX-1 and NPTX-R levels did not differ significantly. Interestingly, NPTX-2 and, to a lesser extent, NPTX-R levels of AD & MCI A-beta positive subjects correlated significantly with MMSE scores.
Thy1-hTau.P301S transgenic mice exhibited age- and pathology-dependent reduction of NPTX-2 and NPTX-R levels in the CSF, while NPTX-1 was unchanged over the investigated age range of 2 to 5 months. Plasma levels did not correlate with CSF showing no group differences.
Conclusions: Our data supports current literature data suggesting neuronal pentraxins as promising biomarkers for synaptic health and cognitive dysfunction in AD. Further analysis, preferably in human AD cohorts with longitudinal samplings, would substantiate these findings. The translation of human data into transgenic mouse models of AD indicate a utility of neuronal pentraxins as biomarker to monitor synaptic health and disease progression in preclinical drug development studies.

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P0390 / #2444

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

TRACKING THE PROGRESSION OF ALZHEIMER'S DISEASE WITH BLOOD-BASED RNA BIOMARKERS

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Aims: It has been observed that AD patients display signs of systemic inflammation, suggesting that it could precede the well-established AD hallmarks. Indeed, we showed that the innate immune response in the form of monocyte activation is detectable at the pre-clinical stage (Munawara U et al. Immun Ageing. 2021). Our goal is to characterize changes of gene expression in peripheral blood monocytes from patients at different stages of AD progression and validate potential RNA biomarkers for a better prognosis and diagnosis of AD clinical spectrum.
Methods: We collected blood from three groups of patients: healthy subjects, Mild Cognitive Impairment (MCI) and AD patients (n=9 for each group). We purified the monocytes from each sample and performed a whole transcriptome analysis by RNA-seq. We established the list of genes differentially expressed in monocytes of AD patients compared to those of healthy individuals.
Results: We observed that in the top 500 genes differentially expressed, a majority of these were upregulated (65%) during the disease progression. These genes are mainly involved in chemokine activity, cytokine receptor binding, and cytokine-mediated signaling pathways. We further confirmed several RNA biomarkers by quantitative PCR and showed that they are often deregulated at pre-clinical stages of the disease (MCI stage), supporting our results recently published on the hyperactivation of monocytes in MCI patients. We finally confirmed the alteration of these candidates at the protein level, opening the possibility of using these biomarkers with different diagnostic methodologies.
Conclusions: Our findings provide evidence that we can detect the pre-clinical stage of AD in monocytes using a specific set of RNA biomarkers, highlighting the importance to study the early innate immune response as it could mark a new era in neurodegenerative disease research.

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P0391 / #1153

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

BLOOD-BRAIN BARRIER PERMEABILITY IMPACTS THE PERFORMANCE OF PLASMA AMYLOID- B

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Aims: To investigate whether BBB damage impacts the performance of plasma Aβ levels as a proxy of brain Aβ pathology in living individuals.
Methods: We assessed participants in research (TRIAD, Canada, n=96) and clinical (BIODEGMAR, Spain n=128) cohort with plasma and CSF albumin, $A\beta_{42/40}$, phosphorylated tau (p-tau), and/or Aβ/Tau-PET, and clinical assessments. A high CSF/serum albumin ratio (qAlb) indicated increased BBB permeability. Linear regressions adjusted for age, sex and clinical diagnosis were used to test the associations between plasma/CSF biomarkers and qAlb status. Plasma Aβ42/40 discriminative performance was assessed with Receiver Operator Characteristic (ROC) area under the curve (AUC).
Results: Plasma Aβ42/40 better identified CSF Aβ42/40 (TRIAD: AUC=0.99 versus AUC=0.61; BIODEGMAR: AUC=0.84 versus AUC=0.76 for high and low BBB permeability,
respectively, **Fig.1**).

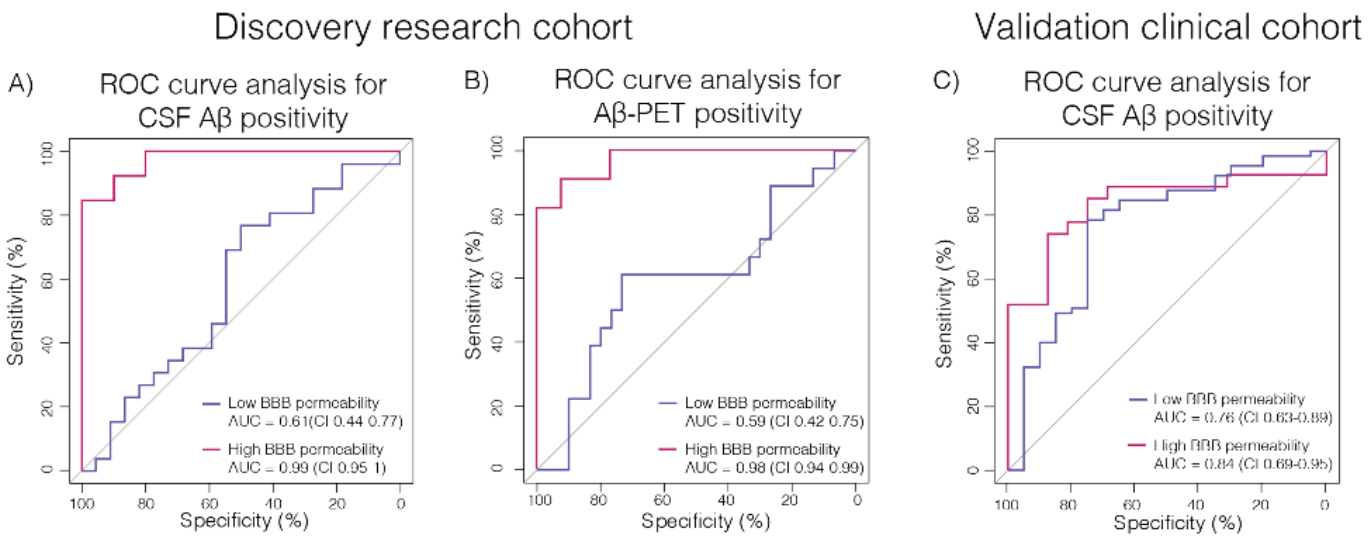
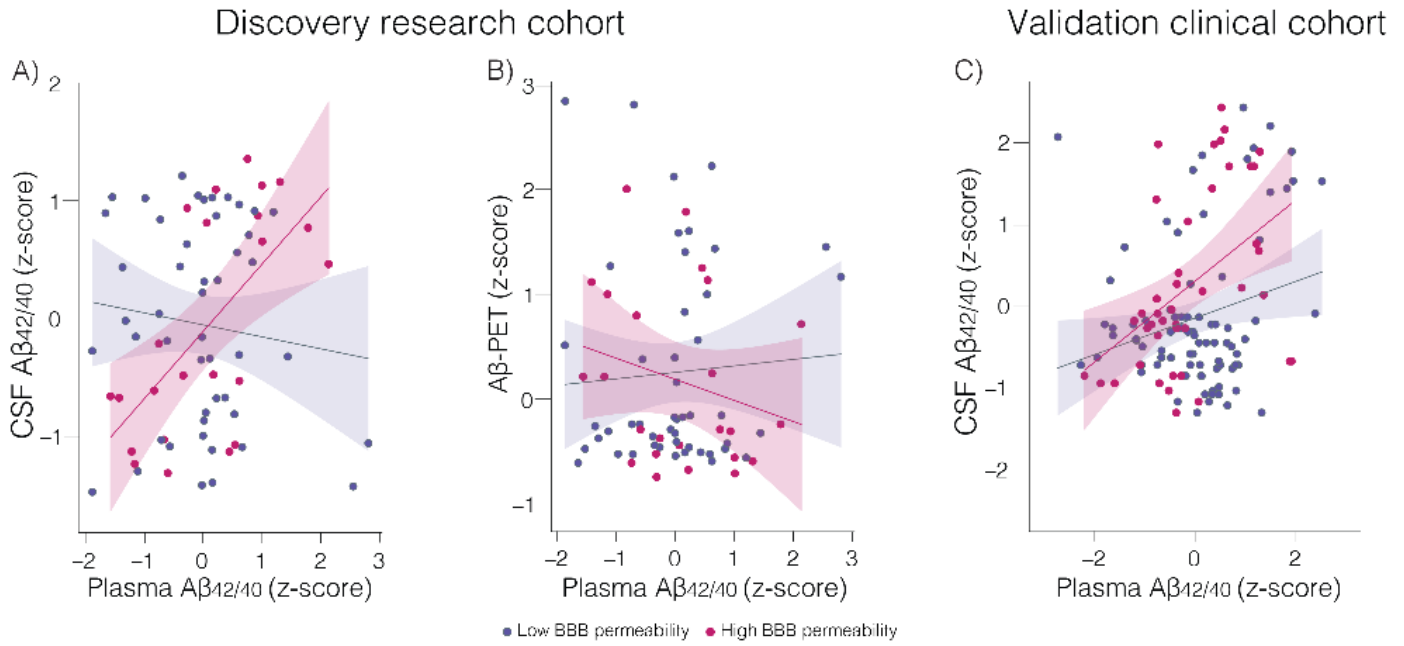


Fig. 1. Discriminative accuracy of plasma Aβ42/40 for brain AD pathology as a function of BBB permeability. Plasma Aβ42/40 AUC for (A) CSF Aβ42/40 and (B) AB-PET positivity in the TRIAD cohort and (C) plasma Aβ 42/40 AUC for CSF Aβ42/40 positivity in the Biodegmar cohort.

An interaction between plasma Aβ42/40 and qAlb status on CSF Aβ42/40 was observed in both cohorts (TRIAD: β=0.66, p=0.002; BIODEGMAR: β=0.35, p=0.04, **Fig. 2**). Voxel-wise models estimated that the association of PET with plasma Aβ was most affected by the abnormal BBB permeability in the brain regions showing the highest levels of Aβ deposition, such as posterior cingulate and precuneus. BBB permeability did not significantly impact the relationship between brain and plasma p-tau
levels.



High BBB permeability: β = 0.66, P = **0.0003***
Low BBB permeability: β = -0.14, P = 0.297
Plasma Aβ42/40*qAlb: β = 0.66, P = **0.0022***

High BBB permeability: β = -0.27, P = **0.037***
Low BBB permeability: β = 0.08, P = 0.607
Plasma Aβ42/40*qAlb: β = -0.16, P = 0.477

High BBB permeability: β = 0.49, P = **0.0027***
Low BBB permeability: β = 0.14, P = 0.117
Plasma Aβ42/40*qAlb: β = 0.35, P = **0.041***

Fig.2 Increased BB permeability modifies the associations of plasma Aβ42/40 ratio with brain levels of Aβ pathology. Scatter plots show the associations between plasma Aβ42/40 with **(A)** CSF Aβ42/40 ratio and with **(B)** neocortical Aβ-PET SUVR in the high and low BBB permeability groups in the TRIAD cohort. **(C)** Scatter plots show the associations between plasma Aβ42/40 ratio with CSF Aβ42/40 ratio in the Biodegmar cohort. Lines indicate regression line with their respective 95% confidence intervals. p-values were computed using linear regression models adjusted by age, sex, and clinical diagnosis. In addition, the plasma Aβ42/40 × CSF/PET Aβ status interaction term was computed.

Conclusions: Our results suggest that plasma Aβ may be a better proxy of brain Aβ pathology in individuals with a more prominent BBB breakdown and might help elucidate the origins of some of the variability found in plasma Aβ studies.

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P0392 / #981

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

DEVELOPMENT OF SENSITIVE IMMUNOASSAY USING SMALL SYNTHETIC PEPTIDE FOR QUANTIFICATION OF AMYLOID-BETA 42 OLIGOMERS IN PLASMA FROM ALZHEIMER'S PATIENTS

Payel Bhattacharjee[1], Sanjana Patra[2], Ranit Pariyari[3], Siddharth Anand[4], Anirban Bhunia[3], Subhra Hui[2], Siddhartha Roy[3]
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Aims: The Amyloid beta (Abeta) oligomers, the major pathological agent of Alzheimer's disease (AD) are abundant in cerebrospinal fluid (CSF), but due to low abundance in plasma, it is difficult to detect using conventional ELISA. Due to poor availability, CSF is difficult to use for routine diagnosis. This study aims at developing a modified ELISA using small peptide which will facilitate detection of the Abeta oligomers in plasma.
Methods: The Abeta 42 peptide, its modified beta-sheet mimic (KLVFFKKKK) and few non-specific peptides were synthesized by solid-phase peptide synthesis method and the interaction of those peptides with Abeta 42 peptide were demonstrated using ThioflavinT assay, confocal and atomic force microscopy (AFM), nuclear magnetic resonance and fluorescence correlation spectroscopy. Initially plasma samples from age and sex-matched AD patients (n=12) and non-demented controls (n=10), were used for optimization of the immunoassay method to detect plasma Abeta 42 oligomer in absence and presence of KLVFFKKKK peptide.
Results: The KLVFFKKKK peptide was found to specifically promote Abeta 42 oligomerization (51.4 ± 7.8% increase) by reducing the lag-phase of the aggregation when added after 0.5 h during the course of aggregation at an equimolar concentration. The KLVFFKKKK peptide increased the aggregation, whereas, the beta-sheet breaker KLVFF peptide decreased the aggregation in a concentration dependent manner using ThT assay and AFM. The amplified signal (~2 fold increase) of Abeta oligomers in presence of KLVFFKKKK peptide was quantified at a concentration of 50-100 pg/ml in pooled plasma of AD patients using ELISA and increased fluorescence of oligomers were detected in confocal microscopy.
Conclusions: This method will be validated using more plasma samples from AD and healthy controls to use this cost-effective method for routine diagnostic purpose in future.

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P0393 / #1374

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

RELATIONSHIP BETWEEN CSF INTERLEUKINS, BRAIN DECLINE AND AD BIOMARKERS IN COGNITIVELY HEALTHY OLDER ADULTS

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Aims: Aging and Alzheimer's disease (AD) have been associated with chronic neuroinflammatory processes that may lead to neurodegeneration over time. We investigated in normal older adults (OA), whether baseline cerebrospinal (CSF) biomarkers of neuroinflammation (IL-6, IL-8) predict longitudinal brain atrophy, memory decline, and CSF core AD biomarkers changes over time; and whether the first two associations are moderated by baseline CSF beta-amyloid ($A\beta_{42}$) and phosphorylated tau ($p\text{-}tau_{181}$)
Methods: Longitudinal T1-weigthed images and cognitive assessments (up to 9.50 and 6.89 years), and baseline CSF biomarkers levels were collected in 220 OA. Hippocampus, entorhinal cortex, lateral ventricles were selected as regions of interest. Longitudinal CSF $A\beta_{42}$ and $p\text{-}tau_{181}$ were available up to 5.69 years (n=141). Linear mixed models (LME) were used to assess the effect of IL-6/IL-8 on brain change, memory performance and core AD CSF change. The interactions of IL-6/IL-8 with baseline core AD biomarkers were also assessed.
Results: CSF IL-6/IL-8 were not related to brain and memory changes over time ($p>0.05$). However, we found significant interactions between IL-6/IL-8 and CSF $p\text{-}tau_{181}/A\beta_{42}$ ratio: higher level of CSF IL-6/IL-8 were associated with more hippocampal atrophy over time (IL-6: $t=-2.84$, $p=0.004$; IL-8: $t=-1.98$, $p=0.04$) with higher $p\text{-}tau_{181}/A\beta_{42}$ ratio levels (Fig.1). Higher baseline CSF IL-6/IL-8 were associated with core AD biomarkers changes over time: higher IL-8 related to lower CSF $A\beta_{42}$ levels over time ($t=-2.630$, $p=0.009$), while higher IL-6 related to less CSF p-tau change ($t=-2.734$, $p=0.007$) (Fig.2), independently of

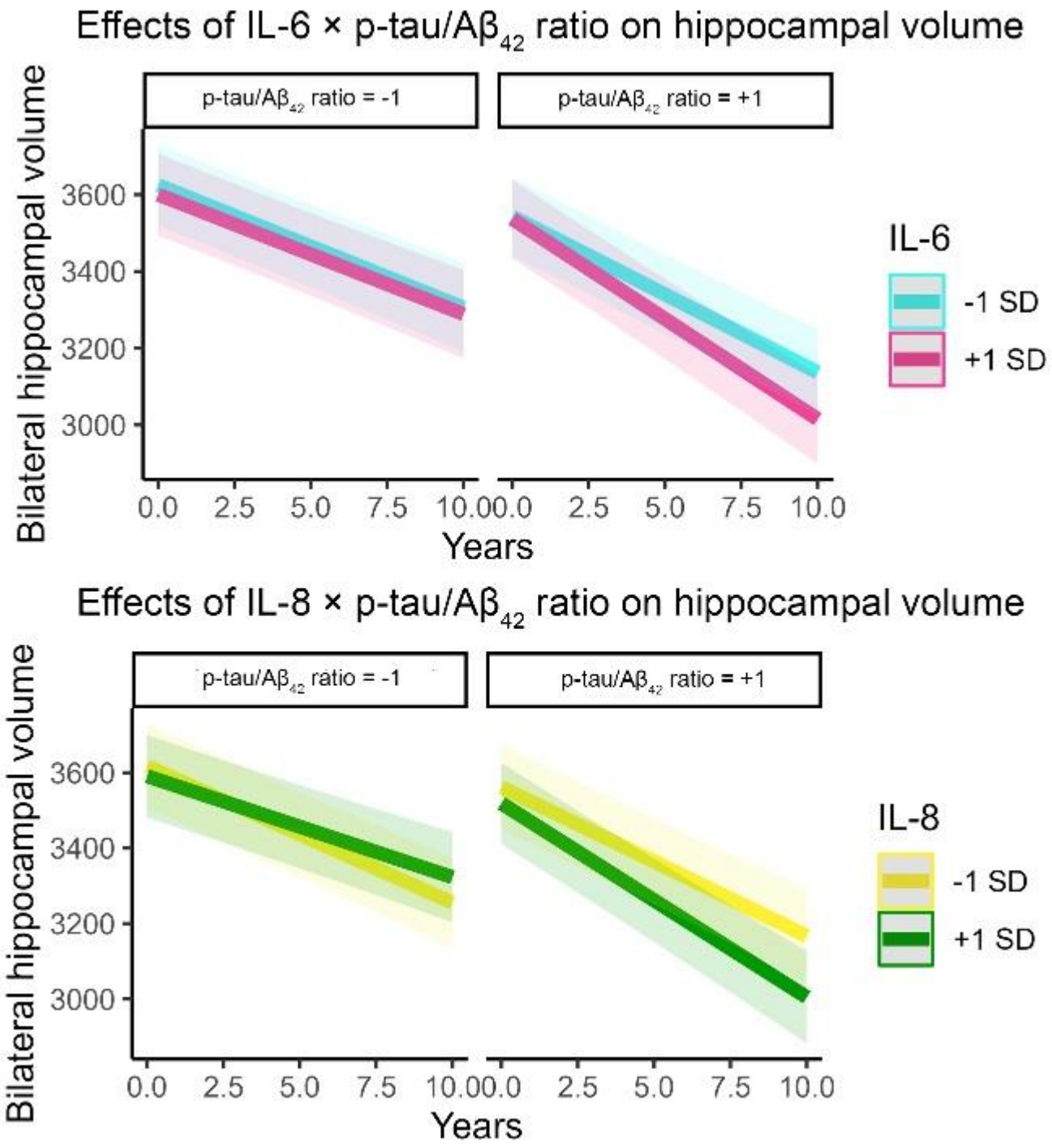

Fig.1 LME interactions CSF IL-6/IL-8 × p-tau$_{181}$/Aβ$_{42}$. Sex, baseline age, cohorts, intracranial volume and APOE4 as covariates; individual identifier as random effect. Green/magenta and yellow/cyan (high/low CSF values) reflect the trajectories of brain atrophy at ±1 SD of the CSF biomarker.

Aβ$_{42}$.

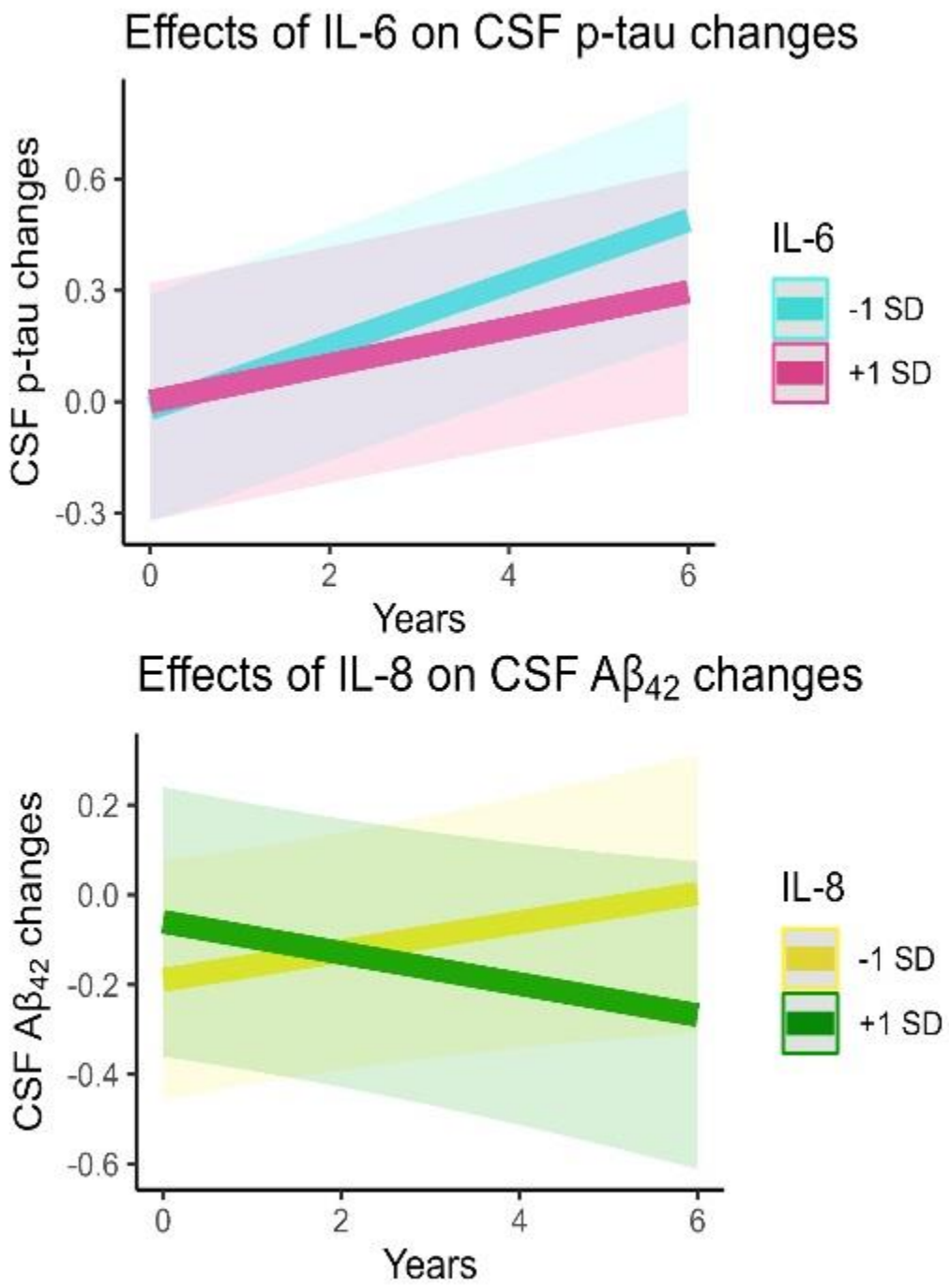

Fig.2 Linear relationship between CSF IL-6/IL-8 and change in core AD CSF biomarkers. Sex, baseline age, cohorts, and APOE4 as covariates; individual identifier as random effect. Green/magenta and yellow/cyan (high/low CSF values) reflect the trajectories of AD CSF biomarkers changes at ±1 SD of the CSF interleukins.

Conclusions: The interplay between CSF IL-6/IL-8 and early AD biomarkers accumulation predicts hippocampal atrophy over time in OA. Yet, CSF IL-6/IL-8 impact differently the trajectories of AD biomarkers changes, suggesting a dynamic association that might reflect different outcomes across stages of aging and AD.

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P0394 / #1448

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

A-T-N BASED BLOOD BIOMARKERS FOR PROOF OF CONCEPT STUDIES IN PRECLINICAL AD MODELS

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Aims: The interest in blood-based biomarkers has significantly increased the last years. Not only in diagnosis and follow up of Alzheimer's disease (AD) patients but also in clinical studies. Since translation between preclinical models and clinical data is of the utmost importance, we set out to investigate the presence of plasma biomarkers in preclinical AD mouse models according to the A-T-N framework.
Methods: Plasma and brain samples were collected from 9, 11 and 13 months old APP-London x TauP301S (APP-TauS), heterozygous TauP301S (hetTauS) and WT mice. In addition, in the hetTauS mice, plasma was repeatedly collected with an interval of 1 month, from an age of 8 till 13 months. IHC was performed on brain sections and ECL based immunoassays were conducted in plasma samples.
Results: IHC clearly indicated A-T pathology progression in our APP-TauS model, accompanied with an increase in microgliosis and astrocytosis. In mouse plasma, NF-L levels are clearly increased, suggesting that persistent neurodegeneration is ongoing. Next to longitudinal markers for neurodegeneration the ratio of Aβ42/40 declines with age, as is observed in AD patients. In addition, (p)Tau levels will be assessed in the obtained plasma samples. Analysis of samples obtained from hetTauS mice is currently still ongoing.
Conclusions: Here we show that A-T-N blood-based biomarkers can be detected in our combined APP and Tau mouse model. Blood biomarkers allow longitudinal follow-up of disease progression and therapeutic compound effects within the same subject, thereby lowering the number of animals needed in pre-clinical research as well. As a next step, we are extending the set of blood biomarkers to a second-generation APP knock-in model.

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P0395 / #1549

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

EVALUATION OF VAMP2 AS A CEREBROSPINAL FLUID BIOMARKER OF ALZHEIMER-RELATED RELATED SYNAPSE DEGENERATION IN THE SPIN COHORT

Alba Cervantes[1], Julie Goossens[2], Érika Sánchez-Aced[1], Natalia Valle-Tamayo[1], Laia Lidon[1], Oriol Dols-Icardo[1], Sònia Sirisi[1], Juan Fortea[1], Daniel Alcolea[1], Alberto Lleó[1], Eugeen Vanmechelen[3], Olivia Belbin[1]
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Aims: To compare the cerebrospinal fluid (CSF) levels of the synaptic protein, VAMP2, in cognitively normal controls, Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) patients.
Methods: VAMP2 was quantified using a Single Molecular Array assay (ADx Neurosciences) in CSF from cognitively normal controls (n=63), preclinical AD stage 1 (n=35) and 2 (n=8), prodromal AD (n=80), AD dementia (n=35) and in DLB (n=44) patients from the Sant Pau Initiative for Neurodegeneration cohort. The DLB patients were stratified by the AD biomarker, CSF ptau/Aβ42 ratio, into "pure DLB" (n=16) and "DLB+AD" (n=28) using our validated cut-off. To determine the best predictors of CSF VAMP2 in controls, AD and DLB groups, we performed backward entry linear regression including age, sex, *APOE* ε4 allele, CSF biomarkers (Aβ42, p-tau, NfL) and cognitive measures (MMSE, cued recall test, CDR-SOB) as predictor variables. We tested group differences using linear regression including age as a covariate.
Results: In AD, CSF VAMP2 was lower in AD stage 1 ($p<.001$) and elevated in AD stage 2 ($p=.048$) compared to controls. CSF VAMP2 was lower in pure DLB ($p=.002$) and elevated in DLB+AD ($p=.003$) compared to controls. CSF VAMP-2 discriminated pure DLB from DLB+AD (AUC=80.5). The best predictive model for CSF VAMP2 across the 3 clinical groups included CSF p-tau, cued recall test (immediate total recall) and CSF Aβ42 (controls; $r^2= .75$, $p<.001$, AD; $r^2=.87$, $p<.001$, DLB; $r^2=.84$, $p<.001$).
Conclusions: AD comorbidity was present in 60% of DLB patients. CSF levels of VAMP2 are associated with AD CSF biomarkers and episodic memory (amnesic deficit associated with AD) not only in AD, but also in DLB and controls. VAMP2 is a promising CSF biomarker of AD-related related synapse degeneration.

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P0396 / #1513

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

BRAIN AMYLOID, TAU AND WHITE MATTER HYPERINTENSITIES: ASSOCIATIONS WITH PLASMA GLIAL FIBRILLARY ACIDIC PROTEIN IN AN ASIAN COHORT WITH CONCOMITANT CEREBROVASCULAR DISEASE

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Aims: (1)Determine the associations between brain amyloid (Aβ), tau and white matter hyperintensities (WMH) with plasma GFAP (2)Examine the serial mediating effect of plasma GFAP and global cortical thickness on the association between (a)plasma P-tau181 and cognition or (b)WMH volume and cognition Plasma P-tau181 (brain tau burden) or WMH volume (WMH burden) →plasma GFAP (astrogliosis) →global cortical thickness (brain atrophy) →Global cognitive scores (cognition)
Methods: This Singapore-based study included 134 non-demented and 63 demented participants with plasma GFAP measured by Simoa. Brain Aβ and tau load were determined by Aβ positron emission tomography (PET) and plasma P-tau181 respectively. Global cortical thickness and WMH volume were measured by magnetic resonance imaging. Global cognitive scores were computed from five non-memory and two memory domains. Linear regression and mediation analyses were performed.
Results: In the overall cohort,both Aβ PET standardized uptake value ratio (SUVR) and plasma P-tau181 were positively associated with plasma GFAP. When stratified by Aβ status, in the Aβ- group,higher Aβ PET SUVR, P-tau181 and WMH volume were associated with increased GFAP. The mediating effects of GFAP and cortical thickness in the pathway from WMH burden to cognition were significant, after adjustment for age,gender, Aβ PET SUVR and P-tau181. In the Aβ+ group,only plasma P-tau181 were associated with plasma GFAP. After adjustment for age and gender, the mediating effects of GFAP and cortical thickness in the pathway from plasma P-tau181 to cognition were significant. In the non-demented subgroup, both Aβ PET SUVR and plasma P-tau181 were positively associated with plasma GFAP. When stratified by Aβ status, WMH volume and P-tau181 were associated with GFAP in the Aβ- and Aβ+ groups respectively.
Conclusions: Elevated plasma GFAP may reflect reactive astrogliosis due to AD and/or WMH burden.

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P0397 / #595

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

REFERENCE INTERVALS FOR PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE

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University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada

Aims: To create reference intervals (RI) for biomarkers of Alzheimer's disease and general neurodegeneration using a large population-based sample, specifically: the ratio of amyloid beta 42 over 40 (Aβ42/40), phosphorylated tau-181 (p-tau-181), neurofilament light (NF-L), and glial fibrillary acidic protein (GFAP).
Methods: 900 plasma specimens from male and female participants aged 3-79 years old were analyzed for Aβ42/40, p-tau-181, NF-L and GFAP. Specimens were obtained from the Canadian Health Measures Survey (CHMS), a national study that collects demographics, health questionnaires, clinical data and biospecimens from participants. Analysis was performed on the Quanterix Simoa HD-X analyzer using the Neurology 4-plex E and p-tau-181 assay. Discrete and continuous RIs were produced for each biomarker. Discrete RIs were produced according to the Clinical Laboratory Standards Institute guidelines (EP20-A3c). Continuous RIs were created using quantile regression.
Results: For discrete RIs, significant age partitions were determined for each biomarker, however, no significant sex partitions were found. The following ranges and age partitions were determined: Aβ42/40: 3-55y = 0.053-0.098 pg/ml, 55-80y = 0.040-0.090 pg/ml; p-tau-181: 3-12y = 1.4-5.6 pg/ml, 12-60y = 0.8-3.1 pg/ml, 60-80y = 0.9-4.0 pg/ml; NF-L: 3-40y = 2.6-11.3 pg/ml, 40-60y = 4.6-17.7 pg/ml, 60-80y = 8.1-47.1 pg/ml; GFAP; 3-10y = 47.0 to 226 pg/ml, 10-60y = 21.2-91.9 pg/ml, 60-80y = 40.7-228 pg/ml. Continuous RIs produced smooth centile curves across the age range, from which point estimates for any age can be calculated.
Conclusions: Both discrete and continuous RIs for plasma Aβ42/40, p-tau-181, NF-L and GFAP may help refine normative cut offs for each biomarker across the lifespan. This will serve as a critical step in the translation of these biomarkers from research to clinical implementation.

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P0398 / #1531

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PREANALYTICAL STABILITY OF PLASMA BIOMARKERS FOR ALZHEIMER'S DISEASE PATHOLOGY

Giovanni De Santis[1], Anita Sunde[2], Ingvild Alsnes[3], Dag Aarsland[2], Nicholas Ashton[1], Diego Tovar-Rios[2], Kaj Blennow[1], Henrik Zetterberg[1], Svein Kjosavik[4]
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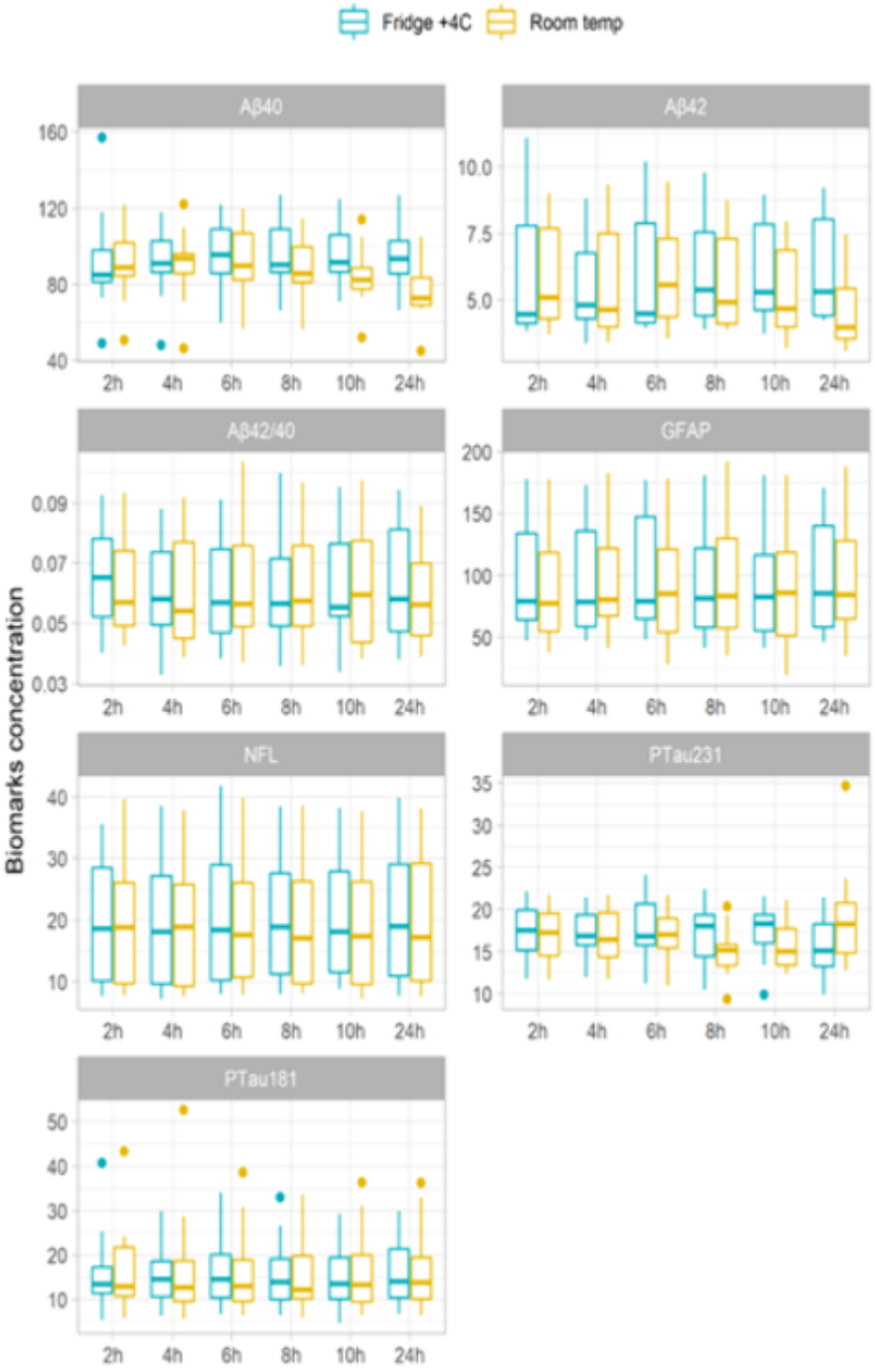
Aims: Plasma tests have demonstrated high diagnostic accuracy for identifying Alzheimer's disease pathology and can be key tools in clinical routine and therapeutic trials. To facilitate the transition to clinical utility, we assessed whether plasma storage duration and temperature affect the biomarker concentrations.
Methods: K2-EDTA plasma samples were stored for 24 hours (h) at +4°C and +18°C. Concentrations of phosphorylated tau 181 (p-tau181), phosphorylated tau 231 (p-tau231), glial fibrillary acidic protein (GFAP), amyloid-β 40 (Aβ40), amyloid-β 42 (Aβ42) and neurofilament light (NfL) were measured by in-house and commercial Single molecule array assays.
Results: P-tau181, p-tau231, NfL and GFAP concentrations showed no significant change when stored for 24h at +4°C and +18°C. Aβ40 and Aβ42 concentrations were stable for 24h at +4°C but declined when stored at +18°C for longer than 6h. This decline did not affect the Aβ42/Aβ40



ratio.

Conclusions: We found that K2-EDTA plasma samples can be stored for 24 hours at +4°C or at a room temperature of +18°C before ultra-low temperature freezing and still result in valid assay results for a panel of phosphorylated tau isoforms p-tau181 and p-tau231, Aβ42/Aβ40 ratio, GFAP, and NfL. Therefore, plasma samples for these biomarkers seem suitable for use in a primary care setting where sample storage and transportation to a facility with ultra-low temperature freezing can be achieved within this frame.

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P0399 / #1852

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CHANGES IN CLINICAL MANAGEMENT AS A RESULT OF ALZHEIMER'S DISEASE CEREBROSPINAL FLUID BIOMARKER TESTING

Mari Demarco[1,2], John Best[3], David Yang[2], Jacqueline Pettersen[4], Philip Lee[4], Alexander Henri-Bhargava[4], Clark Funnell[4], Howard Feldman[5], Dean Foti[4], Ging-Yuek R Hsiung[4], Haakon Nygaard[4]
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Aims: The value of the use of core Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers (i.e., amyloid-beta and tau proteoforms) in improving diagnostic accuracy has been well-established; however, the role of biomarkers in changing patient care pathways has not been comprehensively assessed. To overcome this knowledge gap, we assessed changes in clinical management as part of an observational study of the use of AD CSF biomarker testing in memory clinics in Canada.
Methods: The 'Investigating the Impact of Alzheimer's Disease Diagnostics in British Columbia' (IMPACT-AD BC) study examined the impact of AD CSF biomarker testing on clinical utility, personal utility and health care economics (www.impactAD.org). For the clinical utility arm, the primary outcome was the change in management (pre- v. post-biomarker results) in a composite measure of: 1) AD drug prescriptions, 2) other relevant drug prescriptions, 3) diagnostic procedures, and 4) referrals or counselling.
Results: Participants (n = 142) had a median age of 64 (IQR: 59-69), and 48% were female. At baseline, 6.3% of participants had subjective cognitive impairment, 54.2% mild cognitive impairment, and 39.4% dementia. Changes in overall clinical management occurred in 89% of cases: diagnostic procedures (65%), referrals or counseling (57%), use of available symptomatic AD drug therapies (39%), and use of other relevant drug therapies (19%). Specific changes within each of these categories was further assessed.
Conclusions: This observational study of the role of AD biomarkers in routine care has identified substantial changes in clinical management due to biomarker testing. Notably, the need for costly diagnostic imaging procedures was greatly reduced and appropriate drug utilization improved. Overall, the findings from this study reveal the value of biomarker testing for persons living with dementia, health care providers and the health system.

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P0400 / #2196

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

THE CEREBROSPINAL FLUID GLYCOPROTEIN NONMETASTATIC MELANOMA PROTEIN B (GPNMB) CONCENTRATION IN MILD COGNITIVE IMPAIRMENT (MCI)

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Aims: The most prevalent form of dementia in the world is Alzheimer Disease (AD), which is a common neurodegenerative disorder. Amyloid-β peptides, phosphorylated tau protein, and neuroinflammation are the disease's hallmarks. Seeking new biomarkers that can help in early AD detection is crucial due to the late appearance of the first disease's symptoms. A transmembrane endogenous protein called glycoprotein nonmetastatic melanoma protein B (GPNMB) is known to be involved in neuroinflammation.Although its precise function in AD is still not well understood. Recent research has verified the existence of GPNMB in the microglia, particularly close to amyloid plaques, in the brains of AD patients. Additionally, it has been noted that GPNMB may have a negative influence on macrophages' production of proinflammatory cytokines, making this glycoprotein potentially protective against neuroinflammation. Therefore, the goal of our study was to compare the concentration of GPNMB with traditional AD biomarkers in the cerebrospinal fluid of Mild Cognitive Impairment (MCI) patients and non-demented controls.
Methods: The concentrations of GPNMB were measured incerebrospinal fluid (CSF) of 17 MCI patients and 17 non-demented controls using multiplexing method. The levels of classical biomarkers, such as amyloid beta 1-42, amyloid beta 1-40, tau and pTau181 were assessed by enzyme-linked immunosorbent assay.
Results: GPNMB concentrations were significantly higher in MCI patients in comparison to non-demented controls.Moreover, increased CSF levels of GPNMB correlatedpositively with Tau, pTau181, age and negatively with Aβ-42/Aβ-40 ratio and MMSE in the whole study group.
Conclusions: The results of our study point to a potential involvement for GPNMB in the pathophysiology of AD. However, further research involving a bigger study group is required.

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P0401 / #788

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CHARACTERIZATION OF CSF BIOMARKER FOOTPRINT IN CEREBRAL AMYLOID ANGIOPATHY

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Aims: Emerging evidence suggests that cerebral amyloid angiopathy (CAA) shows a characteristic pattern of Alzheimer´s disease core biomarkers in cerebrospinal fluid (CSF). Our aim is to determine the differences in AD core biomarkers between CAA patients compared to healthy controls (HC) and patients with Alzheimer's disease (AD).
Methods: We recruited 105 participants from the Cognitive Decline and Neurovascular Units of Hospital del Mar (Barcelona) and classified them into three groups: (i) probable CAA patients using Boston 2.0 radiological criteria (n=24) (ii) patients with mild dementia due to AD (n=49, NIA-AA 2018 A+T+) and (iii) HC group (n=32). Initial protocol included a) a structural cranial 3T MRI to assess CAA-related lesions following modified Boston criteria; b) a neuropsychological battery c) a lumbar puncture for analysis of CSF concentrations of amyloid-beta 42 (Aβ42), amyloid-beta 40 (Aβ40), threonine-181-phosphorylated-tau (p-tau), and total-tau (t-tau) using Fujirebio's Lumipulse G1200. Afterwards, we compared CSF biomarkers of patients with CAA vs HC and patients with CAA vs AD using t-test.
Results: Mean age was 72.42 years (range: 55-85, SD±5.73) with no significant differences between groups; 56.2% were female. Compared to HC, CAA patients presented lower levels of CSF Aβ42, Aβ40 and Aβ42/40 ratio ($p<0.01$), and higher levels of p-tau and t-tau ($p<0.01$). Compared to AD, CAA patients showed lower levels of CSF Aβ42, Aβ40 ($p<0.01$), p-tau and t-tau ($p<0.01$) and higher Aβ42/40 and Aβ42/p-tau ratios ($p<0.01$).
Conclusions: Our study points to a specific CSF pattern of Aβ42, Aβ40, t-tau, and p-tau in CAA patients that might serve as fluid biomarkers of the disease. The sample size will be increased to corroborate these findings, as well as to carry out further studies.

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P0402 / #2105

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CONTRIBUTION OF PLASMA BIOMARKERS TO DEPICT BRAIN AMYLOID-BETA AND TAU PATHOLOGIES ACROSS THE AD CONTINUUM

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Aims: Compare the contributions of plasma biomarkers to identify the spatial distribution of Aβ and tau pathologies.
Methods: We included 138 cognitively unimpaired (CU) and 87 cognitively impaired (CI) individuals that had available plasma Aβ42/40, p-tau (at threonine 181, 217+, and 231), NfL, and GFAP from the McGill TRIAD cohort. We evaluated the significant additive effect of plasma biomarkers to the model containing demographics-only (sex and age) by comparing the difference in Akaike Information Criterion (ΔAIC). ROC curves tested the predictive performance of plasma biomarkers.

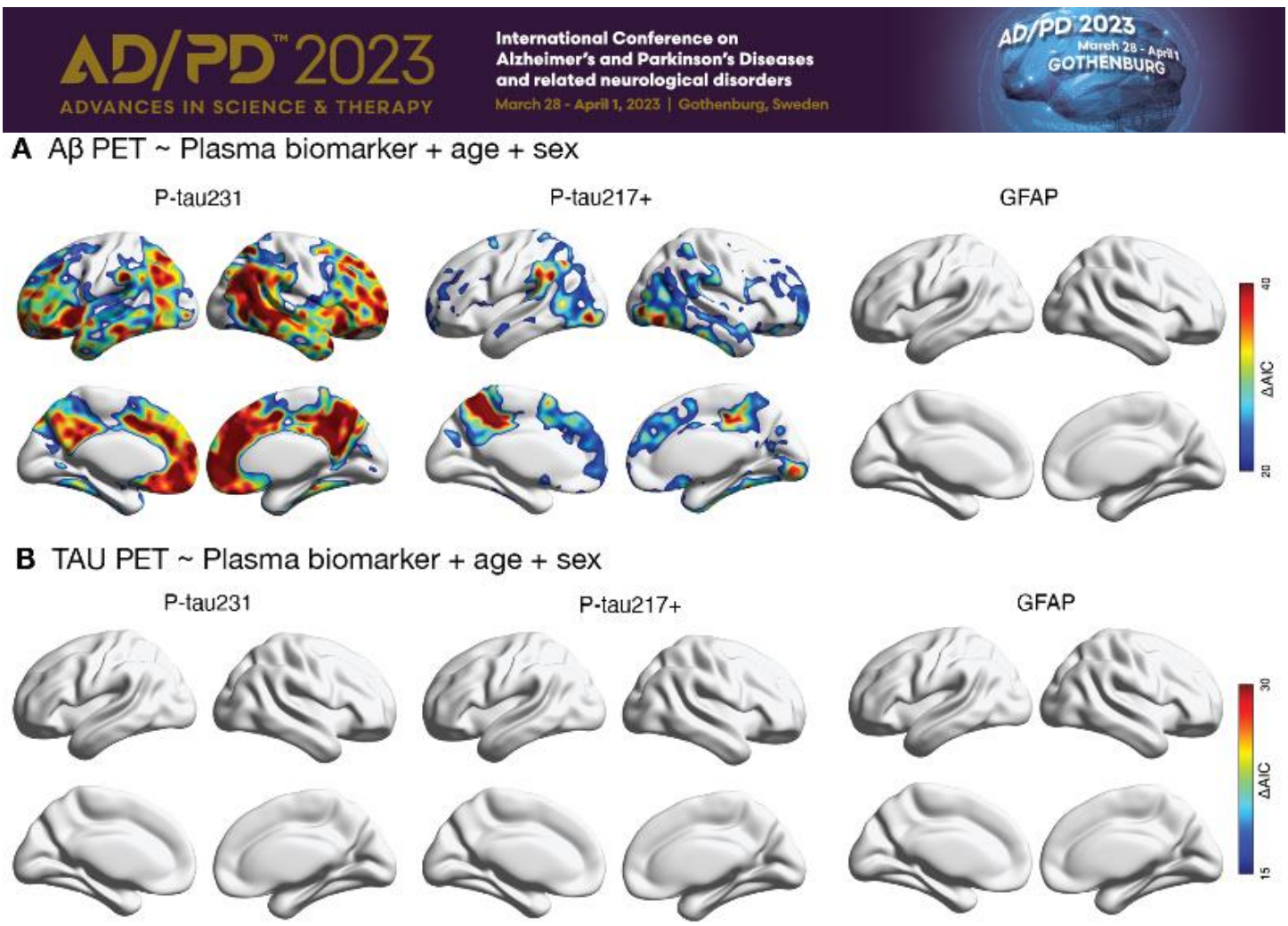

Figure 1 - Voxel-wise associations of Aβ and tau PET with plasma biomarker concentrations in Cognitively Unimpaired individuals. The figure shows voxel-wise AIC maps of regressions between PET SUVR and plasma markers after RFT correction for multiple comparisons at $P < 0.05$. Panel **A** shows the regions with a significant additive contribution between Aβ [^{18}F]AZD4694 PET and plasma markers. Panel **B** shows the regions with a significant additive contribution between tau [^{18}F]MK-6340 PET and plasma markers. The ΔAIC higher than 10 represents the significant additive effect of the plasma biomarker to the demographic-only model. Aβ-42/40 and NfL did not show significant additive effect to the demographic-only model.

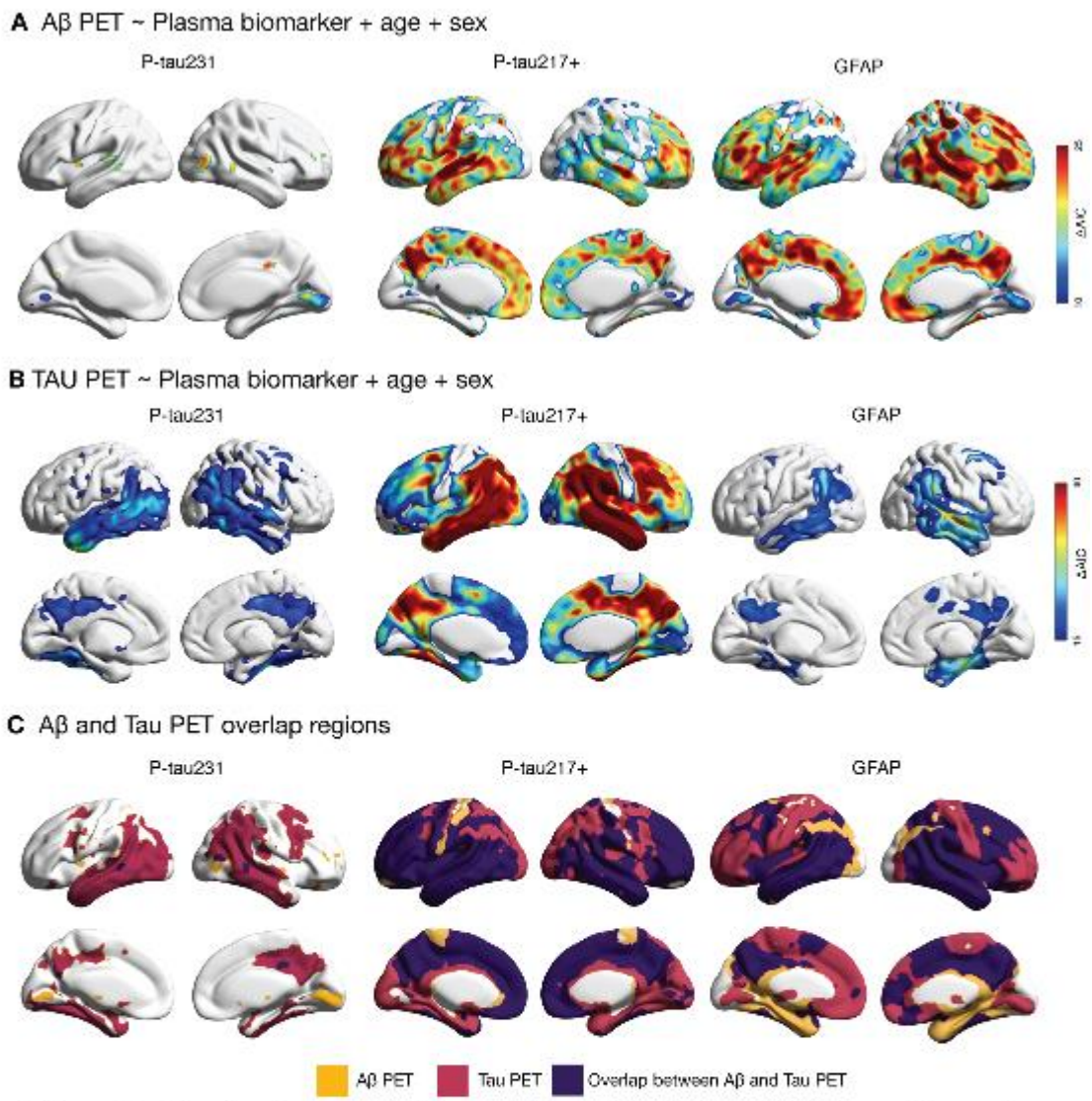

Figure 2 - Voxel-wise associations of Aβ and tau PET with plasma biomarker concentrations in Cognitively Impaired individuals. The figure shows voxel-wise AIC maps of regressions between PET SUVR and plasma markers after RFT correction for multiple comparisons at $P < 0.05$. Panel **A** shows the regions with a significant additive contribution between Aβ [18F]AZD4694 PET and plasma markers. Panel **B** shows the regions with a significant additive contribution between tau [18F]MK-6340 PET and plasma markers. Panel **C** shows the spatial distribution of the regions that significantly added to the demographics-only model and the overlap regions between Aβ and tau-PET of p-tau231, ptau217+, and GFAP. The ΔAIC higher than 10 represents the significant additive effect of the plasma biomarker to the demographic-only model. Aβ-42/40 and NfL did not show significant additive effect to the demographic-only model.

Results: Our results demonstrated that for the CU group, plasma p-tau231 was the biomarker that significantly added to the demographics-only model across the whole cortex (**Figure 1A**). In the CI group, plasma p-tau217+ had a significant additive effect for depict brain tau and Aβ pathology across the whole cortex (**Figure 2A-B**). Plasma p-tau231 and GFAP contribute to increase information about brain tau and Aβ pathology in regions comprising the brain's default mode network. P-tau181, Aβ42/40, and NfL did not significantly add to the demographics-only model in CU or CI groups. In CI, biomarkers were mostly associated with tau or Aβ PET in different brain regions with some regional overlap; 39% for p-tau217+ and 31% for GFAP (**Figure 2C**). The additive effect of plasma biomarkers on the demographics-only model was

confirmed by ROC curves (**Table 1**).

Table 1. Performance of plasma biomarker to predict Aβ-PET and tau-PET positivity.

	Predict Aβ-PET positivity		Predict tau-PET positivity	
	CU	CI	CU	CI
Biomarker	**AUC**	**AUC**	**AUC**	**AUC**
Adjusted for age, sex				
Aβ42/Aβ40	0.694	0.770	0.724	0.766[c]
	(0.562-0.827)	(0.615-0.925)	(0.612-0.836)	(0.637-0.895)
p-Tau231	0.862[a,d,f,g]	0.782[d]	0.781[a]	0.774[a,c]
	(0.784-0.940)	(0.654-0.887)	(0.718-0.905)	(0.668-0.8799)
p-tau217+	0.842[a]	0.808	0.751[a]	0.895[a,b,d]
	(0.744-0.941)	(0.665-0.952)	(0.693-0.932)	(0.859-0.991)
p-Tau181	0.735[b]	0.766	0.746	0.799[a]
	(0.635-0.836)	(0.638-0.894)	(0.649-0.843)	(0.700-0.898)
GFAP	0.793	0.847[a,g]	0.698[b]	0.839[a]
	(0.693-0.893)	(0.756-0.937)	(0.584-0.813)	(0.753-0.924)
NfL	0.699[b,c]	0.639[e]	0.708	0.699[e]
	(0.594-0.805)	(0.493-0.785)	(0.584-0.832)	(0.577-0.822)

DeLong test provided significant differences between groups with biomarker values $P < 0.05$: *a* compared with demographics; *b* compared to p-tau231; *c* compared to p-tau217+; d compared to p-tau181; *e* compared to GFAP; *f* compared to Aβ42/Aβ40 Simoa; *g* compared to NfL.

Conclusions: Our results support plasma p-tau231 as the more sensitive early marker of early Aβ deposition in AD, and p-tau217+ similarly represented both Aβ and tau PET in CI, and GFAP as biomarkers of Aβ deposition in CI individuals.

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P0403 / #1091

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ALZHEIMER DISEASE PLASMA BIOMARKERS IN INDIVIDUALS OF DIVERSE GENETIC ANCESTRAL BACKGROUNDS

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Aims: Plasma concentrations of phosphorylated threonine-181 of Tau (pTau181) and the ratio of amyloid beta isoforms Aβ40/Aβ42 are biomarkers for differential diagnosis and preclinical detection of Alzheimer disease (AD). Given differences in risk depending on genetics and environmental factors, generalizability of previous findings primarily from non-Hispanic White individuals is not guaranteed in individuals of diverse ancestries.
Methods: Therefore, we measured plasma pTau181 and Aβ40/Aβ42 ratio with Simoa chemistry in 362 Black Americans (88 AD, 274 cognitively intact controls), 750 Puerto Ricans (344 AD, 406 controls), 133 Peruvians (42 AD, 91 controls), 55 Cuban Americans (24 AD, 31 controls), and 238 non-Hispanic, European ancestry (65 AD, 173 controls). Samples were randomized, measured in duplicate, and non-parametric Kruskal-Wallis test used to detect differences in levels between cases and cognitively intact individuals (CI) overall and in each cohort. Receiver operating characteristic (ROC) area under the curve (AUC) were generated to test the predictive ability in each cohort.
Results: Overall and in every cohort, pTau levels in AD cases were significantly higher and Aβ40/Aβ42 significantly lower ($p \leq 0.05$) in cases than CI. ROC analyses including age, sex, pTau and Ab40/Ab42 levels showed that European and Black Americans had higher predictive value (AUC = 0.78) than in Hispanic cohorts (AUC = 0.73 in Puerto Ricans, 0.70 in Cubans, and 0.62 in Peruvians).
Conclusions: These results suggest AD biomarkers are generalizable across ancestries, though the predictive value may differ depending on specific backgrounds. Ultimately, combining genomic and biomarker data from diverse individuals will increase understanding of genetic risk and refine clinical diagnoses in individuals of diverse ancestries.

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P0404 / #1497

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PERFORMANCE OF PHOSPHORYLATED TAU-181, -217, -231 AND SNAP-25 IN A MIXED MEMORY CLINIC COHORT

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Aims: Cerebrospinal fluid (CSF) biomarkers greatly aid the diagnosis of patients presenting with cognitive decline. In this regard, Aβ42/40, phosphorylated tau181 (p-tau181) and total tau are widely utilized in clinical routine for Alzheimer's disease (AD) diagnostics. However, recent evidence suggests that additional p-tau species or assay designs may have greater diagnostic utility. In this study, we investigated several recently developed CSF biomarkers of tau phosphorylation and synaptic dysfunction in a mixed memory clinic cohort.
Methods: All CSF biomarkers were measured on the Single molecule array (Simoa) platform. P-tau181, p-tau217 and p-tau231 assays were developed at the University of Gothenburg. SNAP-25 was measured with a commercial kit (Quanterix). We included 145 participants of the mixed memory clinical cohort. The samples included healthy controls (n=16), patients with AD dementia (n=29), amyloid-positive mild cognitive impairment (MCI, n=27), amyloid-negative dementia (n=29), amyloid-positive dementia (n=29) and amyloid-negative MCI (n=15).
Results: All biomarker levels were highest in patients with clinical diagnosis of AD and were able to significantly differentiate between all MCI stages and AD. However, the largest mean fold-changes across diagnostic groups were observed for p-tau217, being >5.6-fold and >3.4-fold increase in AD patients compared to controls and patients with MCI, respectively. Interestingly, p-tau biomarkers were significantly lower in other dementias, despite having confirmed amyloid pathology (Figure
1).

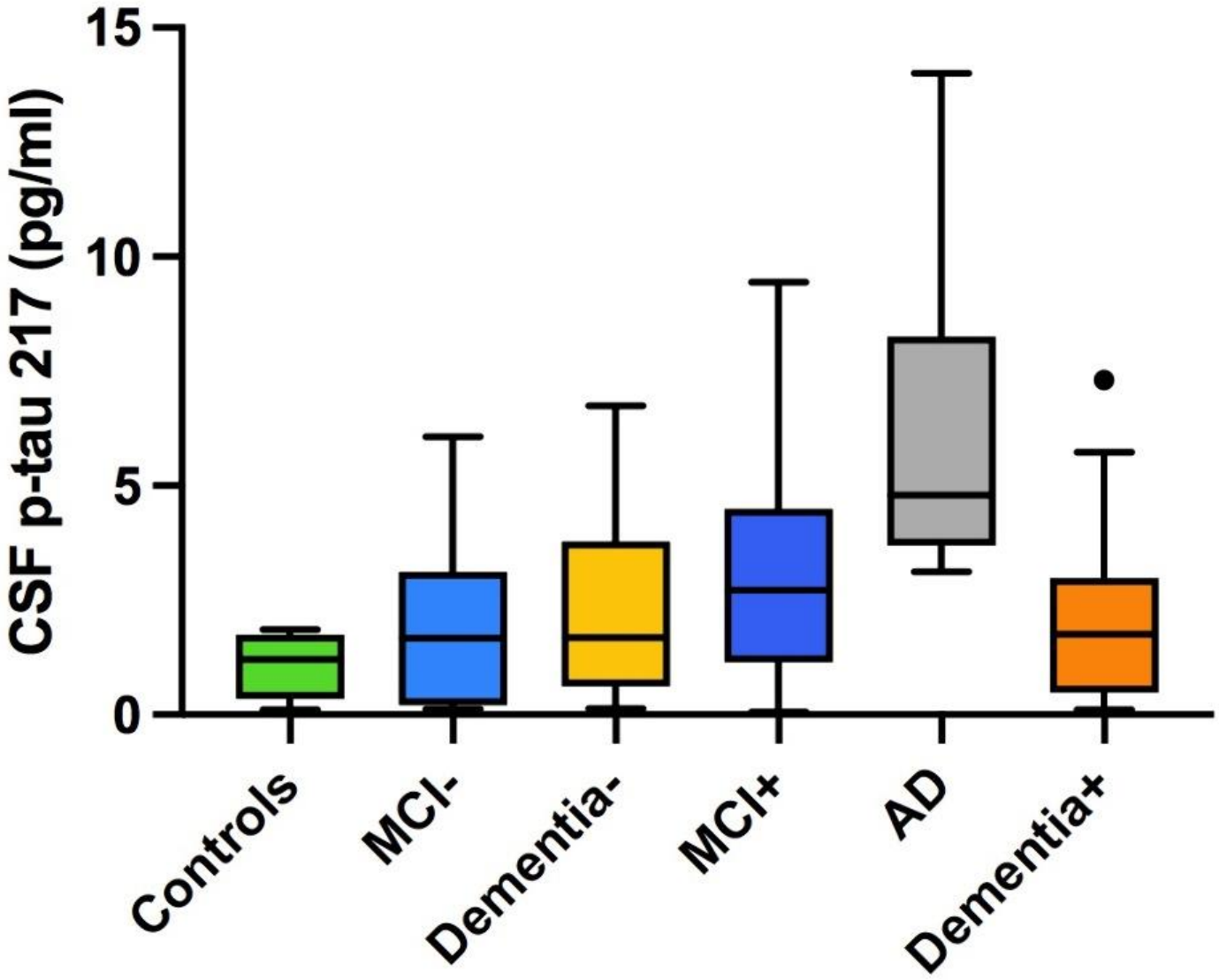

Figure 1: Concentration of CSF p-Tau 217 in CSF in the mixed memory clinic cohort.

Conclusions: All CSF p-tau biomarkers, and to a lesser extent SNAP-25, work well to identify AD in a mixed memory clinic cohort. However, the larger fold change of p-tau217 that occurs with the clinical features of AD dementia suggests it could be a more specific biomarker in memory clinic settings.

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P0405 / #2254

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PLASMA BIOMARKERS FOR ALZHEIMER'S DISEASE

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Aims: Despite inflammation and infection being implicated in Alzheimer's disease (AD), biomarkers of inflammation and infection for AD have not been identified. Thus, we explored whether plasma LL-37, the only cathelicidin antimicrobial peptide found in humans, could differentiate AD from controls. We also measured Serum Amyloid P component (SAP) in plasma to explore whether levels of this amyloid associated acute phase protein are altered in AD compared to controls.
Methods: Blood plasma samples from patients with AD (n=20) and age-matched controls (n=22) were used to quantify levels of LL-37 and SAP using Enzyme-Linked Immunosorbent Assays (ELISAs). A t-test was used to compare the differences between the groups.
Results: Patients with AD had an elevated plasma LL-37 level (AD: 30.4 (IQR 14.4, 74.9) ng/mL vs control: 12.4 (IQR 10.6, 16.0) ng/mL, $p<0.001$) but a reduced SAP level (AD: 19.9 (IQR 15.6, 22.9) µg/ml vs control: 25.3 (IQR 22.2, 33.2) µg/ml, $p=0.003$) compared to controls.
Conclusions: These findings suggest that AD patients have elevated levels of LL-37 antimicrobial peptide compared to controls and show that AD patients have decreased levels of SAP which would reduce the capacity of SAP to bind amyloid in blood compared to controls.

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P0406 / #330

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

THE IMPACT OF DEMOGRAPHIC FACTORS ON PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE IN COGNITIVELY UNIMPAIRED OLDER ADULTS

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Aims: Objectives: There is increased interest in the use of plasma biomarkers of neurodegeneration as categorizing or outcome variables due to their cost-effective and less invasive nature. The development of reference ranges would significantly increase their utility. A number of factors not directly related to pathological changes may impact the level of these markers. The current study evaluates the effect of age, sex and education on levels of Aβ40, Aβ42, total Tau and Neurofilament Light in samples of cognitively unimpaired Mexican Americans and Non-Hispanic Whites.
Methods: The levels of the plasma biomarkers for 2407 community based, cognitively unimpaired older adults (Mexican Americans= 775; Non-Hispanic Whites =1632) was determined using Simoa technology. The impact of age, sex and education was assessed using linear regression for each of the biomarkers separately for the two ethnic groups.
Results: For Mexican Americans the significant predictors were Aβ40 education (p=.032); Aβ42 age (p=.037); total tau age (p=.012)) and NfL education (p=.028). For Non-Hispanic Whites the significant predictors were; Aβ40 age (p=.004) and education (p=.000), Aβ42 age (p=.000) and education (p=.000); age (p=.000) and education (p=.000) predicted total tau and education (p=.000) predicted NfL.
Conclusions: The current results show that demographic factors impact the level of plasma biomarkers and that the impact varies between ethnic groups. Education which is seldom considered in utilizing these biomarkers, has a significant impact on all four markers for Non-Hispanic Whites and on NfL for Mexican Americans. Developing useful reference ranges will need to take into consideration demographic factors.

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P0407 / #1870

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PHARMACODYNAMIC EFFECTS OF THE S2R MODULATOR CT1812 IN ALZHEIMER'S DISEASE (AD) PATIENTS OBSERVED IN A META-ANALYSIS OF CSF PROTEOMES FROM SPARC AND SHINE PART A

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Aims: A meta-analysis of CSF proteomes from Alzheimer's disease (AD) patients from the SHINE and SPARC clinical trials was performed to identify pharmacodynamic biomarkers of the sigma-2 receptor (S2R) modulator CT1812.
Methods: SHINE (part A) and SPARC were randomized double-blinded placebo-controlled trials assessing the effects of two doses of CT1812 (100 mg, 300 mg) given once daily for 6 months in mild to moderate AD patients. Previously, tandem-mass tag mass spectrometry (TMT-MS) was performed on baseline and end of study CSF samples from each trial. CSF proteome data from SHINE-A (NCT03507790; N=18) and SPARC (NCT03493282; N=18) were combined (N=36 patients) following removal of batch effects to increase statistical power needed for a robust analysis. Treatment effects were assessed ($p \leq 0.05$) through differential expression and pathway analyses, using MetaCore and STRING, and via weighted gene co-expression network analysis (WGCNA).
Results: A total of 2,102 proteins were detected across all CSF samples in both trials. Differential expression analyses identified proteins significantly altered (one-way ANOVA; $p \leq 0.05$) by CT1812, compared to placebo. Some biomarkers were altered ($p<0.05$) to a similar degree in both dose groups, whereas others appeared dose-dependent. A subset of the proteins significantly altered by treatment with CT1812 compared to placebo ($p \leq 0.05$) overlapped with known AD biomarkers, including proteins known to regulate amyloid beta pathology (SPON1), and others genetically linked to AD (clusterin (CLU). Pathway analysis identified statistically significant pathways ($p \leq 0.05$) altered by CT1812 and pointed to an impact of CT1812 in regulating amyloid biology, inflammation, and synaptic function, supportive of a synaptoprotective mechanism of action.
Conclusions: This meta-analysis identified pharmacodynamic biomarkers altered by CT1812 in patients participating in two AD clinical trials. These findings may help elucidate pathways involved in CT1812's mechanism of action.

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P0408 / #2155

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LONGITUDINAL DYNAMICS OF CEREBROSPINAL FLUID ABETA, PTAU, AND STREM2 REVEAL PREDICTIVE PRECLINICAL TRAJECTORIES OF ALZHEIMER'S PATHOPHYSIOLOGY

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Aims: The most effective treatments for Alzheimer's disease (AD) will be those that prevent disease manifestation. Such preventative treatments, however, are not available due to the lack of effective and reliable biomarkers that can accurately detect high risk patients prior to symptom onset. Cerebrospinal fluid (CSF) biomarkers for amyloid beta (ABeta), phosphorylated-tau (pTau) and sTREM2 have the potential to detect preclinical changes in AD. However, the vast majority of studies evaluating these three CSF biomarkers have focused on univariate and cross-sectional analyses, which fail to capture the dynamic and multifactor complexity of AD. Hence, integrated multivariate longitudinal analysis of CSF ABeta, pTau, and sTREM2 may dramatically increase their predictive potential. We conducted multivariate analyses of longitudinal CSF ABeta, pTau, and sTREM2 to determine if their joint covariance would reveal hidden subgroups of older adults who exhibit either high risk trajectories of AD pathology or low risk trajectories of neurotypical aging. We hypothesized that multiple distinct subgroups would be identified according to their CSF risk trajectories.
Methods: We identified patients who have fully harmonized multifactor longitudinal CSF ABeta, pTau, and sTREM2 from the Alzheimer's Disease Neuroimaging Initiative. Following data curation, we implemented a novel multivariate data integration technique known as similarity network fusion to identify networks of individuals who cluster together according to their multivariate patterns of longitudinal change in CSF.
Results: Consistent with our hypothesis, we identified multiple clusters of older adults grouped according to distinct CSF risk trajectories. Post-hoc analysis further confirmed that the dynamic CSF trajectories for the high risk individuals are associated with higher genetic and cognitive risk.
Conclusions: Our findings indicate the utility of tracking dynamic simultaneous changes in multiple CSF biomarkers to better predict preclinical trajectories of AD.

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P0409 / #2110

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LEVELS OF NICASTRIN ARE INCREASED IN ALZHEIMER'S DISEASE CEREBROSPINAL FLUID

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Aims: Previous studies demonstrated that presenilin-1 (PS1), the active component of the intramembrane γ-secretase complex can be detected as soluble heteromeric aggregates in cerebrospinal fluid (CSF). The γ-secretase components, APH-1 (anterior pharynx-defective 1) and PEN-2 (presenilin enhancer 2), co-exist within these CSF complexes, while nicastrin is not detected. Nicastrin plays a role in the complex regulation, and substrate recognition, being the unique γ-secretase component that is a Type I, single-pass, and not a multi-pass transmembrane protein. Here, we aim to characterize and compare the levels of CSF nicastrin in AD and non-AD control patients.
Methods: Nicastrin species were determined in the CSF by western blotting employing antibodies against the ectodomain and the intracellular domain to distinguish cleaved fragments from proteolytically unprocessed full-length forms, also present in human fluids. All samples were also analyzed for core AD CSF biomarkers. We also assessed whether CSF nicastrin and PS1 are present in extracellular vesicles (EVs).
Results: Here, we show that nicastrin is present in CSF as full-length species of 130 and 105 kDa, and C-terminal truncated fragments of 110 kDa. We demonstrated that nicastrin full-length species are increased in AD patients in comparison with non-AD controls, and that the levels of the 105 kDa form positively correlate with p-Tau levels in AD patients. Nicastrin was found to be present in extracellular vesicles, different from PS1.
Conclusions: The increased levels of nicastrin in the CSF of AD patients confirmed the potential alteration of γ-secretase subunits during pathology progression. Further studies are required to evaluate if these proteins could act as biomarkers of diagnosis or progression of the disease.

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P0410 / #1494

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

FOOD INTAKE IS INFLUENCING THE CONCENTRATION OF AD-RELATED PLASMA BIOMARKERS IN HEALTHY ADULTS

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Aims: Blood biomarkers are considered to indicate Alzheimer's disease (AD) pathophysiology in an accurate, cost-effective and non-invasive manner (1, 2). However, influencing peripheral factors have yet not been well studied. Therefore, we aimed to investigate the influence of food intake on AD-related biomarker concentrations in healthy adults.
Methods: 111 participants (60±7 y, 64 females) underwent a standardized test meal (Postprandial group, PG; Boost High Protein drink, Nestlé). Plasma neurofilament light (NfL), glial fibrillary acidic protein (GFAP), amyloid-beta (Aβ) 40 and 42, and phosphorylated tau (pT) 181 and 231 concentrations were measured via ultra-sensitive Single molecule array assays fasting and 15, 30, 45, 60, 120, and 180 min after drink ingestion. In addition, we followed a fasting subgroup (n=26) over the same time period (Fasting group, FG). Statistical analysis was performed using two-sided t-tests and linear mixed models with polynominal spline of degree 3.
Results: In the PG group, all biomarkers changed significantly over time after drink ingestion with a decrease in the early postprandial phase and a subsequent increase. Moreover, a significant difference in the time course of NfL, GFAP, Aβ42/40, pT181, and pT231 levels between FG and PG was found (all $p<0.05$).
Conclusions: Our data suggest that the concentration of AD-related biomarkers is altered by food intake. We assume that this should be taken into account when using AD-related biomarkers for screening and diagnostic purposes.

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P0411 / #2210

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PLASMA BIOMARKER PROFILES IN A SWEDISH COHORT OF AUTOSOMAL DOMINANT ALZHEIMER DISEASE

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Aims: The aim was to explore plasma biomarkers in mutation carriers (MC) compared to non-carriers (NC) in autosomal dominant Alzheimer disease (ADAD) over the disease continuum.
Methods: Mutation carriers (n=33) and non-carriers (n=42) in a Swedish cohort of ADAD (*APP* p.KM670/671NL, *APP* p.E693G and *PSEN1* p.H163Y) were selected for inclusion. The longitudinal analysis included 164 samples (87 for MC and 77 for NC) from the same 75 individuals. The mean number of plasma sampling occasions per subject was 2.3 ± 1.6 (mean ±SD), with a range of 1 to 8, and the mean total follow-up time was 6.1 ± 7.5 (range of 0 to 23) years. Plasma phosphorylated tau (P-tau181), total tau (T-tau), neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) concentrations were measured with a single-molecule array method. Cross-sectional analyses and explorative longitudinal analyses were performed, applying mixed models. Plasma biomarkers were also correlated to Alzheimer disease core biomarkers in the CSF.
Results: Longitudinal analyses confirmed that plasma P-tau181, NfL and GFAP concentrations were higher in MC compared to NC. This change was initiated in the presymptomatic phase. GFAP concentrations were increased approximately 10 years before estimated symptom onset, followed by increased levels of P-tau181 and NfL closer to expected symptom onset. Plasma P-tau181 levels were correlated to levels of P-tau181 and T-tau in the CSF.
Conclusions: The increase of plasma GFAP concentration is an early event that might reflect Alzheimer disease pathology up-stream to accumulation of hyperphosphorylated tau and neurodegeneration. The findings need additional validation in a larger cohort.

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P0412 / #2662

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PROTEIN BIOMARKERS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE CEREBROSPINAL FLUID IDENTIFY EARLY CHANGES IN BRAIN GLUCOSE METABOLISM AND THE MATRISOME

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Aims: We aimed to better understand how pathological changes in Alzheimer's disease (AD) evolve over the course of the disease as reflected by cerebrospinal fluid (CSF) biomarkers.
Methods: 59 proteins were measured in 286 autosomal dominant AD (ADAD) mutation carriers and 184 non-carriers in the Dominantly Inherited Alzheimer Network (DIAN) by targeted mass spectrometry. Baseline measurements for each subject were placed in a longitudinal framework by the estimated year of disease onset (EYO). We used a Bayesian regression model to estimate protein levels in mutation carriers and non-carriers across EYO intervals. The proteins were mapped to different AD brain pathologies as recently described in a consensus proteomic brain co-expression network of late-onset AD.
Results: 33 proteins out of the 59 targeted for measurement were found to be different between mutation carriers and non-carriers at any EYO time point, with most proteins increased in mutation carrier CSF. Proteins derived from the brain matrisome co-expression module associated with Aβ deposition were among the earliest to change in mutation carriers—earlier than the absolute decreased levels of Aβ42 and nearly 30 years prior to symptom onset—followed by synaptic proteins and proteins associated with glucose metabolism. Multiple proteins associated with inflammation were noted to increase concomitantly with decreases in brain tissue and metabolism as assessed by MRI and metabolic imaging. Decreased levels of neurosecretory proteins were found to be associated with cognitive impairment and functional decline.
Conclusions: Proteomic approaches are able to identify novel brain-based biomarkers for AD. Measurement of these AD biomarkers in DIAN provides insight into the natural history of AD pathophysiology, which begins approximately three decades prior to the onset of cognitive symptoms in ADAD.

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P0413 / #761

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LOWER DIAGNOSTIC ACCURACY FOR ALZHEIMER'S DISEASE WITH AGE-ADJUSTED CSF T-TAU AND NFL

Stephanie Knudtzon[1,2], Kaja Nordengen[3,4], Per Selnes[3], Lene Pålhaugen[3,4], Jacob Espenes[1,2], Knut Waterloo[1,2], Tormod Fladby[3,4], Bjørn-Eivind Kirsebom[1,2]
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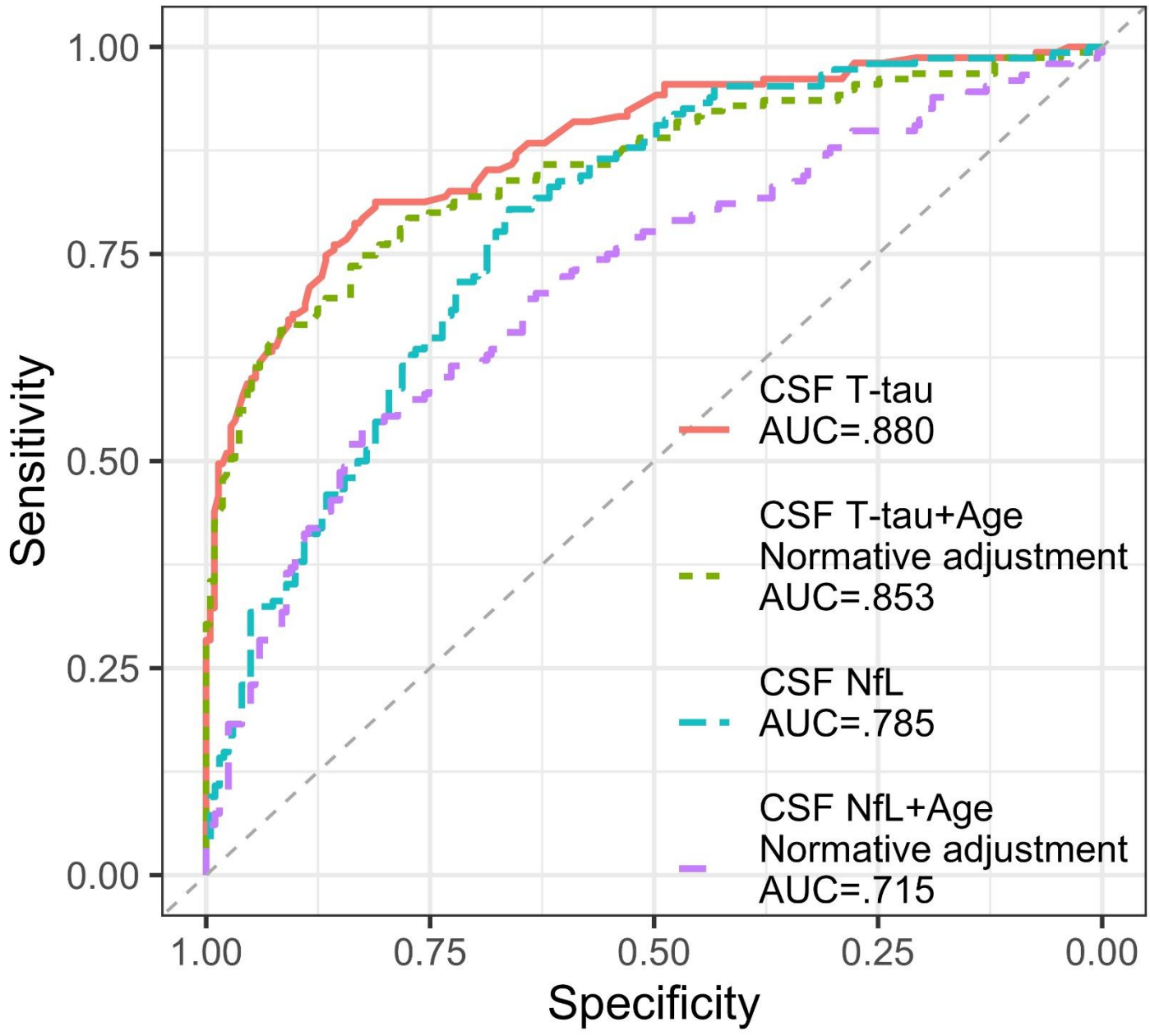
Aims: Cerebrospinal fluid (CSF) total-tau (t-tau) and neurofilament light chain (NfL) are markers of neurodegeneration (ND) and increased in Alzheimer's disease (AD). However, markers increase with ageing and the use of age-adjusted cut-offs to determine pathological levels have been suggested. We here sought to develop and validate age-adjusted norms for CSF t-tau and NfL based on cognitively healthy adults, and to assess a potential improvement in diagnostic accuracy of CSF $A\beta_{42/40}$ pathology.
Methods: We developed age-adjusted regression-based norms for CSF t-tau and NfL in cognitive normal adults (CN, n=76, adults without Aß pathology and no experience of subjective cognitive decline (SCD)) and validated them in an independent sample of CN (n=142, also without Aß pathology, but reporting experience of SCD while still performing normal on objective neuropsychological tests). Furthermore, we compared models with or without age-adjustments in receiver operating characteristic curve (ROC) analyses to determine which model offered the best diagnostic accuracy for CSF $A\beta_{42/40}$ pathology (n=155).
Results: Higher age was associated with increased CSF t-tau and NfL levels in the CN normative sample, and both were adjusted for age in the CN validation sample. However, age-adjustments did not improve diagnostic accuracy of CSF $A\beta_{42/40}$ pathology.



Conclusions: Although fluid ND markers increase with age in cognitively healthy adults, this may relate to underlying disease processes and using cut-offs based on age-adjusted norms may obscure associated ND.

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P0414 / #1895

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

RETICULON-4 AS A POTENTIAL BIOMARKER IN THE DIFFERENTIAL DIAGNOSIS OF NEURODEGENERATIVE DISEASES

Agnieszka Kulczynska-Przybik[1], Julia Doroszkiewicz[1], Maciej Dulewicz[1], Renata Borawska[1], Ala Litman-Zawadzka[1], Agnieszka Slowik[2], Barbara Mroczko[1]
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Aims: Neurodegenerative diseases (NDs) are the top global causes of mortality worldwide. Diagnostic approaches are constantly being sought to improve these disorders' early diagnosis and differentiation. Alzheimer's (AD) and Parkinson's disease (PD) are the most common NDs. It is suggested that Reticulon-4 (RTN4) could play an essential role in the pathogenesis of both conditions. However, little is known about the RTN4 concentration changes in the cerebrospinal fluid (CSF) patients with AD and PD. Therefore, we aimed to assess and compare RTN levels in CSF patients with NDs and subjects from the control group. We also evaluated a relationship between CSF concentrations of RTN4 and other markers indicating the development of dementia disorder.
Methods: The concentrations of RTN4, α-synuclein, amyloid beta 1-42 (Aß-42), amyloid beta 1-40, Tau, as well as pTau181 were measured in cerebrospinal fluid patients with neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's disease (PD), as well as individuals from control group by means of quantitative enzyme-linked immunosorbent *assay* (ELISA).
Results: The CSF concentration of RTN4 was significantly increased in AD and PD groups in comparison with the control group. Furthermore, in a group of patients with AD it was observed statistically significant higher CSF levels of RTN4 than in the group of individuals with PD. Additionally, the CSF levels of RTN4 significantly correlated with tau proteins in AD group. Similarly, in patients with PD the association between RTN4 Tau, pTau181, and α-synuclein was observed.
Conclusions: Our preliminary study indicates a potential role of RTN4 protein in the pathology of AD and PD diseases, and its potential usefulness as a candidate biomarker for NDs, but these investigations need to be further clarified.

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P0415 / #1044

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

MULTIOMICS-BASED PREDICTION OF TRAJECTORIES OF GLOBAL COGNITIVE FUNCTIONING IN THE ADNI COHORT

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Aims: Cognitive impairment is the first manifestation of dementia. However, the rate of changes in cognitive function varies between individuals and unraveling heterogeneity in the trajectory of cognitive decline and dementia is crucial for adopting a suitable treatment. In this study, first, we aimed at identifying distinct trajectories of cognitive function, and next we used extensive machine learning approaches on CSF proteomics, plasma lipidomics and metabolomics data for classification of the trajectories identified in the initial analysis.
Methods: Three-year trajectories of global cognitive functioning were defined using six longitudinal measurements of the Mini-Mental State Examination (MMSE) on 640 individuals in the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort. To compute the trajectories of cognitive function, we applied Latent Class Mixed Modeling adjusted for age, sex, and education. We used multiple machine learning algorithms, including Random Forest, Conditional Random Forest, Generalized Linear Models, and (sparse) Partial Least Square Discriminant Analysis. The best performing models were selected based on a set of prediction performance metrics.
Results: We identified three distinct trajectories of global cognitive function: Stable, Slow decliner (SD) and Fast Decliner (FD). The Random Forest algorithm performed best in prediction of the Stable versus Decliners (SD + FD), using the combined omics data. (AUC: 0.83 and a Matthews Correlation Coefficient (MCC): 0.59). The model is based on seven molecular features, among which we found lipids belonging to the ceramide pathway which has already been implicated in cognitive impairment and AD.
Conclusions: Defining trajectories of individuals with distinct patterns of cognitive changes over time, paired with omics-based data, will allow the identification of new biomarkers for early detection of dementia. Additionally, they might unveil novel subtype-specific molecular pathways which can contribute to more precise drug discovery processes.

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P0416 / #1348

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ANTE-MORTEM PLASMA LEVELS CORRELATE WITH POST-MORTEM AMYLOID-BETA LOAD IN BRAINS OF CENTENARIANS

Linda Lorenz[1,2,3], Susan Rohde[1,2,3,4], Patricia Fierro-Hernández[1,4], Mariam Gouda[5], Annemieke Rozemuller[4], The Netherlands Brain Bank[6], Philip Scheltens[2], Jeroen Hoozemans[4], Charlotte E. Teunissen[5], Henne Holstege[1,2,3,7]
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Aims: The applicability of Alzheimer's disease (AD)-associated biomarkers as an *in-vivo* proxy for neuropathological changes in the brain may be age-dependent. Here we questioned whether *post-mortem* Amyloid-Beta *load* and Amyloid-Beta *spread* correlate with *ante-mortem* AD-associated plasma biomarker levels in centenarians. This may shed light on the applicability of plasma biomarkers in the oldest-old.
Methods: *Ante-mortem* plasma levels of Amyloid-Beta-40, Amyloid-Beta-42, pTau181, NfL and GFAP, with matched *post-mortem* brain tissue were available for 46 centenarians of the Dutch 100-plus Study. We evaluated Amyloid-Beta pathology in donated brains using: I) Thal staging for the spatiotemporal spread of Amyloid-Beta; and II) a quantitative approach for cortical Amyloid-Beta load. Additionally, we evaluated spatiotemporal spread of NFT using Braak stages. The median time between blood and brain donation was 1.2 years (IQR:0.45-1.73), median age at brain donation was 103.5 years (IQR:103.1-104.0).
Results: We observed moderate correlations between *post-mortem* brain Amyloid-Beta load and *ante-mortem* plasma Amyloid-Beta-40 levels (r=0.31, CI:0.01-0.56, *P*=0.036), Amyloid-Beta-42/40 (r=-0.34, CI:-0.57--0.05, *P*=0.020), and strong correlations with plasma pTau181 levels (r=0.51,CI:0.25-0.71, *P*<0.001). Plasma pTau181 levels also correlated with Thal phases (r=0.44, CI:0.23-0.62, *P*=0.002), but not Braak NFT stages (r=0.16, CI:-0.13-0.43, *P*=0.274).
Conclusions: In the oldest-old, *ante-mortem* plasma biomarkers can predict *post-mortem* brain Amyloid-Beta load, and to a lesser extent Amyloid-Beta spread. Our findings indicate robustness of *in-vivo* plasma biomarkers to predict neuropathological changes, even in the non-demented oldest-old. **References**

[1]Rohde et al., in prep
[2]DOI:10.1002/alz.12639

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P0417 / #1006

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

EFFECT OF AGE, COGNITIVE STAGE, SEX AND APOE GENOTYPE ON PLASMA GFAP LEVELS IN A MEMORY CLINIC POPULATION

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Aims: Plasma glial fibrillary acidic protein (GFAP) is an emerging AD biomarker. We aimed to study how plasma GFAP changed with age, clinical status, sex, and apolipoprotein E (APOE) genotype in a memory clinic population.
Methods: Three hundred and twenty-five individuals ranging from cognitively unimpaired to dementia from the Geneva Memory Center. Plasma GFAP was measured using single-molecule array (Simoa) technology. The effect of age, cognitive stage, sex and APOE genotype on plasma GFAP was assessed using linear models, one for each factor and one with all factors.
Results: We found a very strong effect of age and cognitive stage ($p<0.0001$), a strong effect of APOE genotype ($p=0.0003$), and a weak effect of sex ($p=0.05$) on plasma GFAP levels. When all factors were entered into one model, the effect of APOE genotype disappeared ($p>0.05$) while that of sex emerged ($p<0.001$). Finally, this model explained 50% of the total variance of plasma GFAP.
Conclusions: These results show that in a memory clinic population, plasma GFAP levels are influenced by age, sex, and APOE genotype. The development of future GFAP cut-offs for the diagnosis of AD should take these factors into account.

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P0418 / #436

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

SELENIUM COMPOUNDS AND FE2+/FE3+-RATIO IN SERUM AND CEREBROSPINAL FLUID REVEAL MARKERS FOR OXIDATIVE STERSS AND ARE ASSOCIATED WITH LOW MMSE-SCORES

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Aims: Objectives: In the central nervous system, imbalances of Se- and Fe-species are implicated in pathophysiology of neurodegenerative diseases. Elevated concentrations of inorganic Se species, for instance, were associated with an increased risk of neurodegeneration. Other Se compounds may have beneficial and adverse effects on human health. In neuronal tissue elevated Fe^{2+}/Fe^{3+}-ratio is closely related to oxidative stress (OS). Aim of this study was to apply Se- and Fe^{2+}/Fe^{3+}-redox speciation analysis to paired serum/CSF samples and correlate results to mild cognitive impairment progression.
Methods: Methods: Se- and Fe^{2+}/Fe^{3+}-speciation were performed in paired serum/CSF samples using IEC-ICP-MS and CE-ICP-MS techniques. We applied linear and cubic spline regression analysis for assessing associations between Se-species or Fe^{2+}/Fe^{3+}-ratio from serum or CSF and mild cognitive impairment, as reflected by MMSE-scores.
Results: Results: In serum and CSF low MMSE-scores were associated with higher SELENOP, Seleno-methionine, Se(IV) and in CSF with elevated Fe^{2+} values or an increased Fe^{2+}/Fe^{3+}-ratio. In turn, higher serum-GPX or Fe-ferritin values were associated with highest MMSE-scores. Serum-TXNRD showed no clear association to MMSE-scores but in CSF it was higher at lower MMSE-scores. Serum-Se correlated positively with CSF-Se, but serum-GPX correlated negatively with CSF Fe^{2+}/Fe^{3+}-redox balance. In CSF total Se correlated positively with Se(VI) and GPX, whereas GPX negatively correlated with SELENOP paralleled by the negative correlation of the Fe^{2+}/Fe^{3+}-ratio with Fe-ferritin.
Conclusions: Conclusions: Changes in Se- and Fe-speciation appear to be related to MMSE/MCI. We hypothesize that OS could be the mediator of such relation, i.e. the mechanisms underlying it.

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P0419 / #512

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

COMPREHENSIVE ANALYSIS OF EPIGENETIC CLOCKS REVEALS ASSOCIATIONS BETWEEN DISPROPORTIONATE BIOLOGICAL AGEING AND HIPPOCAMPAL VOLUME

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Aims: Using the highly characterised prospective longitudinal Australian Imaging, Biomarkers and Lifestyle (AIBL) study cohort we aimed to comprehensively investigate several methods of assessing DNAm age to assess 1) whether accelerated ageing is associated with cross-sectional measures of cognition and AD-related neuroimaging phenotypes (volumetric MRI and Aβ-PET) and, 2) whether an individual's current DNAm age is a predictor of future longitudinal changes in these two phenotypes. Then we sought to test the robustness of our findings through validation within a comparable longitudinal cohort, the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Methods: We comprehensively investigated the relationship between five measures of age acceleration, based on DNA methylation patterns (DNAmage), and cross-sectional and logitudinal cognition and AD-related neuroimaging phenotypes (volumetric MRI and Amyloid-β PET) in the Australian Imaging, Biomarkers and Lifestyle (AIBL) and the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Results: Significant associations were observed between age acceleration using the Hannum epigenetic clock and cross-sectional hippocampal volume in AIBL and replicated in ADNI. In AIBL, other findings were observed cross-sectionally, including a significant association between hippocampal volume and the Hannum and Phenoage epigenetic clocks. Further, significant associations were also observed between hippocampal volume and the Zhang and Phenoage epigenetic clocks within Amyloid-β positive individuals. However, these were not validated within the ADNI cohort. No associations between age acceleration and other Alzheimer's disease-related phenotypes, including measures of cognition or brain Amyloid-β burden were observed, and there was no association with longitudinal change in any phenotype.
Conclusions: This study presents a link between age acceleration and hippocampal volume that was statistically significant across two highly characterised cohorts. The results presented in this study contribute to a growing literature that supports the role of epigenetic modifications in ageing and AD-related phenotypes.

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P0420 / #915

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

TWO-STEP BLOOD-BASED ALZHEIMER'S DISEASE BIOMARKER IMMUNOASSAY DEVELOPMENT AND OPTIMIZATION

Barbara Morgado[1], Hermann Esselmann[1], Hans Klafki[1], Katharina Waniek[2], Dirk Osterloh[2], Ingolf Lachmann[2], Jens Wiltfang[1]
[1]University Medical Center Goettingen, Psychiatry And Psychotherapy, Goettingen, Germany, [2]Roboscreen GmbH, Roboscreen Gmbh, Leipzig, Germany

Aims: Blood-based biomarkers are needed for supporting an early diagnosis of Alzheimer disease (AD) in research and ultimately routine clinical practice. We report on the further development and optimization of our two-step immunoassay approach for the study of amyloid-beta variants and phosphorylated Tau species in human plasma samples.
Methods: A study cohort was pre-selected from our local biobank that included 80 subjects classifed as amyloid-positive or amyloid-negative according to the amyloid-beta 42/40 ratio in cerebrospinal fluid. The experimental workflow of the two-step immunoassay approach consists of semi-automated magnetic bead immunoprecipitation of amyloid-beta peptides and Tau followed by biomarker measurements preferentially on the fully-automated Lumipulse immunoassay platform. In addition, the same panel of biomarkers will be measured directly in parallel aliquots of the same set of blood plasma samples.
Results: The fully-automated Lumipulse immunoassays currently in use in our lab show great sensitivity and reproducibility for the biomarkers of interest and appear to allow for reliable direct biomarker measurements in undiluted blood plasma samples. Preliminary findings indicate that pre-analytical immunoprecipitation of amyloid-beta peptides and Tau proteins is compatible with the fully automated amyloid-beta 42/40 and phospho-Tau assays. Direct comparisons of the diagnostic performance of the assays with and without pre-analytical immunoprecipitation for detecting study participants with low CSF amyloid-beta 42/40 will be presented.
Conclusions: A head-to-head comparison of blood-based biomarker assays on the fully automated Lumipulse assay platform without and with pre-analytical immunoprecipitation will be presented.

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P0421 / #1486

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

MULTIVARIATE CSF PROTEIN PROFILES REFLECT AMYLOID AND TAU PATHOLOGY

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Aims: Amyloid plaques and tau tangles are largely associated with Alzheimer's disease (AD). However, the underlying mechanisms of the disease pathophysiology are not fully uncovered. Detailed understanding of the processes and molecules involved is critical to identify new biomarkers for early diagnosis and diseases progression, and for finding suitable treatment targets. This study investigates CSF protein profiles in relation to amyloid and tau CSF levels to provide insight into proteins and processes involved in AD pathology.
Methods: We used a multiplex antibody-based suspension bead array technology to analyse the relative levels of 53 proteins in CSF from 289 Swedish patients with either dementia (mainly AD), or mild or subjective cognitive impairment (MCI/SCI). An additional cohort of 52 CSF samples (AD or SCI) from the Netherlands used for validation.
Results: Correlation analysis of the measured proteins revealed two protein clusters with positive correlation to each other but with different association to amyloid and tau CSF markers. While proteins in one cluster showed strong correlation to t-tau and p-tau and weaker correlation to aβ42, proteins in the other cluster showed the opposite trend. Further analysis using support vector machine modelling revealed that protein pairs combined from the two different clusters had higher potential to separate amyloid- and tau-positive individuals from negative individuals compared to single proteins or protein pairs from the same cluster. The best separation was found using the two proteins GAP43 and CCK with AUC = 0.95. The results were further validated in an independent cohort.
Conclusions: This study shows that combining proteins as biomarkers could decrease background variability between individuals and increase the understanding of AD pathology as well as increase the potential of secondary biomarkers to be used for diagnosis or in clinical trials.

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P0422 / #301

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CEREBROSPINAL FLUID ALPHA-SYNUCLEIN, AMYLOID BETA, TOTAL TAU, AND PHOSPHORYLATED TAU IN TREMOR DOMINANT PARKINSON'S DISEASE

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Aims: We aimed to explore the cross-sectional and longitudinal level of the CSF α-synuclein (α-syn), amyloid βeta (Aβ1-42), total tau (t-tau), and phosphorylated tau (p-tau) in Parkinson's disease (PD) subjects with tremor dominant (TD) and a non-tremor dominant (nonTD) subtype.
Methods: We enrolled 411 early-stage PD patients and 187 healthy controls (HCs) from the Parkinson Progression Markers Initiative (PPMI). We compared the level of CSF biomarkers at four time points including baseline, 6 months, 1 year, and 2 years. To investigate longitudinal changes in CSF proteins within each group we used linear mixed models.
Results: The level of CSF biomarkers was significantly lower in PD patients compared to HCs at any visit. Moreover, there was no statistically significant difference in the level of CSF α-syn, Aβ1-42, t-tau, and p-tau between PD-TD and PD-nonTD. Longitudinal analysis showed significant CSF α-syn reduction after one year from baseline in PD-TD patients (*P*= 0.047). Also, there was a significant reduction in the level of CSF Aβ1-42 after two years in PD-nonTD patients but not HCs and PD-TD (*P*= 0.033).
Conclusions: Our results indicate that different patterns in longitudinal changes of CSF biomarkers could be due to different pathophysiological mechanisms involved in each PD motor subtype.

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P0423 / #505

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ESTABLISHING FLUID BIOMARKERS ASSOCIATED WITH CELLULAR SENESCENCE IN ALZHEIMER'S DISEASE

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Aims: Chronological age is the biggest non-genetic risk factor of Alzheimer's disease (AD). However, there is a wide range in age at onset (AAO) such that chronological age itself is a poor predictor of risk or AAO. Biological age may offer a more precise molecular measure of ageing, but it is currently unclear how biological ageing is associated with AD. We set out to test fluid biomarkers of biological ageing specifically linked to cellular senescence in AD and explore their utility in the clinical setting.
Methods: Using cerebrospinal fluid (CSF) samples from a biomarker discovery cohort in Sweden and clinically characterised AD/birth cohorts at University College London, we quantified the levels of multiple candidate biomarkers associated with ageing and cellular senescence with various immunoassays. The levels of biological ageing markers were then analysed with clinical and pathological data from the sample donors.
Results: The levels of Growth differentiation factor-15 (GDF-15), Interleukin-6 (IL-6), Osteopontin and Klotho in human CSF were measured (n = 67) to assess their relevance in the context of existing CSF biomarkers of AD. The levels of all four candidate biomarkers change with chronological age (increase, except decrease for Klotho), and both GDF-15 and Osteopontin levels can differentiate individuals with high level of CSF amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) from those with low levels of $A\beta_{1\text{-}42}$. In addition, the levels of Osteopontin correlate positively with those of phosphorylated tau-181 while the levels of IL-6 correlate positively with both GDF-15 and Osteopontin.
Conclusions: Our data support the relevance of biological ageing in the context of AD and the need for further investigation. The abovementioned candidate biomarkers, among others, will be quantified in clinically characterised AD cohorts to result in a consolidated molecular signature for biological ageing.

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P0424 / #615

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ASSOCIATION OF CEREBROSPINAL FLUID GAP-43 WITH PROGRESSION TO DEMENTIA, BRAIN ATROPHY, AND THE RATE OF COGNITIVE DECLINE IN AMYLOID-POSITIVE INDIVIDUALS

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Aims: To evaluate associations between cerebrospinal fluid (CSF) GAP-43 and biomarkers of AD pathophysiology, and investigate how well CSF GAP-43 predicts cognitive decline, brain atrophy, hypometabolism and clinical progression to dementia.
Methods: CSF GAP-43 levels were analyzed in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (N=786). The participants were classified in cognitively unimpaired (CU) Aβ-negative (n_{CU-}=197); CU Aβ-positive (n_{CU+}=55), MCI Aβ-negative (n_{MCI-}=228), MCI Aβ-positive (n_{MCI+}=193) and AD dementia Aβ-positive (n_{AD}=113). Linear regression models tested the associations between biomarkers of AD (Aβ and tau pathologies, neurodegeneration and cognition) adjusted by age, sex and diagnosis. Linear mixed effect models (LME) evaluated how baseline GAP-43 predicts brain hypometabolism, atrophy and cognitive decline over time. Cox-proportional hazard regression models tested how GAP-43 levels and Aβ status, at baseline, increased the risk of progression to AD dementia over time.
Results: We report that baseline levels of GAP-43 is associated with more rapid rate of hypometabolism and more rapid rate of brain atrophy over time. In addition, high baseline levels of GAP-43 predict faster cognitive decline and higher risk of dementia. The study also shows that baseline levels of GAP-43 better reflect tau pathology than Aβ pathology.
Conclusions: In this study, high baseline levels of GAP-43 were mostly linked to increased tau pathology as well as associated with future decline in brain metabolism, progressive brain atrophy, cognitive decline and higher risk to progress to dementia. Altogether, these findings point to GAP-43 as a potential marker of clinical progression particularly in subjects with Aβ pathology, being a valuable tool for enrolling participants in clinical trial.

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P0425 / #426

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

TIME OF THE DAY AT SAMPLING AFFECTS AMYLOID-BETA LEVELS IN CSF AND PLASMA

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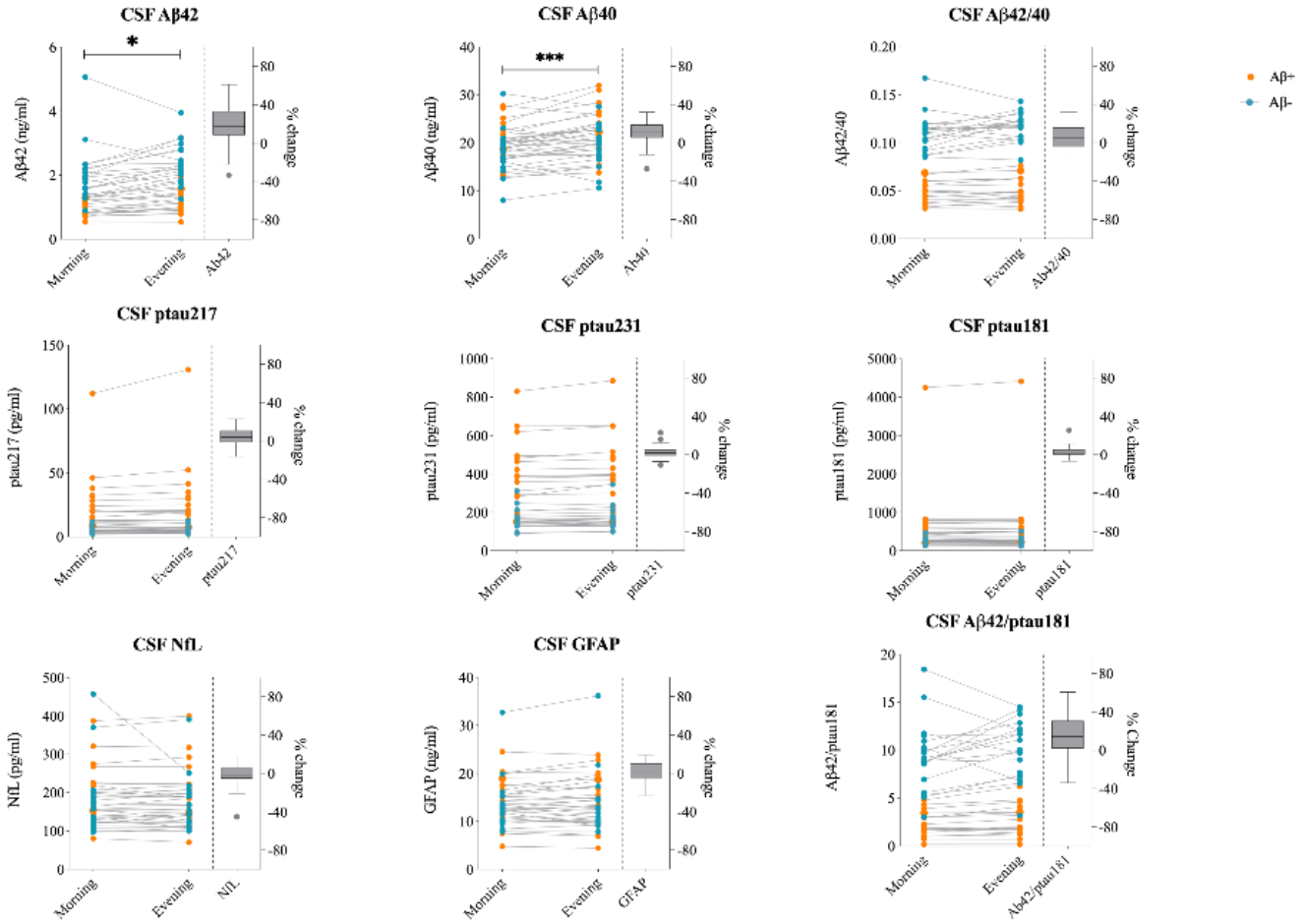
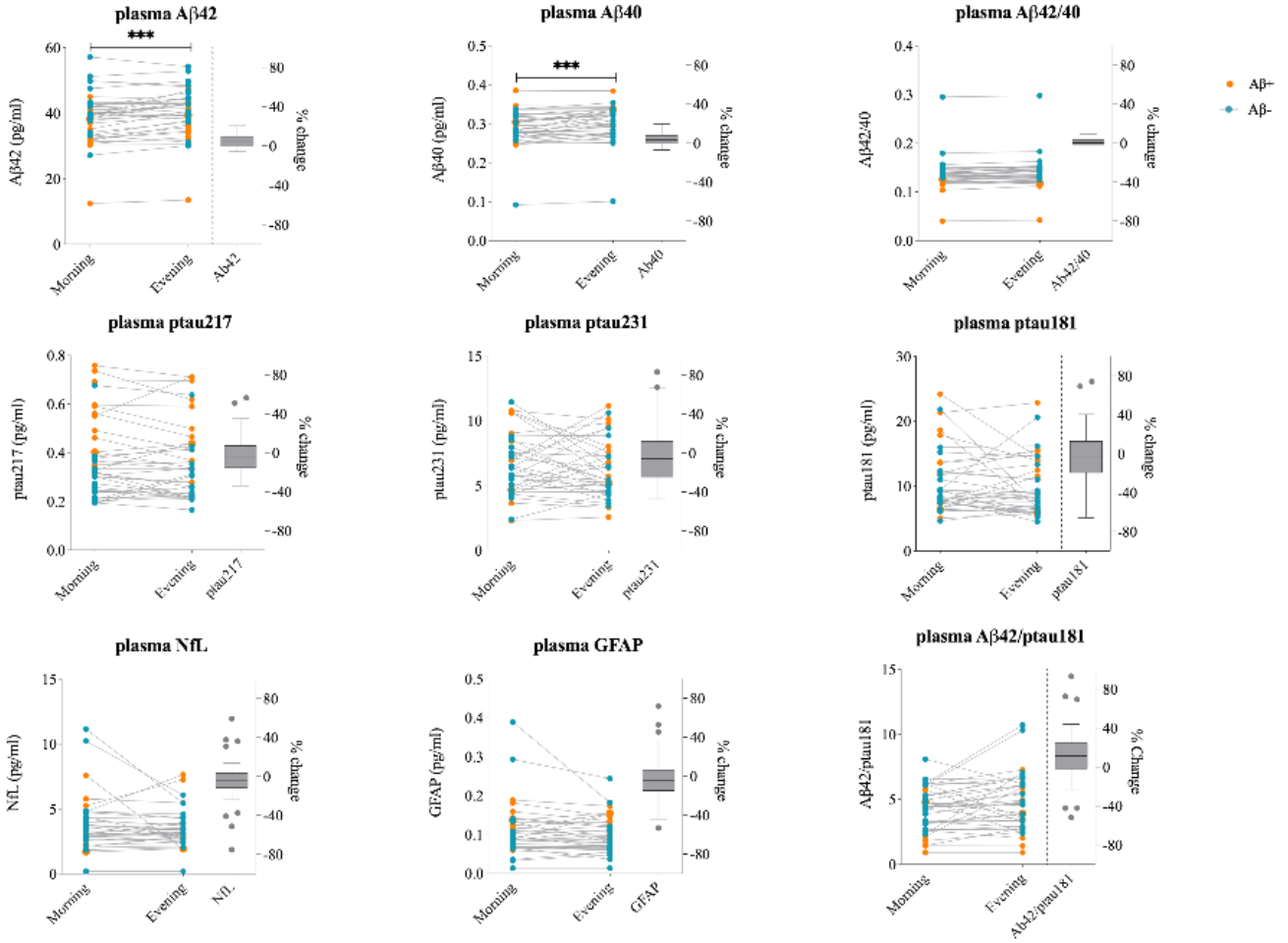
Aims: Studies suggest that CSF levels of AD biomarkers, amyloid-β and tau, follow a circadian rhythm. However, the methodology used in most of these studies might have affected the observed fluctuations. We investigated concentrations of AD biomarkers in CSF and plasma collected in the morning vs evening with extractions performed on two different occasions.
Methods: We included 38 individuals with either normal(N=18) or abnormal CSF Aβ status(N=20). CSF and plasma were collected at the same visit. All participants underwent two lumbar punctures and venepunctures separated by an average of 53 days. The first sample collection was performed in the morning for 17 participants and the order was reversed for the remaining participants. CSF and plasma samples were analyzed for Aβ42, Aβ40, GFAP, NfL, ptau181, ptau231, and ptau217. Differences in levels between samples collected in morning and evening were assessed by repeated measures two-way ANOVA correcting for multiple comparisons.
Results: CSF Aβ42 (mean differences[95%CI] p-value; -0.2082ng/ml [0.3489, -0.0675] 0.043), CSF Aβ40 (-1.85ng/ml [-2.615, -1.087] p<0.001), plasma Aβ42 (-1.652pg/ml [-2.469, -0.8357] 0.002) and plasma Aβ40 (0.0114 pg/ml [-0.01724, -0.005658] 0.003) levels were increased in the evening compared with morning. No significant differences were found between morning and evening levels for any of the other biomarkers. There were no significant interactions between either time of day at sample collection and amyloid status or order of sample obtention.



CSF biomarkers levels for each subject on two different collection time points (morning and evening), both measures from each individual subject are connect by a line. Blue dots represent subjects with negative amyloid status whereas orange dots represent subjects with positive amyloid status. Percentage change between time points is shown as a boxplot with the Tukey method. Time of the day where sample were obtained is on the x-axis, percentage change between is noted on the right y-axis and levels of the biomarkers on the left y-axis. (Statistical significance; Main Effects repeated measures two-way ANOVA; *=p-value<0.05 and ***=p-value<0.005).



Plasma biomarkers levels for each subject on two different collection points (morning and evening), both measures from each individual subject are connect by a line. Blue dots represent subjects with negative amyloid status whereas orange dots represent subjects with positive amyloid status. Percentage change between time points is shown as a boxplot with the Tukey method. Time of the day where sample were obtained is on the x-axis, percentage change between is noted on the right y-axis and levels of the biomarkers on the left y-axis (Statistical significance; Main Effects repeated measures two-way ANOVA; ***=p-value<0.005).

Conclusions: Our findings provide evidence for diurnal fluctuations in CSF and plasma Aβ42 and Aβ40 but not the Aβ42/40 ratio, suggesting that changes induced by increased production or decreased clearance of Aβ peptides during day time similarly affect the CSF and plasma levels of the Aβ42 and Aβ40 and consequently the Aβ42/40 ratio remains unaltered.

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P0426 / #525

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ASSOCIATION OF PLASMA AB42/AB40 WITH EPISODIC MEMORY PERFORMANCE AND BRAIN ATROPHY IN INDIVIDUALS AT RISK OF ALZHEIMER'S DISEASE

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Aims: To assess the ability of plasma Aβ42/Aβ40 ratio as determined by a high-sensitivity antibody-free mass spectrometry-based assay (ABtest-MS, Araclon Biotech) to detect early alterations in episodic memory performance and brain atrophy in individuals at risk of Alzheimer's disease (AD).
Methods: Aβ40 and Aβ42 plasma levels were measured with ABtest-MS(1) in 200 individuals with subjective cognitive decline from the FACEHBI cohort(2). Participants underwent the Spanish version of the Face-Name Associative Memory Exam (S-FNAME) and the derived composite S-FNAME Name (SFN-N) to evaluate episodic memory performance(3). Brain atrophy was assessed using MRI measures of ventricular and hippocampal volume normalized by total intracranial volume. Participants were classified as plasma Aβ42/Aβ40(+) or Aβ42/Aβ40(-) by applying a cutoff of 0.241 corresponding to the maximum Youden index derived from ROC curve analyses to detect early Aβ-PET positivity(4). Group differences were examined using the Mann-Whitney test.
Results: Subjects classified as plasma Aβ42/Aβ40(+) performed significantly worse on S-FNAME total score and SFN-N composite score, than those Aβ42/Aβ40(-) (P=.023 and P<.001, respectively). A significant positive correlation was found between plasma Aβ42/Aβ40 and the SFN-N composite score (rho=0.193, P<.006). Plasma Aβ42/Aβ40 was also associated with brain atrophy, as evidenced by increased ventricular volume and reduced hippocampal volume in Aβ42/Aβ40(+) individuals (P=.022 and P=.097, respectively).
Conclusions: Individuals with low plasma Aβ42/Aβ40 values performed worse on the S-FNAME and presented increased brain atrophy to some extent, suggesting that plasma Aβ42/Aβ40, as determined by this MS-based assay, could detect the first subtle alterations in AD. (1) Jang H *et al.*, *Alzheimers Res Ther*. 2021; 13:179. (2) Rodriguez-Gomez O *et al.*, *J Prev Alzheimers Dis*. 2017;4(2):100. (3) Alegret M *et al., Alzheimers Res Ther*. 2020;12(1):25. (4) Bullich S *et al*., *Alzheimers Res Ther*. 2021;13(1):67.

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P0427 / #1841

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PLASMA BIOMARKERS ABILITY TO DETECT ALZHEIMER S DISEASE IN CLINICAL SETTING

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Aims: Plasma p-tau, NfL and amyloid markers are promising markers of Alzheimer's disease (AD). Aim of the study was to evaluate the ability of detect Alzheimer's disease related pathology in clinical setting.
Methods: each patient underwent standard clinical and cognitive assessment and CSF analyses for biomarker-based AD diagnosis. Plasma p-tau181, p-tau231, NfL, GFAP, T-tau abeta 1-42, Abeta 1-40 Tau, P-tau and Abeta amyloid, NfL, using SIMOA analyses. The ability of different biomarkers to distinguish AD from other neurodegenerative diseases.
Results: sixty-five AD and 50 other neurodegenerative disease with CSF analyses and 60 HC were included in the analyses. Several markers showed higher levels in AD compared to controls, namely p-tau181, p-tau231, GFAP and NfL, whereas Abeta1-42 and abeta40 was similar between groups. p-tau181 and p-tau231 exhibited the highest ability to distinguish AD from both controls and other neurodegenerative disorders.
Conclusions: this study confirmed the increased p-tau 181 and p-tau231 as the most reliable markers for identifying AD diagnosis in clinical setting.

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P0428 / #449

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LEVERAGING PRECISION MEDICINE FOR TREM2-TARGETED THERAPEUTICS IN ALZHEIMER'S DISEASE

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Aims: Triggering receptor expressed on myeloid cells (TREM2) partial loss-of-function gene variants (TREM2v+) and apolipoprotein E4 (APOE4) genotype are associated with increased risk for Alzheimer's disease (AD). We characterize the influence of TREM2v and APOE4 carrier status on AD biomarkers and disease progression, to inform on a precision medicine-guided approach to development of TREM2-targeted therapeutics in AD.
Methods: We examined baseline and longitudinal profiles of CSF levels of sTREM2, ABeta42, t-tau and p-tau181 and clinical scales (MMSE, CDR-SB) from ADNI stratified by Beta-amyloid burden, disease stage and genetic status (TREM2v+/-, APOE4+/-). A coefficient of variation was derived to quantify between and within subject variability relative to group mean in each of the biomarker and clinical measures.
Results: ABeta42 levels decreased with increasing disease severity, while t-tau and p-tau181 levels generally increased as a function of increasing disease severity and genetic burden. In ABeta42+ MCI subjects, the presence of both TREM2v and APOE4 was associated with a synergetic increase in levels of sTREM2, t-tau and p-tau181. The baseline coefficient of variation of t-tau, p-tau181, MMSE and CDRSB decreased with increasing genetic burden. Lastly, presence of TREM2v, and more considerable, a combination of TREM2v and APOE4 was associated with relatively faster and more homogeneous disease progression.
Conclusions: Genetic and biomarker defined AD subpopulation represent a relatively more homogeneous patient population with increased likelihood of disease progression over time. Patient enrichment strategies based on biomarkers and genetic status relevant to therapeutic mechanism of action may enable design of efficient proof-of-concept clinical trials.

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P0429 / #573

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ASSESSING THE ROBUSTNESS OF THE ATN FRAMEWORK USING MULTIPLE THRESHOLD METHODOLOGIES ACROSS DISTINCT COHORTS

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Aims: Numerous Alzheimer's disease (AD) studies have categorized participants according to the ATN framework. These studies focused on single cohorts and often applied a data-driven approach to determine cerebrospinal fluid (CSF) biomarker thresholds. To universally apply the ATN categorization across cohorts, it is vital to assess the robustness of widely-used methodologies, the interchangeability of achieved thresholds, and how chosen thresholding procedures can bias subsequent data analysis across cohorts.
Methods: For a comprehensive analysis, we identified 11 AD cohorts and 5 commonly-used thresholding methodologies. We applied each methodology to all cohorts to obtain thresholds for CSF biomarkers. We systematically compared thresholds across methodologies and cohorts and assessed their impact on patient categorization. Further, we clustered ATN-categorized participants and compared patients' cluster membership to their dataset origin to determine how comparable subjects from the same ATN were across cohorts.
Results: We found substantial variation among the obtained thresholds and, depending on the chosen methodology, the resulting patients' categorization differed drastically. Additionally, the clustering showed that participants of the same cohort were often clustered together which could potentially be due to bias resulting from differing thresholds.
Conclusions: Our findings confirm that the selected methodology for extracting thresholds highly influenced the participants' categorization. The variation among the thresholds across cohorts indicates that the thresholds are not directly interchangeable even when biomarkers were measured using the same assay. Finally, ATN-categorized participants may not be comparable to participants from another cohort that were assigned to the same ATN category, which can limit the generalizability of ATN-based results.

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P0430 / #1805

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

SPECIFIC ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND POST-MORTEM AMYLOID PLAQUE AND NEUROFIBRILLARY TAU TANGLE LOADS

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Aims: To investigate and compare independent associations between multiple plasma biomarkers (p-tau181, p-tau217, p-tau231, Aβ42/40, GFAP and NfL) and neuropathologic measures of amyloid and tau.
Methods: We included 105 participants from the Arizona Study of Aging with antemortem collected plasma samples and a post-mortem neuropathological exam, 48 of whom had longitudinal p-tau217 and p-tau181 (Table 1). Independent associations between plasma biomarkers and plaques and tangles were assessed using plasma as outcome and both neuropathologic measures as independent variables in the same model. Contribution of these pathologies on plasma levels were assessed with partial-R^2. We selected the best combination of biomarkers for an optimal prediction of presence of Alzheimer's disease neuropathologic change (ADNC) based on the corrected Akaike criterion. Rates of change of longitudinal plasma measures were compared based on presence/absence of ADNC (none/low *vs* intermediate/high) at death.
Results: All markers except NfL were associated with plaques ($|b|\geq0.37$, $p<0.001$) and tangles ($|b|\geq0.27$, $p<0.008$, Figure 1), in univariable analyses. In multivariable models, the Aβ42/40 ratio and p-tau231 were only associated with plaques ($b_{Aβ42/40}$=-0.59, $b_{p\text{-}tau231}$=0.32, $p\leq0.007$), while GFAP was only associated with tangles (b_{GFAP}=0.39 $p<0.001$). P-tau217 and p-tau181 were associated with both plaques ($b_{p\text{-}tau217}$=0.46, $b_{p\text{-}tau181}$=0.41, $p<0.001$) and tangles ($b_{p\text{-}tau217}$=0.40; $b_{p\text{-}tau181}$=0.30, $p\leq0.004$). In both cases, amyloid had a higher contribution (p-tau217=40.4%, p-tau181=35.7% of the total variance) than tau (p-tau217=30.7%, p-tau181=17.1%, Figure 2). Combining p-tau217 and the Aβ42/40 ratio was optimal to accurately predict presence of ADNC (AUC=0.90, Figure 3). P-tau217 rates of change (b[95%CI]=0.13[0.02,0.24], p=0.018), but not those of p-tau181 (b[95%CI]=0.12[-0.05,0.29], p=0.152), differed between those with/without presence ADNC at death (Figure 4).
Conclusions: High-performing assays of plasma p-tau217 and Aβ42/40 might be an optimal biomarker combination to detect Alzheimer's disease pathology *in vivo*.

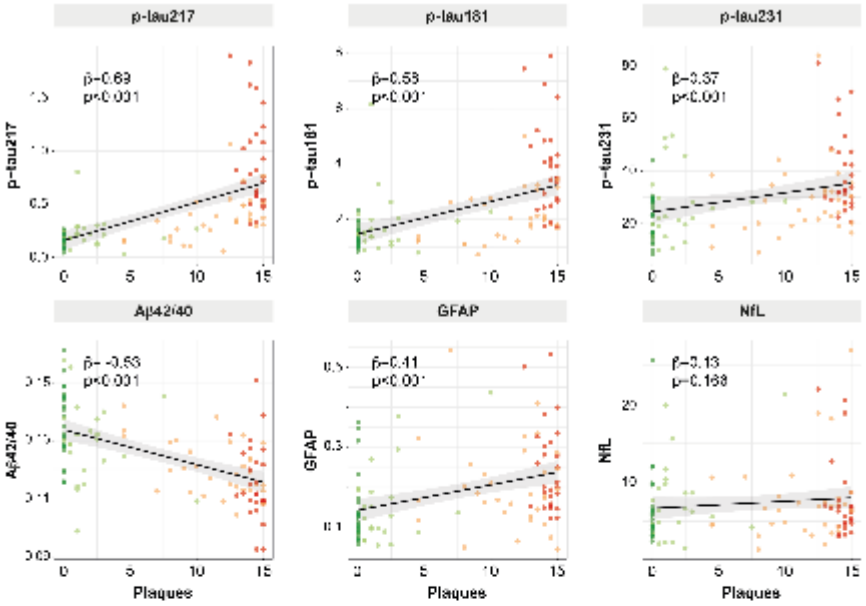
	Overall (n=105)	ADNC – negative (n=46)	ADNC – positive (n=59)	p-value
Age, mean(SD)	84.7 (7.99)	83.5 (7.99)	85.7 (7.93)	0.174
Women, n(%)	43 (41.0%)	21 (45.7%)	22 (37.3%)	0.506
APOE-e4 carrier, n (%)	34 (32.4%)	5 (10.9%)	29 (49.2%)	<0.001
Time between blood and death, days, mean(SD) [range]	482 (355) [9 - 1760]	414 (300) [9 - 1120]	536 (387) [9 - 1760]	0.137
Plaque total, mean(SD)	7.60 (6.34)	1.03 (1.99)	12.7 (2.83)	<0.001
Tangle total, mean(SD)	7.93 (3.69)	5.54 (2.41)	9.79 (3.44)	<0.001

Table 1 Demographic characteristics at baseline

ADNC was dichotomized as: negative (none/low) and positive (intermediate/high).

Abbreviation: ADNC, Alzheimer's disease neuropathologic change.

A) Plaques



B) Tangles

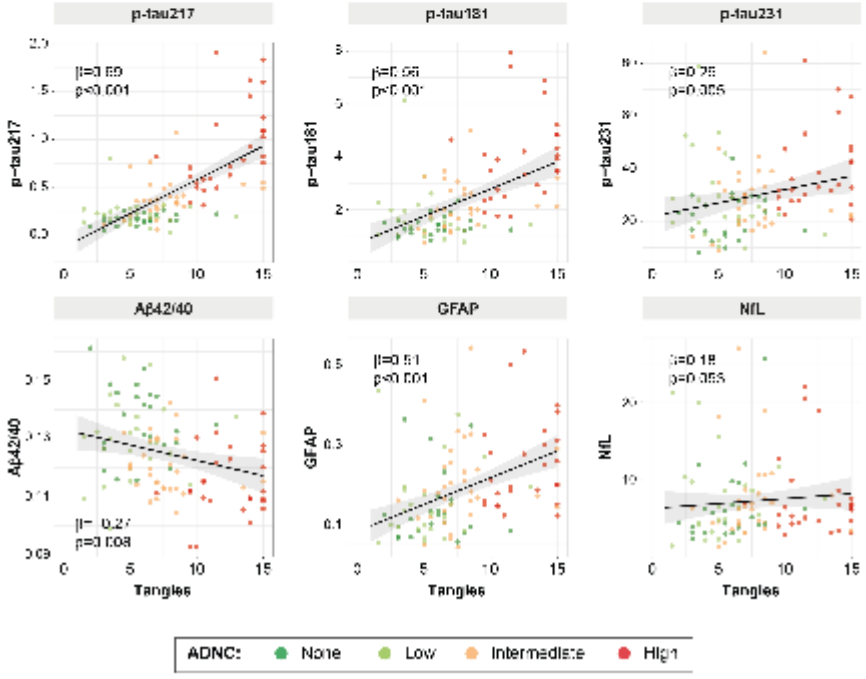


Figure 1 Associations between plasma biomarkers and amyloid plaque or neurofibrillary tau tangle loads

Bold lines represent the association between plasma biomarkers and amyloid plaque (top) and tangle (bottom) loads, after regressing out the covariates age, sex, and time between blood sampling and death. Solid dots represent raw data. Subplots are colored based on the ADNC classification. Standardized beta and p-values of the association between plasma biomarkers and load of amyloid plaques or tangles are shown in the plot. Abbreviations: Aβ, amyloid-β; ADNC, Alzheimer's disease neuropathologic change; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; p-tau, phosphorylated tau

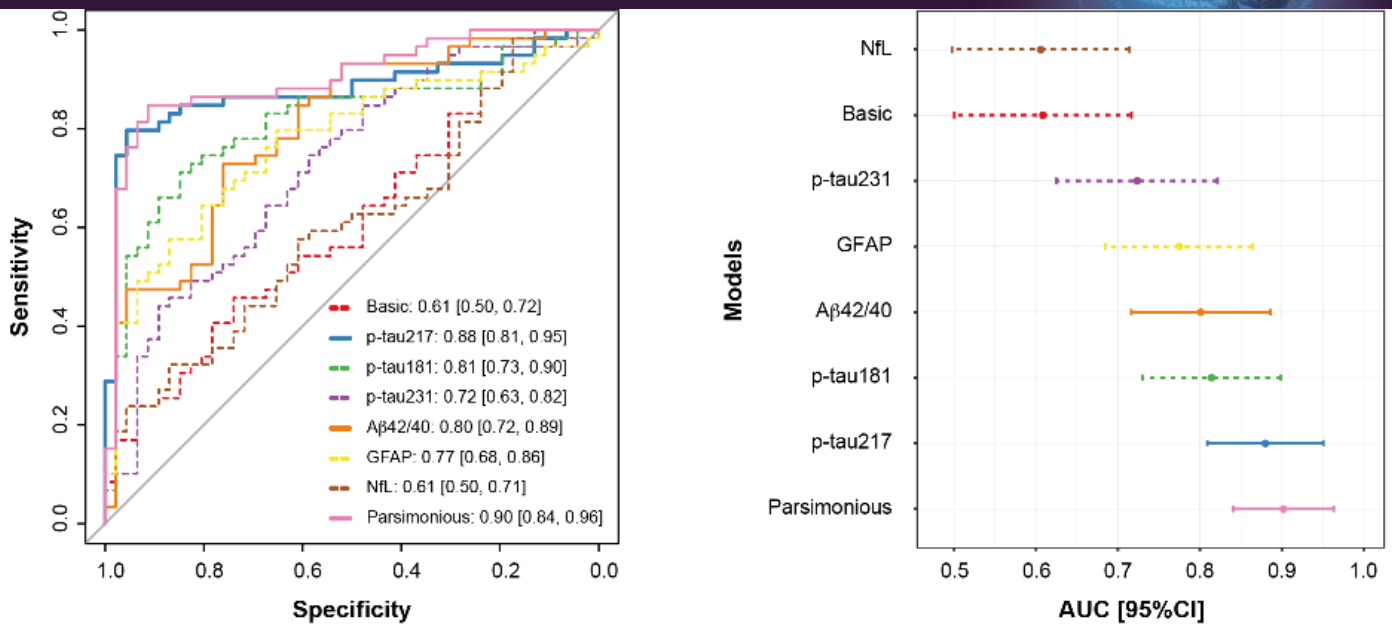


Figure 3 Plasma biomarkers for predicting presence of ADNC

ROC curves for all individual plasma biomarkers are shown in the left column and the correspondent AUC and 95%CI are shown in the right column. Models for all individual plasma biomarkers as well as the parsimonious model are shown. All models included: age, sex and time between blood sampling and death as covariates. The parsimonious model for ADNC included p-tau217 and A□42/40 as predictors. The basic model includes only covariates. ADNC was dichotomized as negative (none/low) or positive (intermediate/high). The individual biomarker with best performance is shown as a solid bold line. Dashed lines represent individual biomarkers with significant ($p<0.05$) lower AUC than the best individual biomarker (p-tau217 in all cases). Other models with solid lines represent AUC equivalent to that of the best individual biomarker.

Abbreviations: Aβ, amyloid-β; ADNC, Alzheimer's disease neuropathologic change; AUC, area under the curve, CI, confidence interval; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; p-tau, phosphorylated tau; ROC, receiver operating characteristic.

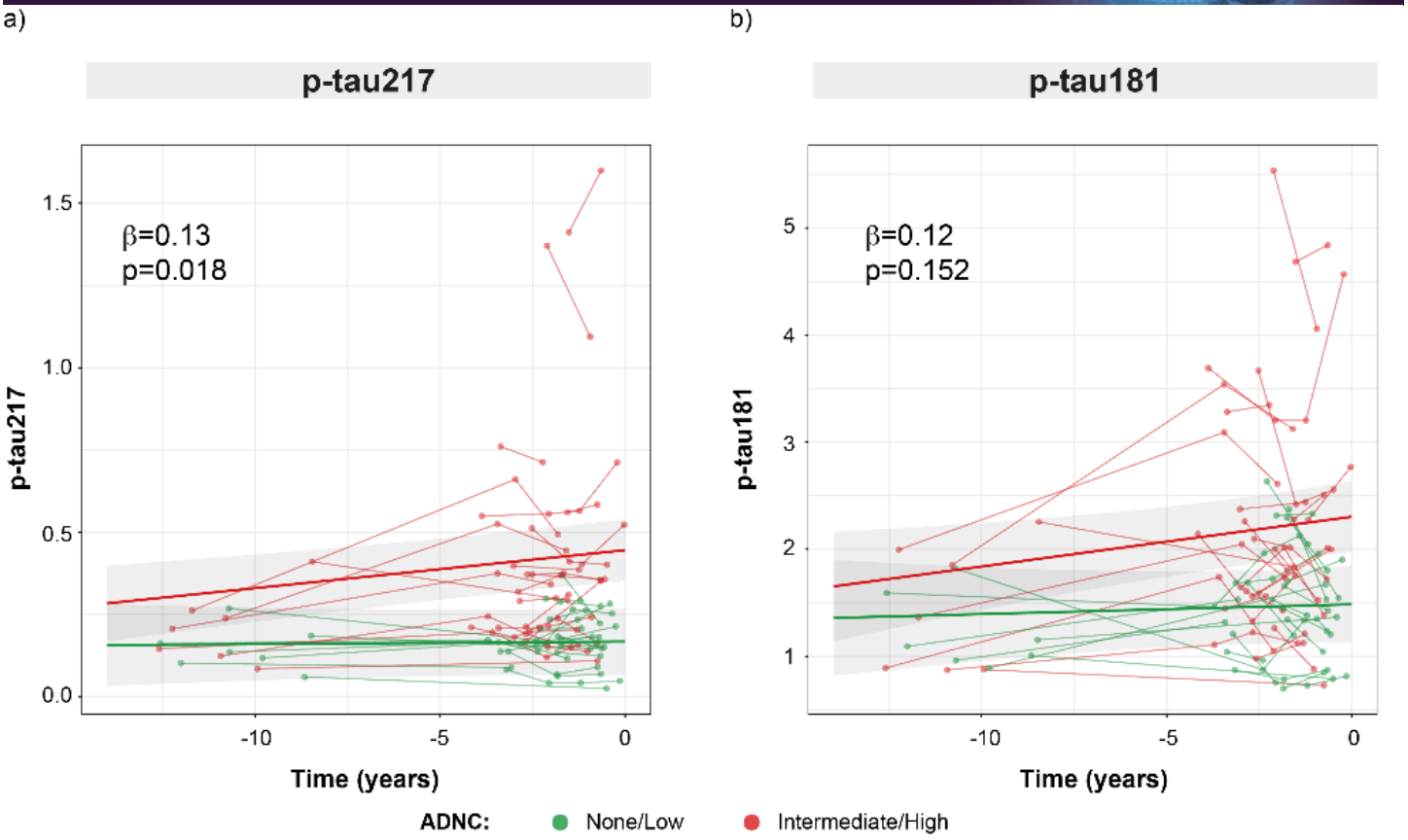


Figure 4 Associations between longitudinal changes of plasma biomarkers and presence of ADNC at death
Bold lines represent mean longitudinal changes of plasma p-tau217 (a) and plasma p-tau181 (b) by ADNC groups at death. Linear mixed effect models were used to derive these associations in independent models including: age at baseline and sex as covariates using and random intercepts and fixed time-slopes. ADNC was dichotomized as negative (none/low) or positive (intermediate/high). ADNC*time interaction standardized betas and p-values are shown in the figure.
Abbreviations: ADNC, Alzheimer's disease neuropathologic change; p-tau, phosphorylated tau.

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P0431 / #2244

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

IMAGING AND QUANTIFICATION OF FIBRILLAR PROTEIN AGGREGATES IN CSF AND ON RED BLOOD CELLS WITH ATOMIC FORCE MICROSCOPY AS NOVEL DIRECT BIOMARKER OF AD

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Aims: To resolve and quantify amyloid fibrils in cerebrospinal fluid (CSF) and deposited on red blood cells (RBCs) with atomic force microscopy (AFM) as novel direct biomarkers for AD.
Methods: Here, we present preliminary results of 34 of 238 patients enrolled at the Memory Clinic St. Gallen. AFM measurements were conducted on air-dried blood smear and CSF samples. AFM could resolve the morphology and assembly pattern of protein aggregates and measure potential AD biomarkers: a) the surface coverage of RBC with fibrils (prevalence) and b) the mean fibril length in CSF. The fibril prevalence on RBCs and fibril lenght in CSF were correlated with the CSF beta-Amyloid 42/40 ratio and p-tau levels, compared between disease groups and used to classify the amyloid and tau-status.
Results: AFM could resolve and characterize fibrilar, spherical and anular protein depositis on RBCs with fibrilar aggregates being present in all patients.The fibrillar aggregate surface coverage of RBCs was negatively correlated with the CSF Aβ 42/40 ratio and was observed to be highest in patients with AD dementia. Using a cutoff of ≥40% fibril prevalence, the CSF Aβ status was classified with 88% accuracy (sensitivity 100%, specificity 73%). In CSF, small spherical proteins and few short, immature fibrils were found in patients without amyloid-pathology, whereas dense networks of ultalong amyloid fibrils were present in patients with AD dementia. The mean fibril length was again negatively correlated with the CSF Aβ 42/40 ratio and predicted the CSF Aβ status with 95% accuracy (sensitivity 95%, specificity 92%).
Conclusions: The findings from our study provide new insights into the aggregation of fibrils on RBCs and in CSF in AD and could represent novel direct biomarker of pathologic protein fibrillization in AD.

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P0432 / #1814

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

UMAN TYPE NF-L ANTIBODIES ARE EFFECTIVE REAGENTS FOR THE IMAGING OF NEURODEGENERATION

Gerry Shaw
EnCor Biotechnology Inc., Na, Gainesville, United States of America

Aims: Recent work shows that certain immunological assays for neurofilament light chain NF-L detect informative signals in the CSF and blood of human and animals affected by a variety of CNS injury and disease states. Much of this work has been performed using two mouse monoclonal antibodies to NF-L, UD1 and UD2, also known as 2.1 and 47.3 respectively. These are the essential components of the Uman Diagnostics NF-Light™ ELISA kit, the Quanterix Simoa™ bead based NF-L assay and others. We have characterized the epitopes to which these antibodies bind and also discovered novel, useful and interesting features of these reagents.
Methods: We used appropriate recombinant constructs and peptides based on the human NF-L sequence, followed by direct peptide binding and peptide competition experiments to localize the epitopes for the two Uman monoclonals. We then used the epitopic region to generate a novel panel of monoclonal and polyclonal antibodies to this region.
Results: The Uman NF-L antibodies bind to NF-L 311-362 including the "stutter 2" of the α-helical coiled coil region of the NF-L "rod" domain. Antibodies raised against this region and also both Uman antibodies fail to stain healthy neurons and their processes, but strongly stain degenerating and degenerated processes seen after experimental spinal cord and brain injury. The novel antibodies show that the hidden epitopic region in NF-L is considerably longer than the short 311-362 peptide.
Conclusions: The hidden epitopic region on NF-L could be revealed experimentally by protease treatment, suggesting the in vivo mechanism. This work illuminates the properties of the NF-L biomarker, describes novel and useful properties of Uman type and NF-L tail binding antibodies and provides a hypothesis relevant to further understanding of neurofilament assembly.

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P0433 / #790

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ACTIVITY OF PIEZO1 RECEPTORS IN RED BLOOD CELLS AS A NOVEL FUNCTIONAL BIOMARKER FOR ALZHEIMER'S DISEASE

Valeriia Sitnikova[1], Dilyara Nurkhametova[1], Silja Kuivamäki[1], Paula Korhonen[1], Raisa Giniatullina[1], Ilkka Fagerlund[1], Juho Kalapudas[2], Elina Penttilä[3], Heikki Löppönen[3], Katja Kanninen[1], Anne Koivisto[2], Rashid Giniatullin[1], Tarja Malm[1]
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Aims: During circulation through the body red blood cells (RBCs) experience substantial mechanical forces. RBCs are equipped with mechanosensitive Piezo1 channels which help these cells to squeeze through narrow capillaries in the microcirculatory bed. Brain microcirculation is essentially impaired in Alzheimer's disease (AD) which might require a compensatory change in the function of Piezo1 channels. Here we aimed to investigate whether the Ca^{2+} gating properties of Piezo1 are altered in RBCs in the context of AD.
Methods: We used a small molecule agonist, Yoda1, to activate Piezo1 in RBCs. Fresh mouse blood samples, taken from *v. saphena* at specific timepoints (19, 21, 23, 25 weeks) of wild-type and 5xFAD mice, and human blood from cubital vein of healthy control (HC), patients with mild cognitive impairment (MCI) and patients with Alzheimer disease (AD) were stained with Fluo4 dye. Yoda1-induced Ca^{2+}- responses were evaluated using a flow cytometry assay in a time-lapse mode.
Results: RBCs obtained from the 5xFAD transgenic mouse model of AD showed significantly decreased Ca^{2+}- response to Yoda1 application in female mice at the age of 17-19 weeks and in male mice at the age of 23 weeks. RBCs obtained from patients with MCI (prodromal AD) and AD patients showed significantly higher responses compared to RBCs from age-matched healthy controls. The Yoda1 elicited responses in mouse and human RBCs correlated with the plasma levels of Aβ. Our data indicate that AD-linked alterations in the plasma levels of Aβ modulate the Ca^{2+} gating properties of Piezo1 channels.
Conclusions: The intensity of Yoda1 elicited activation of Piezo1 in RBCs may be used as a functional biomarker of AD.

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P0434 / #2245

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PROTEOMIC AND TRANSCRIPTOMIC CONTENT OF PLASMA EXTRACELLULAR VESICLES FROM AD PATIENTS DIFFERS FROM HEALTHY CONTROLS

Maria Solaguren-Beascoa Negre[1], Ana Gámez-Valero[1,2], Ana María Ortiz[3], Carla Minguet-Parramona[4], Ricardo Gonzalo[4], Georgia Escaramís[1,2], Montserrat Costa[4], Eulàlia Martí[1,2]
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Aims: Biomarkers for Alzheimer's disease (AD) are important for diagnosis, prognosis and for treatment eligibility. Transcriptomic deregulation is an early event in the course of AD, occurring at pre-symptomatic stages. Several studies have explored the utility of plasma miRNAs and cell-free mRNA as biomarkers for AD. However, other highly abundant RNAs in plasma, especially regulatory non coding RNA species, have been largely overlooked. Extracellular RNA can be found as freely circulating and/or enclosed inside extracellular vesicles (EVs). EVs are known to mediate cell-to-cell communication and their content can reflect the physiological and/or pathological state of the cell/tissue of origin. In AD, EVs have been reported as important players in spreading AD pathology between brain cells. Nevertheless, the biomarker potential of plasma EVs content (proteins and small RNAs, sRNAs) has been scarcely explored in previous studies on AD. The aim of the present proposal is to characterize the molecular of plasma EVs in AD patients in comparison to healthy individuals to identify new molecules with high biomarker potential.
Methods: Plasma samples from mild-to-moderate AD patients (n=10) and age matched healthy non-cognitive affected individuals (n=10) were processed by size exclusion chromatography to obtain EVs following the MISEV guidelines.
Results: comprised the identification of upregulated proteins in AD EVs which were mainly involved in protein folding processes as predicted by pathway enrichment analyses. Regarding sRNA vesicular content, s AD-EVs overexpressed sRNAs mapping onto genes already described as altered in AD, and some deregulated miRNAs previously reported in plasma of AD patients.
Conclusions: The current study suggests that the content of plasma EVs from AD patients differ from healthy controls and deserve further investigation as it could contribute to assess a new specific diagnostic blood biomarker panel.

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P0435 / #2459

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LC- MS/MS-BASED BLOOD TEST FOR DETECTION OF EARLY STAGES OF COGNITIVE IMPAIRMENT BY USING PLASMA PROTEIN BIOMARKER PANELS

Makoto Inoue[1], Shan Liu[2], Hideaki Suzuki[1], Kohji Meno[1], Tatsumi Korenaga[1], Hiroyasu Akatsu[3], Noriyuki Matsukawa[3], Takashi Asada[4], Tetsuaki Arai[5], Kazuhiko Uchida[2]
[1]MCBI, Research Division, Tsukuba, Japan, [2]MCBI, Institue For Biomedical Research, Tsukuba, Japan, [3]Nagoya City University, Faculty Of Medicine, Nagoya, Japan, [4]Memory Clinic, Memory Clinic, Tokyo, Japan, [5]University of Tsukuba, Faculty Of Medicine, Tsukuba, Japan

Aims: For the prevention of dementia, noninvasive screening methods which detect the signs of cognitive decline before clinical symptom occurs are needed. A combination of blood proteins could be a promising biomarker for monitoring the progression of cognitive decline from early stages of the disease. Here, we developed LC-MS/MS-based blood test using 9 plasma protein panels to explore accurate and practical screening of cognitive impairment at early stages.
Methods: We constructed a robust and reproducible LC-MS/MS blood test system equipped with MRM to quantify plasma proteins with relatively high amounts using isotope-labeled synthetic peptide. The levels of plasma biomarker proteins and plasma Aβ 42/40 from 1059 cases (485 cognitive normal, 64 SCD, 285 MCI, 225 AD) were determined. Multinomial regression and C statistics were performed to identify the combination of the plasma protein panels that could discriminate NDC vs. MCI and/or AD. Relationship between these protein levels and cognitive assessment scores and hippocampal volumes was analyzed.
Results: We found 9 interpretable protein biomarker candidates in plasma for MCI and AD, which were related to protein nutrition, lipid metabolism, innate immunity/inflammation, and contact system. Some of them are involved in the neurovascular unit injury. Levels of α2-antiplasmin and complement protein C3 were significantly reduced, and α2-macroglobulin was significantly increased in MCI and AD comparing to cognitive normal. α2-antiplasmin and albumin levels were positively correlated with Aβ 42/40 ratio. Hemopexin was positively related to CDR-SB. Furthermore, we constructed composite scores optimized for male and female using these plasma protein panels to discriminate early stages of cognitive impairment from NDC.
Conclusions: LC-MS-based plasma protein panels interpretable for pathophysiology of AD detect signs of cognitive decline and progression of the disease.

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P0437 / #1089

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CSF DIAGNOSTICS OF ALZHEIMER'S DISEASE IN INPH

Aleksi Vanninen[1,2], Heikki Lukkarinen[1,2], Tuomas Rauramaa[3,4], Merja Kokki[5,6], Tadeusz Musialowicz[5,6], Anne Koivisto[7,8,9,10], Mikko Hiltunen[11], Tarja Kokkola[7], Sanna-Kaisa Herukka[7,8], Ville Leinonen[1,2]
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Aims: Alzheimer's disease (AD) is a common comorbidity in idiopathic normal pressure hydrocephalus (iNPH) and leads to worse surgical outcome. Diagnosis of AD in iNPH patients is challenging because of the effect of iNPH on cerebrospinal fluid (CSF) biomarkers. Our aim was to estimate the effect size of iNPH on CSF biomarker levels to improve their diagnostic value.
Methods: Our cohort features 222 iNPH patients from whom CSF AD biomarker ($A\beta_{42}$, T-Tau, P-Tau_{181}) data, clinical data and brain biopsy data has been collected into Kuopio iNPH and AD registry. These patients were divided into groups according to the presence of AD pathology. For controls we had a cognitively healthy cohort (N = 33) and AD cohort (N = 39). CSF samples were analyzed with Innotest and Roche-Elecsys kits. SPSS by IBM was used for analyses. Independent samples t-test was used to compare biomarkers between groups. Sensitivity and Specificity for differentiation between AD pathology was calculated. Ratio of $PTau_{181}/A\beta_{42}$ for cutoff was obtained from linear regression analysis.
Results: All investigated biomarkers between groups were statistically significant except for tau between control groups and iNPH AD+ groups. Table 1 presents Sensitivity and specificity for AD pathology from CSF diagnostics. $PTau_{181}/A\beta_{42}$ ratio yielded a sensitivity of 0.75 and specificity of 0.76 and ROC AUC of 0.806. Table 1

	AD biomarkers no correction	AD biomarl
Sensitivity	0.008	0.024
Specificity	1	1

Cutoff values were: < 715 pg/ml for $A\beta_{42}$, > 260 pg/ml for Tau, > 26 pg/ml for $PTau_{181}$
Conclusions: Correcting for the effect of iNPH on CSF markers of AD yielded only modest effect on the diagnostic performance. $PTau_{181}/A\beta_{42}$ ratio seems to be moderately effective for predicting AD pathology in iNPH patients.

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P0438 / #2370

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

THE EUROPEAN PLATFORM FOR NEURODEGENERATIVE DISEASES (EPND)

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Aims: Biomarker discovery, development, and validation are reliant on large-scale analyses of high-quality samples and data. Discovery, access, and sharing of data and samples are hindered both by silos that limit collaboration, and by complex requirements for secure, legal, and ethical sharing. The European Platform for Neurodegenerative Diseases (EPND) project was set-up to address these challenges. In this presentation we will give an overview of the design of EPND and the achievements in the first year of the project.
Methods: EPND is a multidisciplinary consortium of 29 partners with expertise on data discovery, ethical, legal and regulatory aspects of data sharing, biomarker studies, stakeholder engagement and sustainability. EPND will leverage an existing data platform developed by the Alzheimer's Disease Data Initiative (ADDI), which will allow the platform to connect to a global network of datasets. The project is funded by the Innovative Medicines Initiative (IMI, grant agreement number 101034344). It is a 5-year project that started 1-11 2022 (EPND.org).
Results: In this first year of the study, the design of the data platform has been finalised. We completed a white paper on ethical, legal and regulatory aspects of data and sample sharing. We have developed standardized operational procedures on sample selection, biobanking, and data harmonisation. The project engaged 60 cohorts that give access to data of over 40000 patients and to 30000 CSF samples. We performed studies on ATN biomarkers and complement factors in plasma and blood in 350 patients with Alzheimer's disease, Parkinson's disease and Lewy Body dementia.
Conclusions: We initiated a multidisciplinaty consortium with the goal to accelerate research into the discovery and validation of biomarkers to support development of diagnostics and disease-modifying therapies for Alzheimer's disease and other neurodegenerative diseases.

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P0439 / #1027

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

AB42/40 RATIO IN PLASMA AND CSF - PERFORMANCE OF TWO ULTRASENSITIVE IMMUNOASSAYS TARGETING AMYLOID N-TERMINUS AND MID-REGION

Anna Wojdala[1], Davide Chiasserini[1], Giovanni Bellomo[1], Silvia Paciotti[1], Andrea Toja[1], Federico Paolini Paoletti[1], Lorenzo Gaetani[1], Dandan Shan[2], Lucilla Parnetti[1]
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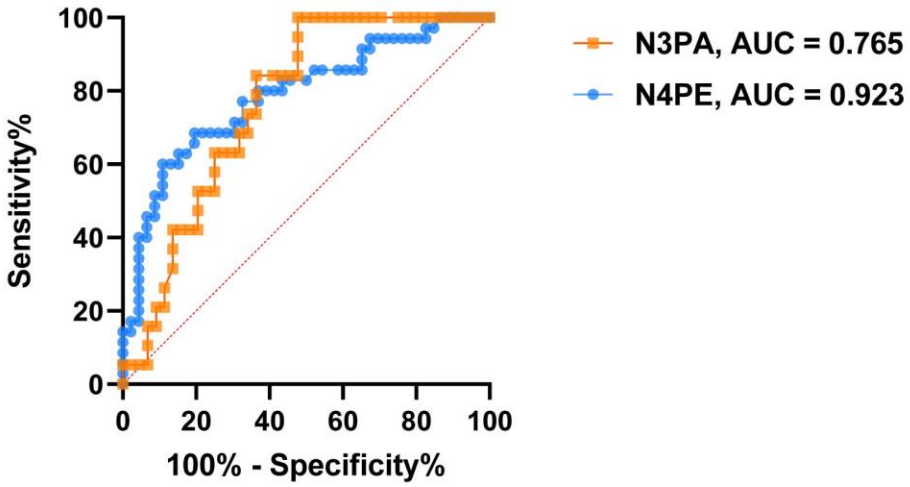
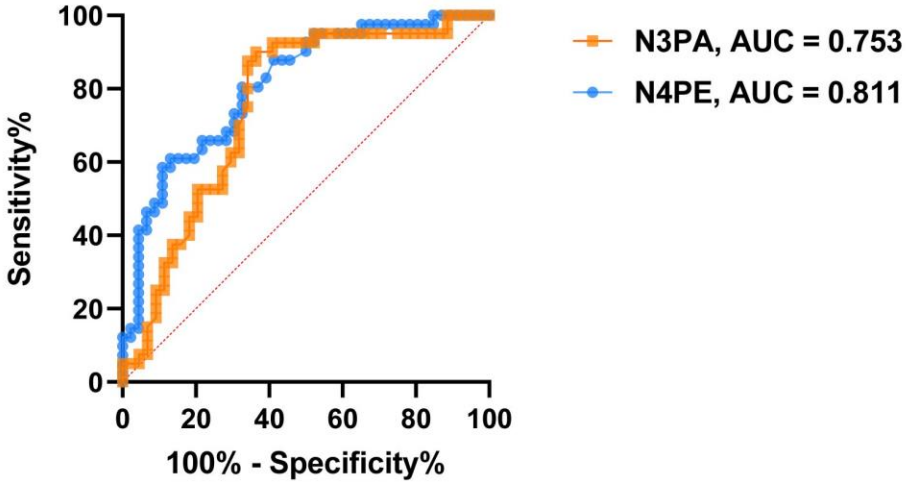
Aims: Decreased CSF amyloid beta 42/40 ratio (Aβ42/40) reflects brain amyloidosis and is one of the core biomarkers of Alzheimer's disease (AD). The validity of plasma Aβ42/40 for diagnosis of AD is still a matter of debate. In the current study, we aimed to evaluate diagnostic performance of two ultrasensitive immunoassays targeting distinct regions of the amyloid peptides in both CSF and plasma.
Methods: We used Simoa® N4PE and N3PA kits to analyze cerebrospinal fluid (CSF) and plasma levels of Aβ42, Aβ40, and calculate Aβ42/40 in a cohort of 141 patients (CSF core AD biomarkers measured with the LUMIPULSE® G600II, Fujirebio). The two assays use detector antibodies targeting different amyloid regions, namely N-terminus (N4PE) and mid-region (N3PA). The enrolled cohort included: 1) patients across the AD continuum: preclinical AD (pre-AD; positive CSF biomarker profile without a cognitive impairment), mild cognitive impairment due to AD (MCI-AD), and AD-dementia (AD-dem), 2) cognitively healthy individuals with other neurological disease and negative AD CSF biomarker profile (CTRL).
Results: CSF Aβ42/40 measured by both assays enabled an optimal differentiation of all AD stages from CTRL. For both N4PE and N3PA assays, AUC CTRL vs. all combined AD continuum groups was significantly more accurate for CSF when compared with plasma. Plasma measurements of Aβ42/40 exhibited lower ability to discriminate AD stages from CTRL (AUC range pre-AD/MCI-AD/AD-dem vs. CTRL=0.73-0.92). N4PE assay for plasma Aβ42/40 provided a better performance in discriminating AD from CTRL when compared with N3PA assay.

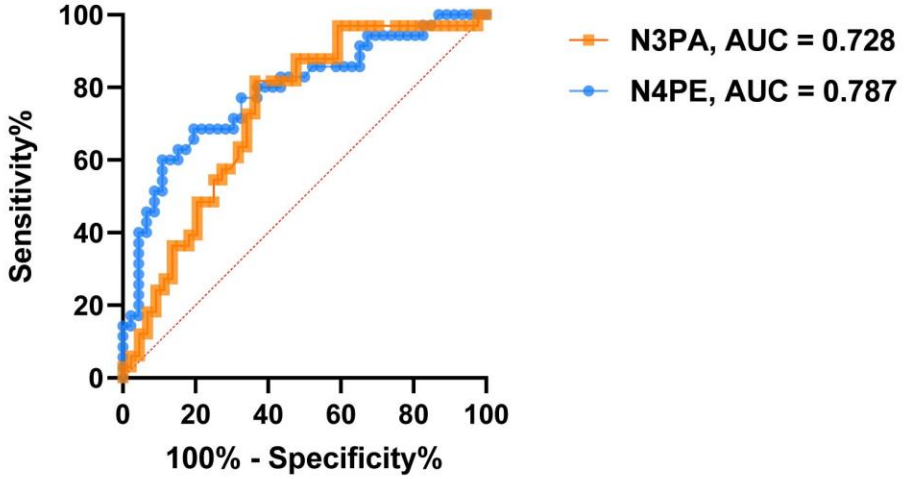
ROC curve - plasma Aβ42/40 CTRL vs. pre-AD



ROC curve - plasma Aβ42/40 CTRL vs. MCI-AD



ROC curve - plasma Aβ42/40 CTRL vs. AD-dem



Conclusions: CSF Aβ42/40 allows to discriminate AD from CTRL, irrespective of the type of Simoa® immunoassay used. Plasma Aβ42/40 measured by N4PE assay exhibits higher ability to identify AD when compared with N3PA assay.

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P0440 / #1042

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CSF AND PLASMA LEVELS OF CLASSICAL AND CANDIDATE BIOMARKERS ALONG THE ALZHEIMER'S DISEASE CONTINUUM

Anna Wojdala[1], Giovanni Bellomo[1], Lorenzo Gaetani[1], Dandan Shan[2], Silvia Paciotti[1], Andrea Toja[1], Elena Chipi[1], Federico Paolini Paoletti[1], Davide Chiasserini[1], Lucilla Parnetti[1]
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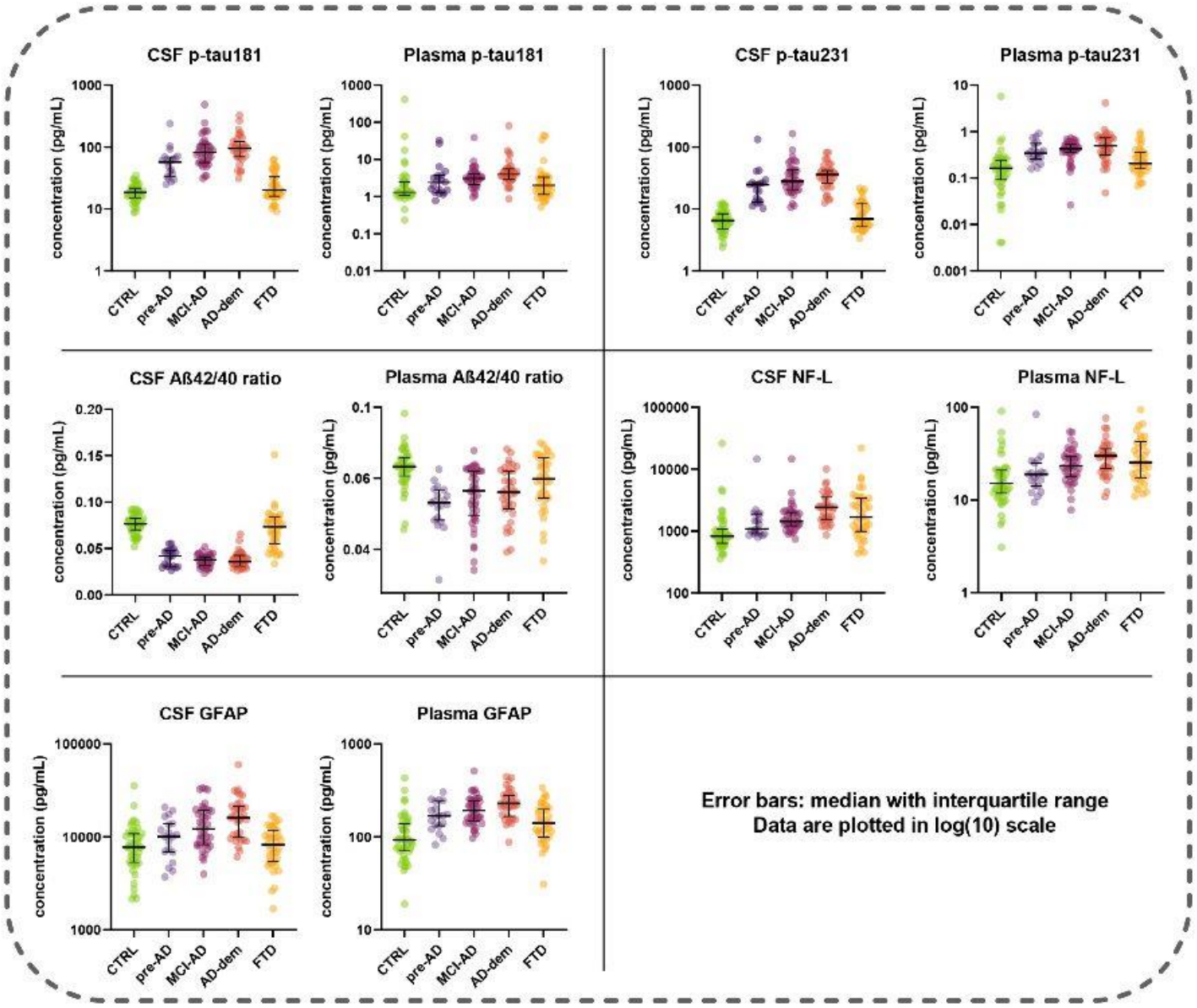
Aims: The rapid development of ultrasensitive technologies is enabling measurement of Alzheimer's disease (AD) biomarkers in plasma. We aimed to evaluate whether the disease-related changes in levels of classical and candidate AD biomarkers are concordant in cerebrospinal fluid (CSF) and plasma across all the stages of AD continuum.
Methods: We used Simoa® kits to analyze CSF and plasma levels of p-tau181, p-tau231, total-tau, NF-L, GFAP, and UCHL-1, and CSF levels of SNAP-25 in a cohort (n=180) with CSF core AD biomarkers measured (LUMIPULSE® G600II, Fujirebio). The cohort included preclinical AD (pre-AD; positive CSF AD biomarker profile without cognitive impairment), mild cognitive impairment due to AD (MCI-AD), AD-dementia (AD-dem), frontotemporal dementia (FTD), and cognitively healthy subjects with other neurological disease and negative CSF AD biomarker profile as a control group (CTRL).
Results: 1) Classical AD biomarkers: CSF and plasma Aβ42/40, p-tau181, and p-tau231 levels were significantly correlated; plasma Aβ42/40 and p-tau231 enabled accurate differentiation between pre-AD vs. CTRL (AUC=0.92 and 0.85, respectively). AUC AD vs. FTD for plasma Aβ42/40 and p-tau231 were 0.67 and 0.75, respectively. 2) Candidate biomarkers: CSF and plasma levels of NF-L and GFAP were highly correlated; biomarkers enabling differentiation between pre-AD vs. CTRL and AD vs. FTD were CSF SNAP-25 (AUC pre-AD vs. CTRL=0.89, AD vs. FTD=0.87) and plasma GFAP (AUC pre-AD vs. CTRL=0.81, AUC AD vs. FTD=0.72). 3) Spearman's correlations analysis indicated that CSF NF-L (ρ=0.45), p-tau181 (ρ=0.36), and GFAP (ρ=0.31), as well as plasma NF-L (ρ=0.36), p-tau181 (ρ=0.31), and GFAP (ρ=0.28) were significantly correlated with AD staging (pre-AD, MCI-AD, AD-dem).



Conclusions: Head-to-head comparison of selected CSF and plasma biomarkers revealed matrix-dependent differences in their potential diagnostic utility for an early and specific diagnosis within the AD continuum.

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P0441 / #886

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

DOMINACE OF PLASMA BIOMARKERS IN ALZHEIMER'S DISEASE, PARKINSON'S DISEASE AND FRONTOTEMPORAL DEMENTIA

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Aims: Amyloid plaques and tau tangles are pathological hallmarks of Alzheimer's disease (AD). Parkinson's disease (PD) results from the accumulation of α-synuclein. TAR DNA-binding protein (TDP-43) and total tau protein (T-Tau) play roles in FTD pathology. All of the pathological evidence was found in the biopsy. However, it is impossible to perform stein examinations in clinical practice. Assays of biomarkers in plasma would be convenient. It would be better to investigate the combinations of various biomarkers in AD, PD and FTD.
Methods: Ninety-one subjects without neurodegenerative diseases, seventy-six patients with amnesic mild cognitive impairment (aMCI) or AD dementia, combined as AD family, were enrolled. One hundred and nine PD patients with normal cognition (PD-NC) or dementia (PDD), combined as PD family, were enrolled. Twenty-five FTD patients were enrolled for assays of plasma amyloid β 1-40 ($A\beta_{1-40}$), $A\beta_{1-42}$, T-Tau, α-synuclein and TDP-43 using immunomagnetic reduction (IMR).
Results: The results show that Aβs and T-Tau are major domains in AD family. α-synuclein is superdominant in PD family. FTD is closely associated with TDP-43 and T-Tau. The dominant plasma biomarkers in AD family, PD family and FTD are consistent with pathology.
Conclusions: This implies that plasma biomarkers are promising for precise and differential assessments of AD, PD and FTD in clinical practice.

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P0442 / #1402

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

IDENTIFYING VARIANTS OF POSTERIOR CORTICAL ATROPHY USING CLINICAL CLASSIFICATION OR MR-BASED MACHINE LEARNING

Elisa Canu[1], Federica Agosta[1,2,3], Camilla Cividini[1], Maria Antonietta Magno[1], Maxime Montembeault[4], Silvia Basaia[1], Giulia Visentin[1], Francesca Caso[2], Giuseppe Magnani[2], Richard Levy[5,6], Raffaella Migliaccio[5,6], Massimo Filippi[1,2,3,7,8]

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Aims: To detect variants of posterior cortical atrophy (PCA) using clinical classification or a data driven machine learning approach based on MRI network metrics.
Methods: We recruited 36 PCA patients and 69 healthy controls. All subjects underwent cognitive examinations, lumbar puncture and a 3T MRI. Patients were first categorized in ventral (vPCA,N=19) and dorsal (dPCA,N=17) variants based on the current diagnostic criteria. Sociodemographic, clinical, cognitive as well as topological brain network properties using graph analysis and connectomics were compared between groups. K-means clustering was performed on the whole group of patients considering both demographics and graph metrics of the occipital, temporal, and parietal lobes, as informative features. Sociodemographic, clinical, cognitive and CSF characteristics of the two clusters were compared.
Results: vPCA and dPCA were similar for sociodemographic, clinical and CSF features. Relative to controls, only vPCA patients showed alterations of all global, temporal, and parietal metrics. The k-means analysis identified two clusters of 26 and 10 subjects, similar for clinical and cognitive features. However, patients from Cluster 1 were significantly younger and had lower levels of CSF amyloid-b compared to Cluster 2 patients.
Conclusions: Our findings suggest the potentially high sensitivity of graph-analysis and connectomic in capturing signs of neurodegeneration in PCA. The MRI-based machine learning approach, albeit unable to capture clinical phenotype differences, provided indications about underlying disease pathology. These findings offer potential biomarkers for non-invasive diagnosis of neurodegenerative conditions. **Fundings.** Italian Ministry of Health (#GR-2010-2303035; #GR-2011-02351217), Philippe Chatrier and France Alzheimer Foundations, Fondation pour la Recherche sur Alzheimer.

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P0443 / #2791

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

EEG-BASED EARLY PREDICTION OF COGNITIVE DECLINE IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT AND EARLY-STAGE ALZHEIMER'S DISEASE

Ofir Laufer, Eran Riva, Tehila Stern, Gil Issachar
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Aims: Alzheimer's disease (AD), the most common cause of dementia, is becoming increasingly prevalent in modern society. In some cases, mild cognitive impairment (MCI) can progress into AD, but not all subjects with MCI do. By predicting cognitive deterioration before it is behaviourally evident, AD could be treated earlier and more effectively. Electroencephalography (EEG), measured in a non-invasive and relatively affordable manner, may be used to predict future deterioration and, ultimately, conversion to AD. Nonetheless, studies of EEG-based biomarkers for early-detection of cognitive decline are few and fail to achieve sufficient accuracy. Here, we aim to combine the information from multiple EEG features into a prognostic biomarker in order to improve the accuracy of predicting cognitive deterioration within a 0.5-1-year period.

Methods: Subjects diagnosed with MCI (N=26) and early-stage Alzheimer's disease (EAD, N=14) from The Villages Health centers (FL, USA) were followed for 1 year, while their resting-EEG data and clinical measures were recorded. Subjects were divided into cognitively stable ('No Change') and 'Cognitive Deterioration' groups based on the overall change in MMSE scores, using a 2-point decrease as a threshold for deterioration. EEG features were selected for analysis based on three criteria: indication in scientific literature; sensitivity to baseline differences between healthy subjects and subjects diagnosed with MCI or Early-stage Alzheimer's disease; and high test-retest reliability (calculated on an internal database of normative subjects). EEG features were then compared between the cognitive change groups within MCI subjects, and highly predictive scores were validated on EAD subjects.

Results: Multiple baseline EEG measures related to activity in the theta- and alpha-frequency ranges (4-8 and 8-12 Hz, respectively) were associated with subsequent cognitive deterioration in MCI subjects (ROC-AUC=0.90), resulting in better performance compared to classification using baseline MMSE scores (AUC=0.58) and a word list memory task performance (AUC=0.73). The predictive performance of the EEG measures was further validated by adding the EAD subjects (ROC-AUC=0.81).

Conclusions: We suggest that a combination of resting-EEG markers are more sensitive to disease trajectory compared with standard behavioural tests. These EEG markers can improve the monitoring of disease progression and may prevent its advance, and also increase statistical power and facilitate the early demonstration of proof of concept in clinical trials by accurately identifying patients who are at a greater risk for disease deterioration that the drug is intended to decrease.

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P0444 / #1997

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

RESTING-STATE BRAIN ACTIVITY ASSOCIATED WITH COGNITIVE DECLINE IN PATIENTS WITH PARKINSON'S DISEASE

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Aims: Electrophysiological measurements, such as magnetoencephalography and electroencephalography, provide promising biomarkers for cognitive impartment and dementia. They measure oscillatory intensity of brain activities whose changes are associated with patients' cognitive status. Enhanced low-frequency oscillatory activities accompanied by attenuated high-frequency oscillatory activities are the typical characteristics found in electrophysiological data of patients with dementia. However, patients with Parkinson's disease, who are at risks of dementia, sometimes show atypical changes in their activities including enhanced high-frequency oscillatory activity. We hypothesised that the enhanced high-frequency oscillatory activity among patients with Parkinson's disease reflect the levels of their cognitive impairment.
Methods: We analysed clinical data acquired from 25 patients with Parkinson's disease retrospectively. The data include resting-state magnetoencephalography recordings with eyes-closed for 5-min, and Mini-Mental State Examination (MMSE) scores which represent global cognitive status. Magnetoencephalography data were converted into regional brain activities using a spatially coherent source model in Statistical Parametric Mapping software at each frequency band of delta, theta, alpha, beta, low-gamma, and high-gamma. The relationships between intensities of the regional brain activities and MMSE scores at each frequency band were evaluated using regression analysis, where patients' age was considered as a covariate of no-interest.
Results: Enhanced intensities of high-frequency oscillatory activities (i.e., alpha, beta and low-gamma) at around bilateral central gyrus were associated negatively with MMSE score, which was accompanied with enhanced low-frequency oscillatory activities (i.e., delta and theta) in the left parietal lobes.
Conclusions: The results demonstrated that enhanced high-frequency oscillation can be a sign of cognitive impairment of patients with Parkinson's disease. The additional focus on the activity, as well as the typical attenuated high-frequency oscillation, may improve the accuracy of electrophysiological biomarkers for cognitive impairment.

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P0445 / #1285

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

PREDICTION OF LONG TERM TREATMENT OUTCOME IN ALZHEIMER'S DISEASE BASED ON EEG CONNECTIVITY

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Aims: Both acetylcholinesterase (AChE) inhibitor and non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptor are approved for the clinical treatment of Alzheimer's disease (AD). However, it is difficult to predict of long-term treatment response of AD to medical treatment when starting medication. We explored EEG brain connectivity as a potential biomarker for long-term medication outcomes in patients with AD.
Methods: Resting-state EEG was recorded from a total of 56 AD patients (mean age = 73.23 ± 6.39) when starting medication after diagnosis of AD. EEG was recorded in 32 channels. EEG signals were amplified and digitized at 400 Hz. We divided the patients into good and poor respondent groups according to clinical evaluation after treatment and dosage changes of AD medication with MMSE and CDR change. We analyzed brain EEG connectivity among the 246 cortical regions defined by the Brainnetome atlas using the fieldtrip toolbox by evaluating spectral coherence for five frequency bands (delta, theta, alpha, beta, and gamma). We then analyzed each EEG connectivity between groups using ANCOVA with age, sex, and the initial MMSE scores as covariates.

Results: Intrahemispheric regional connectivity in gamma frequency bands, is increased in multiple regions of the right hemisphere, such as between Brodmann Area (BA) 44 and BA 39, such as DLFPC and hippocampal areas, DLFPC and caudate nucleus, middle frontal and inferior parietal areas in the poor respondent group ($p<0.00001$)
Conclusions: This study shows increased gamma bands EEG connectivity between right anterior and posterior areas in the poor respondent group. In general cortical gamma-band activity is increased by selective attention in normal populations and is related to the cholinergic system.

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P0446 / #302

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

NORMS FOR THE TMA 93 (BINDING BY IMAGES) BY COGNITIVE RESERVE

Maria Bernal Sánchez-Arjona[1], Jose Arriola Infante[1], Ernesto Garcia Roldan[1], Alba Marín Cabañas[1], Gonzalo Mendoza[2], Carlota Méndez Del Barrio[2], Andrea Luque Tirado[1], Silvia Rodrigo Herrera[2], Emilio Franco Macías[1]
[1]Universitary Hospital Virgen del Rocio, Neurology, Seville, Spain, [2]Hospital Juan Ramón Jiménez, Neurology, Huelva, Spain

Aims: TMA-93 examines relational binding using images. The test has demostrated been discriminative for diagnosing early Alzheimer's disease by biomarkers. The effect of cognitive reserve on TMA-93 performance has not yet been studied. Our aim was to study the effect of cognitive reserve on TMA-93 performance and to provide norms for the test including the construct.
Methods: Cognitively unimpaired people aged 55 and over were systematically recruited for this cross-sectional normative study undertaken in Southern Spain. Age, gender, and scores on the Cognitive Reserve Questionnaire (CRQ, maximum score: 25 points) were collected, and the TMA-93 was administered and scored (maximum score: 30 points). Percentile-base reference data according to combinations of socio- demographic variables that demonstrated significant effect on TMA-93 total score were provided.
Results: 902 participants were included (62.5% female; age: median=68, IQR=68-75, range=55-90). CRQ total score was globally low (median=8, IQR=5-13, range=0-24). TMA-93 total score was better predicted by a model than included age ($p < 0.001$), and CRQ total score ($p < 0.001$). TMA-93 total scores at 10-percentile varied from 28/30 for participants aged ≤ 60 and scored >11 on CRQ to 15/30 for those aged ≥75 and scored ≤6 on CRQ.
Conclusions: Visual relational binding ability depends on cognitive reserve. TMA-93 total scores fitted perfectly the normative framework made up of combinations of age and CRQ total score.

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P0447 / #603

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

DISCRIMINATIVE ROLE OF NEUROCOGNITIVE TESTS IN THE DIAGNOSIS AND CLASSIFICATION OF DEMENTIA: A RETROSPECTIVE STUDY IN A LARGE COHORT

Amber Eker[1], Asya Meseli[2], Bugu Azizoglu[2], Cagla Albayrak[2], Musbah Khdeir[2], Nezayet Saral[2], Saadet Aktuglu[2]
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Aims: In this study, our aim is to find similarities and differences between test results of dementia and MCIpatients and between different dementia types.
Methods: In this retrospective cohort study the data was collected between the years 2011-2021. The data including demographics and neurocognitive tests of the patients from dementia clinic of Neurology Department.
Results: Out of 265 patients, 207 have dementia and 58 have MCI. The average MMSE score is 17.93 for dementia patients and 25.79 for MCI patients. Semantic fluency decline and Trail A test dysfunction are observed both in dementia and MCI(p-value >0.05). Visuospatial skill dysfunction is seen 43.1% in MCI and 85% in the dementia patients(p-value <0.05). Enhanced Cue Recall Memory Test mean score in Vascular Dementia(VD) is 38.75 and 24.69 in Alzheimer's Disease(AD). The majority of VD and Lewy Body Dementia(LBD) patients displayed Trail A attention dysfunction. Semantic fluency and categorical fluency tests are seen to be mainly impaired in Frontotemporal Dementia(FTD).
Conclusions: Different neurocognitive tests can be used to differentiate dementia types and MCI from dementia. However, some tests such as Trail A and semantic fluency testS are highly impaired in MCI as in dementia. Trail A attention. semantic fluency and categorical fluency tests are useful in the discrimination of LBD and FTD. In the end, a set of tests that is helpful in differentiation and early detection of non-invasive biomarkers can be combined to develop a battery of tests. This would be useful in the assessment of MCI and the differentiation of different degenerative dementia types. Furthermore, these batteries of tests can be adapted to artificial intelligence so there would be the availability of easily reached and self-applicable tests for physicians and the public.

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P0448 / #2495

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

APOE RS429358 AND ABCA7 RS115550680 ARE ASSOCIATED WITH GENERALIZATION OF PRIOR LEARNING BUT NOT EPISODIC MEMORY IN OLDER AFRICAN AMERICANS

Bernadette Fausto
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Aims: Hippocampal-dependent functions–such as episodic memory and generalization of prior learning–are among the first cognitive abilities to decline in preclinical Alzheimer's disease (AD). Here we aimed to: 1) elucidate which demographic, health, lifestyle and genetic factors are associated with episodic memory performance and 2) whether those factors differ from those associated with generalization of prior learning.
Methods: The sample included 467 older African American participants from the *Pathways to Healthy Aging in African Americans* longitudinal cohort study (M_{age} = 68.34 years, *SD* = 6.99; $M_{education}$ = 13.93 years, *SD* = 2.36; M_{MMSE} = 27.65, *SD* = 1.95). Participants responded to demographic, health, and lifestyle questionnaires. Participants also completed cognitive tests of episodic memory (Rey Auditory Verbal Learning Test [RAVLT]) and generalization of prior learning (Concurrent Discrimination and Transfer Task) and provided a saliva sample for APOE rs429358, ABCA7 rs115550680, and ABCA7 rs3764650 genotyping. Bayesian Additive Regression Trees (BART)–a machine learning modeling technique that accounts for missing data in both outcomes and covariates–was used rank order demographic, health, lifestyle, and genetic variables in terms of relative importance to episodic memory and generalization of prior learning outcomes.
Results: Among 25 different factors, the top three ranked factors associated with episodic memory were diastolic blood pressure, resting heart rate, and median household income. The top three factors related to generalization of prior learning included APOE rs429358, ABCA7 rs115550680, and ABCA7 rs3764650.
Conclusions: Generalization of prior learning performance may be captured by genetic risk for AD whereas episodic memory may be tapping into socio-demographic, health and lifestyle factors.

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POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

CHARACTERIZATION OF COGNITIVE DOMAINS IN INDIVIDUALS WITH MCI AND AD DEMENTIA WITH THE ALTOIDA DIGITAL NEURO SIGNATURE (DNS)

Alberto Ferrari[1,2], Maria Florencia Iulita[1,2], Robbert Harms[2], Adria Tort Merino[1,3], Maximilian Bügler[2], Ioannis Tarnanas[2,4,5,6], Antonella Santuccione Chadha[1,2], Mircea Balasa[3]
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Aims: Digital biomarkers are defined as objective, quantifiable physiological and behavioral data that are collected and measured by means of digital devices. Altoida Inc. developed a software application which uses digital biomarkers extracted from neuro-motoric data to characterize aspects of perceptual, neuro-motor, and memory function linked to human cortical information processing. We used Altoida DNS to characterize the neuro-cognitive signature of individuals who were Cognitively Normal (CN), with Mild Cognitive Impairment (MCI) or with Alzheimer's Disease (AD) dementia at the time of the assessment.
Methods: The study included 1859 cognitively normal subjects and 648 individuals with known clinical and amyloid status (positive/negative). Participants underwent one or more Altoida assessments and a score was assigned to each session in one of 13 cognitive domains (listed in Table 1) for a total 12,417 sessions. To evaluate differences in each score between each group and CN controls, a series of linear mixed effect models were used with "group" (CN, CN/Aβ+, MCI/Aβ-, MCI/Aβ+, AD dementia) as fixed effect and "subject" as random effect. Two-tailed Wald's tests on the coefficients were used to test group differences from controls.
Results: Between-group differences were observed in most cognitive domains (Table 1). Eye movement was consistently different in all groups compared to CN, it was also the only domain, together with Gait, in which the MCI/Aβ- differed from CN. Cognitive Processing Speed, Visual Perception and Planning were lower in MCI/Aβ+ and overt AD, but not MCI/Aβ-.
Conclusions: Altoida DNS can identify a specific cognitive domain signature in individuals with AD dementia and MCI, specifically MCI with Aβ positivity.

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P0450 / #2128

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

EVALUATION OF THE ALTOIDA DIGITAL NEURO SIGNATURE (DNS) IN COGNITIVELY NORMAL AND MCI INDIVIDUALS WITH HEARING LOSS - A PILOT STUDY.

Maria Florencia Iulita[1,2], Alberto Ferrari[1,2], Robbert Harms[3], Adria Tort Merino[4], Sigurd Brandt[5], Alex Costa[5], Maximilian Bügler[1], Ioannis Tarnanas[1,6,7,8], Antonella Santuccione Chadha[1,2], Mircea Balasa[4]
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Aims: Hearing loss is associated with cognitive impairment and is one of the largest modifiable risk factors for dementia prevention. We evaluated whether the Altoida DNS assessment can identify unique neuro-signatures in cognitively normal (CN) and mild cognitive impairment (MCI) individuals with hypoacusia compared with a CN reference population without hypoacusia.
Methods: We recruited CN volunteers and individuals consulting for cognitive impairment at the Alzheimer's disease and other Cognitive Disorders Unit, Hospital Clinic, Barcelona. Participants received a neurological evaluation and a standard neuropsychological assessment, as well as the Altoida test in clinic (Ipad Pro 11"). Hearing impairment was self-reported. Altoida DNS is an algorithm-based software that simulates conducting complex activities of daily living through augmented reality tasks, complemented with several motoric function tests and two speech tasks. The software evaluates the patient's performance on a battery of motor, visual, perceptual, and memory tests. We compared group differences in DNS scores by multiple linear regression with a two-tailed Wald's test on the coefficients, adjusting for age. The correlation between DNS and MMSE was assessed by linear regression.
Results: The study population consisted of 61 participants (50-82 years), grouped by clinical status: CN without hypoacusia (n=15), CN with hypoacusia (n=15), and MCI with hypoacusia (n=31). Among participants with hypoacusia, there were 11 (35.5%) with MCI and 3 CN (20.0%) who had hearing aid dependence. DNS scores were significantly lower in both groups with hearing impairment, CN ($P=0.010$) and MCI ($P<0.001$), compared with CN controls. DNS scores positively correlated with MMSE scores ($R^2=0.11$, $P=0.012$).
Conclusions: Altoida DNS found significant differences in neurocognitive performance between CN individuals with and without hypoacusia. The neurocognitive performance of MCI individuals with hypoacusia can be reliably evaluated with the Altoida DNS assessment.

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P0451 / #1903

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

USING WITHIN-PERSON PATTERNS TO ESTIMATE YEARS BETWEEN RISK INDICATORS AND CLINICAL IMPAIRMENT: RESULTS FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION

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Aims: Using within-person patterns of participants who were cognitively unimpaired (CU) at baseline, we examined years between estimated onset ages of PET amyloid positive (A+), plasma P-tau217+, preclinical cognitive change and clinical impairment (i.e., MCI/dementia).
Methods: We examined data from PET A+ Wisconsin Registry for Alzheimer's Prevention (WRAP) participants who were CU at baseline and had progressed to clinical impairment at a later visit, and who had elevated plasma P-tau217 (n=15). PET amyloid was measured using [C-11]Pittsburgh compound B (PiB); global PiB DVR ratings were used to estimate PET amyloid onset age (EAOA of PiB+ DVR=1.16). Plasma P-tau217 levels (Meso Scale Discovery platform) were used to estimate plasma P-tau217+ onset age (threshold=.37 pg/ml). In a subset, we also identified ages at which participants showed surprisingly low performance or abnormally large declines from baseline on a WRAP Preclinical Alzheimer's Cognitive Composite (PACC3) using internal, demographically adjusted reference centiles (<16th centile). We describe within-person paired differences of age at clinical impairment – ages of these other variables with means and confidence intervals.
Results: Mean(sd) ages at cognitive baseline and first visit with clinical impairment were 57.5(4.2) and 71.6(4.3). The mean(95% CI) time from each risk indicator "onset" (of biomarker+ or abnormal centiles) to clinical impairment was as follows: PiB+ onset, 19.1(14.5, 23.8); plasma P-tau217+ onset, 12.3 (9.0-15.6); abnormal on cross-sectional norms 2.2 (0.7, 3.8); and abnormal on longitudinal norms, 0.9 (-3.0, 4.8).
Conclusions: Within person patterns show variability in years between amyloid onset and plasma P-tau217 elevation to clinical impairment and illustrate how cross-sectional and longitudinal centiles may be useful to identify preclinical change. Larger samples are needed to characterize within-person timelines with other AD biomarkers and/or biomarkers associated with other dementias.

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POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

RELATIONSHIP BETWEEN MEMORY TEST OUTCOMES AND BIOMARKERS FOR ALZHEIMER'S DISEASE IN A MEMORY CLINIC SAMPLE

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Aims: Concomitance of both amyloid-beta and tau positivity is crucial for the diagnosis of Alzheimer's Disease (AD). Specific neuropsychological assessments provide information about the extent of cognitive impairment. Different neuropsychological profiles may also help to distinguish underlying pathology. Assuming that distinct cognitive functions are disturbed by different pathologies we examined the relationship between memory performance in two independent tests and AD biomarkers (amyloid-beta and phosphorylated tau).
Methods: Data of 240 patients of our memory clinic were included. All persons received the diagnostic standard procedure including comprehensive objective testing as well as cerebrospinal fluid analysis. To elucidate the relationship between amyloid, tau pathology and memory performance, respective values derived from the free delayed recall task (CERAD+) and the free and cued total values derived from the Free and Cued Selective Reminding Task (FCSRT) were compared. Binary logistic regression analyses were used to identify memory tests that predict amyloid or tau positivity best.
Results: Patients of our sample had 12 years of education on average, 53% were female and the mean age at diagnosis was 70 years. Binary logistic regression results indicate that both, free delayed recall and free and cued total recall values are significant predictors for amyloid pathology. Tau pathology was only predicted by free and cued total values used in the FCSRT.
Conclusions: Different memory tests seem to be related to either amyloid or tau positivity. Testresults provide information about the underlying pathology. Therefore selection and / or combination of assessments may improve clinical diagnosis of AD.

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P0453 / #1799

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

UNBIASED ANALYSIS OF SPATIAL LEARNING STRATEGIES USING CONVOLUTIONAL NEURAL NETWORKS

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Aims: Objectives. Assessment of spatial learning abilities is central to behavioral neuroscience and a pillar of animal model validation and drug development. Testing the integrity of hippocampal functions is specifically important in Alzheimer's disease (AD) research, however, biases introduced by the apparatus, environment, or the experimenter, represent a critical challenge to the test validity. We have recently developed the Modified Barnes Maze (MBM), a spatial learning paradigm that overcomes the inherent bias of animals in the Barnes maze towards *serial search*; The specific combination of spatial strategies employed by mice is often considered representative of the level of cognitive resources being used. Herein, we have developed an automated strategy classifier for the MBM, that can effectively provide researchers with enhanced insights towards cognitive traits in mice.
Methods: Methods. To circumvent biases introduced by feature selection and apparatus orientation, we harnessed the advantages of Convolutional Neural Networks. Following validation, we have compared the learning performance of male and female C57BL/6 mice, as well as that of male Ts65Dn, a mouse model of Down syndrome, compared with control male mice.
Results: Results. Male mice exhibited a more effective navigation ability compared with females, reflected in almost 70% usage of *direct* and *corrected* strategies by the last day of testing. *Circling*, *random search*, and *long correction* were more prevalent in females. In addition, compared to WT mice, Down syndrome mice exhibited reduced spatial strategies selection that was not reflected in latency to find the target.
Conclusions: Conclusions. We provide a machine-learning based strategy classifier that extend our understanding of mice behavior in the MBM while providing extended and more accurate cognitive assessment.

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P0454 / #1571

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

SPEECH PHENOTYPES IN COGNITIVELY HEALTHY PARTICIPANTS AT RISK OF DEVELOPING ALZHEIMER'S DISEASE

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Aims: The objective of this project was to use data-driven approaches to identify speech phenotypes in a sample of cognitively healthy participants at risk of developing Alzheimer's disease (AD).
Methods: We analyzed Clinical Dementia Rating (CDR) interview recordings from 114 participants (66% women; age range = 59-76). Participants were cognitively healthy but had risk factors for developing AD (APOE4+ and Aβ+). CDR recordings were segmented, diarized and transcribed and 8 acoustic and linguistic categories of speech features were extracted using the Winterlight speech analysis platform. For each of the feature categories we extracted principal components and performed a cluster analysis to identify speech phenotypes.
Results: Silhouette analysis yielded two clusters of participants which differed on the timing and acoustic feature categories, in the "address repeat" and "recent experience" sections of the CDR interview**.** One cluster (blue; Figure 1A) showed a significant increase in average word duration, higher hesitations, more filled pauses, and longer audio duration in the "address repeat" section. The same group also differed on acoustic features in the "recent experience" section. These results suggest that the group of participants who struggled more with the "address repeat" item also present a different speech acoustic phenotype. These clusters did not differ on conventional clinical endpoint scores, such as RBANS and MMSE, indicating that speech measures may be more sensitive than conventional cognitive batteries at preclinical stages of AD. Demographic variables such as gender and age did not have influence on the clusters.

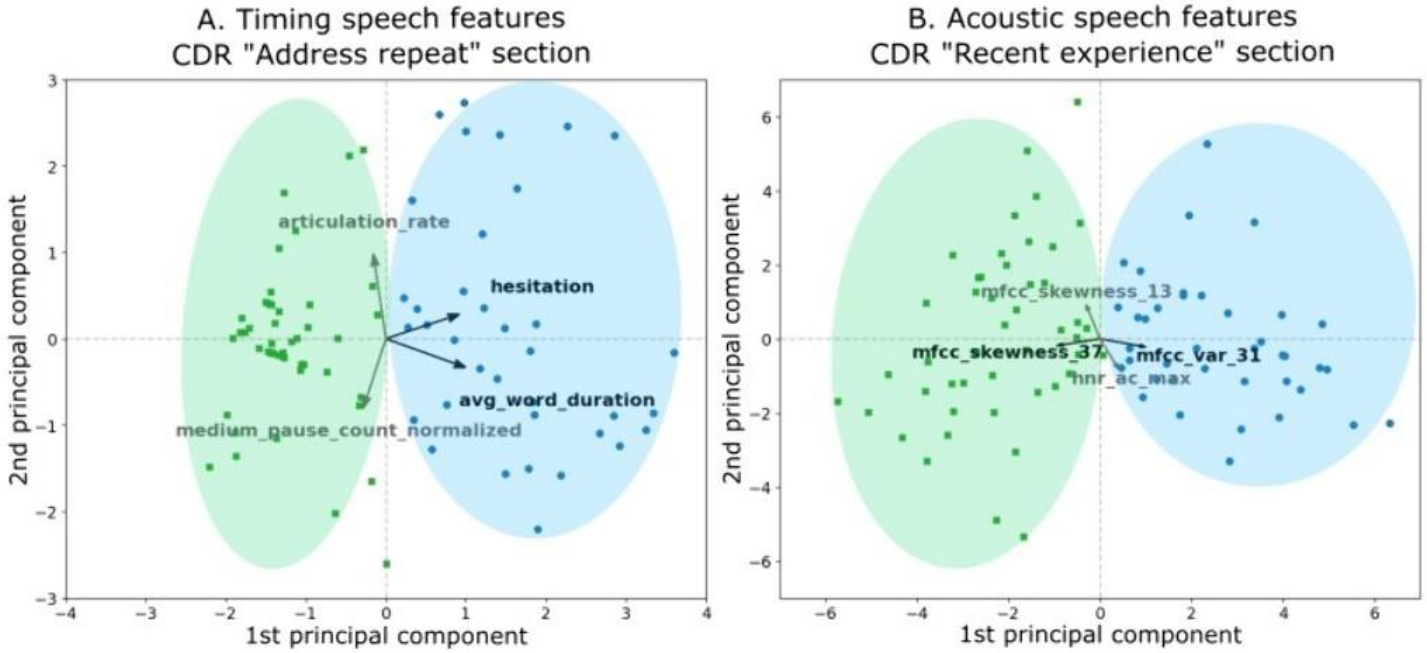

Figure 1. Cluster analysis based on the fisrt two principal components of the speech feature categories. The arrows represent the loadings corresponding to the two most relevant variables contributing to the components (first component: black; second component: grey).

Conclusions: This project demonstrates how data-driven methods can identify speech phenotypes from naturalistic,

passively collected, speech recordings. Nevertheless, more efforts are needed to understand how speech phenotypes relate to disease progression and correlate with other clinical measures and biomarkers.

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P0455 / #648

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

COGNITIVE ASSESSMENT OF FOREIGN-BORN PATIENTS

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Aims: of our studies were to elucidate the interactions between patient, interpreter and healthcare professionals in interpreter-mediated cognitive assessment, and to compare the diagnostic accuracy of Rowland Universal Dementia Scale (RUDAS) to the Mini Mental State Examination (MMSE) for detecting dementia in a multicultural group of outpatients in Swedish memory clinics.
Methods: In the first study the data consisted of audio and video recordings of 19 cognitive assessments conducted in the presence of an interpreter. In the other study we tested 123 outpatients (36 nonnative Swedish), in 4 memory clinics in Southern Sweden with RUDAS-S to supplement the usual cognitive assessment.
Results: the interpreter could affect the patient's performance and results during the dementia assessment. The interpreter could alter the meaning and content of what was communicated, sometimes change information and instructions exchanged between the patient and healthcare professionals, could avoid interpreting everything being said, and occasionally made their own corrections to what was being communicated. RUDAS had moderate to good diagnostic performance for detecting dementia in a multicultural population in Sweden, with an area under the receiver operating characteristic curve (AUC) of 0.81.
Conclusions: Alterations made by the interpreter to what was being communicated could lead to incorrect evaluation of the patient's cognitive abilities and health status. This, in turn, may lead to misjudgment of the patient's remaining resources and symptoms and their required treatment and support. RUDAS-S is at least as accurate as MMSE-SR for detecting dementia in memory clinics in Sweden and can be used for all patients undergoing a cognitive assessment, irrespective of their cultural, language, and educational background. However, there is a need for other cross-cultural cognitive tests to complement RUDAS-S to extend cognitive examination.

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P0456 / #2557

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PROGNOSTIC VALUE OF AMYLOID/TAU/NEURODEGENERATION (ATN) CLASSIFICATION IN ALZHEIMER'S DISEASE COGNITIVE CONTINUUM

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Aims: We aimed at investigating the prognostic value of amyloid/tau/neurodegeneration (ATN) classification for subsequent cognitive decline during the 3 years in the different cognitive stages of AD.
Methods: Among 331 Korean participants enrolled from a prospective, 3-year longitudinal observational study of the validation cohort of Korean Brain Aging Study for the Early Diagnosis and Prediction of AD (KBASE-V), 139 (29 cognitively normal individuals, 58 with subjective cognitive decline, 29 with mild cognitive impairment, and 23 with AD dementia) with ATN classification were included in this study. A+ was determined by abnormal amyloid PET finding or CSF Aβ42 level below cut point; T+ was determined by abnormal CSF p-tau above cut point; and N+ was determined by abnormal atrophy of cortical thickness or hippocampus. Cognitive performance was evaluated by Mini Mental State Examination (MMSE), Consortium to Establish a Registry for AD (CERAD), and Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) scores every one year over 3 years.
Results: The distribution in the subjects was as follows: A-T-N- 25.2%, A-T+N- 2.9%, A-T-N+ 28.8%, A-T+N+ 4.3%, A+T-N- 3.6%, A+T+N- 4.3%, A+T-N+ 9.4%, and A+T+N+ 21.6%. The change of MMSE relative to A-T-N- group over 3 years was significant in four ATN classes: -3.1 in A-T-N+, -5.9 in A+T+N-, -4.6 in A+T-N+, and -10.8 in A+T+N+. The CERAD relative to A-T-N- group over 3 years was significantly decreased in A-T-N+, A+T+N-, A+T-N+, and A+T+N+. The CDR-SB relative to A-T-N- group over 3 years was significantly increased in A+T-N-, A+T-N+, and A+T+N+.
Conclusions: ATN classification has a statistically significant and clinically relevant prognostic value for the course of cognitive decline in a 3-year period in Alzheimer's disease cognitive continuum. Amyloid pathology combined with tau or neurodegeneration results in cognitive decline.

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P0457 / #2737

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

UTILIZATION OF CYCLIC ION MOBILITY SPECTROMETRY FOR DETECTION AND CHARACTERIZATION OF AB(1-42) OLIGOMERS

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Aims: Development of a method for detecting Aβ(1-42) soluble oligomeric species in vitro using a state-of-the-art high-resolution cyclic ion mobility mass spectrometry system. Optimization of instrumental parameters for optimal transmission of oligomer ions and separation of isobaric monomer and oligomer ions by ion mobility.
Methods: Samples of Aβ(1-42) were incubated under various conditions to enhance the generation of soluble oligomers. Detection was performed using a SELECT SERIES Cyclic IMS instrument (Waters) with a static nanoelectrospray ion source operated with in-house pulled borosilicate emitters.
Results: Thorough optimization of instrumental parameters was essential for transmitting labile non-covalent Aβ(1-42) oligomers. Ion optics tuning and pressure gradient optimization were vital for detecting species ranging from dimer to hexamer (9 – 27 kDa). A single-pass ion mobility method was developed to separate the isobaric oligomer ions.
Conclusions: Our results show that Cyclic IMS can be employed to detect, characterize and measure soluble Aβ(1-42) oligomeric species in vitro.

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P0458 / #2346

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

SUPPORT VECTOR MACHINE APPLICATIONS ON ALZHEIMER IDENTIFICATION BY NON-CODING RNA

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Aims: The main objective of this paper is to identify individuals with Alzheimer Disease (AD) using support vector machines as the classification algorithm and non-coding RNA as the input.
Methods: The data was obtained from the publically available database GEO with the accession code GSE 212623 consisting on 130 individuals of which 47 have AD and the rest are healthy control patients. The model controlled for the age as well as the gender of the individuals included in the study. The classification algorithm used to differentiate between control cases and individuals with AD was a support vector machine (SVM) coded in Matlab. The model used as input 33 points on non-coding RNA expression per patient. There were no missing points or other noticeable quality issues in the input data. No additional pre-processing was applied to the non-coding RNA.
Results: The model was able to correctly classify 83% of the cases. The model was computationally inexpensive require less than 30 seconds for training purposes. No statistically significance difference was appreciated between the male and female groups. However, the sample size was too small to be able to extrapolate any statistically significant result regarding gender. The accuracy of the model increased when controlling for the age of the patient.
Conclusions: It seems possible to use non-coding RNA expression data in combination with machine learning techniques such as support vector machines to identify individuals suffering from AD. This can be accomplished in a computationally inexpensive way.

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P0459 / #2348

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PARKINSON IDENTIFICATION THROUGH NON-CODING RNA SIGNATURES USING SUPPORT VECTOR MACHINES

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Aims: To design a non-coding RNA signature biomarker that can identify patients suffering from Parkinson's Disease (PD) using Support Vector machine (SVM).
Methods: Non-coding RNA data was obtained from a publically available database (GEO database). This data set with accession code GSE 16658 contains data of 19 patients with as well as 13 healthy controls individuals. The dataset contains 288 non-coding RNA expression data per patient. The algorithm used for classification purposes was a support vector machine. The algorithm was implemented in Matlab. Ten times cross validation was used but the accuracy might be impacted by the relatively small data sample.
Results: The results generate a correct classification in 79% of the analyzed cases. Here was no obvious indication of overfitting in the analysis. It is acknowledged that the data base is not too large but the applied process appears robust. The training time for the algorithm was on average approximately around 22 seconds. Implementation time (after the algorithm is rained) is negligible.
Conclusions: The results are encouraging suggesting that it is possible to use support vector machine in combination with a non-coding RNA input as a technique for distinguishing between healthy control individuals and patients suffering from PD. The approach proposed should be further tested with larger datasets as they become available.

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P0460 / #2218

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

MACHINE LEARNING AIDED MIRNA ANALYSIS OF TRANSITION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER DISEASE.

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Aims: The main objective of this paper is to be able to differentiate between patients with mild cognitive impairment that evolve into Alzheimer Disease (AD) and patients with mild cognitive impairment that do not evolve into AD by using miRNA data using machine learning techniques
Methods: Data for 197 patients were obtained for the publically available database GEO with accession code GSE150693. The dataset contain miRNA 2,562 miRNA data for all these 197 individuals. 83 of these individuals eventually evolve from the mild cognitive impairment to AD while the rest does not. An artificial neural network was applied to this data to try to differentiate between these two categories of individuals. The structure of the artificial neural network was composed of one hidden layer with 50 artificial neurons. The data was divided into a training and a testing data set. The testing data set was not used during the training phase. The training algorithm used was the gradient secant. All the calculations were carried using the software package Matlab.
Results: The proposed approach, using artificial neural networks as the classification algorithm and miRNA data as input, reached a successful classification rate of 76.7% in the testing dataset. The testing data set if the out-of-sample data set not used during the training phase. The algorithm was computationally inexpensive, requiring less than a minute for training purposes.
Conclusions: Machine learning technique can be applied to miRNA data to differentiate individuals with mild cognate impairment that will developed Alzheimer Disease and those who will also having mild cognitive impairment will not developed the illness.

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P0461 / #2229

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PARKINSON IDENTIFICATION THOUGH MIRNA DATA AND ARTIFICIAL NEURAL NETWORKS

Gerardo Alfonso Perez
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Aims: The main objective is to distinguish between control patients and patients suffering from Parkinson's Disease (PD) using miRNA data by the application of artificial intelligence techniques such as neural networks.
Methods: This paper uses data from the publically accessible database GEO, with an accession code GSE16658, consisting of 32 individuals of which 19 have PD. After some data quality checks 288 miRNA data were used for each individual. Sets with multiple data missing were excluded from the analysis. The techniques used to try to successfully distinguish between control and PD cases was an artificial neural network. Neural networks are a well-known artificial intelligence technique with applications in multiple fields. 25% of the cases were set asides as testing data while the rest was used to train the algorithm. The selection of this 25% testing dataset was carried out randomly to try to avoid introducing biases in the analysis. The division of the data into two datasets (training and testing) is carried out to minimize the risk of overfitting in the model, which is a common problem among many machine learning techniques.
Results: The classification error obtained was relatively small (12.5%). This 12.5% classification error refers to the classification error in the above mentioned testing data set containing 25% of the data (which was not used during the training phase).
Conclusions: The results suggest that it is possible to identify individuals with PD using miRNA data and machine learning techniques such as artificial neural networks.

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POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

MACHINE LEARNING APPROACH TO NON-CODING RNA IN ALZHEIMER DISEASE

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Aims: To use non-coding RNA for the detection of AD in patients using machine learning algorithms such as artificial neural networks.
Methods: 6,658 non-coding RNA data was obtained from the GEO database (accession code GSE157239), consisting of 16 patients. 8 patients had Alzheimer Disease while the rest were control subjects. The tissue analyzed was the temporal cortex. The data, as standard practice, was divided into a training and a testing datatset. The testing data set contained approximately 35% of the cases. The rest of the cases were included in the training dataset. This non-coding RNA data was used as an input in an artificial neural networks, consisting of a hidden layer (with 50 neurons in that layer). The training algorithm was Levenberg-Marquardt.
Results: The algorithm was able to successfully classify the majority of the cases with an error rate of approximately 16.7% (out-of-sample data). The training phase of the algorithm required less than half a minute using the before mentioned artificial neural network configuration.
Conclusions: Non-coding RNA appears to be useful as a potential biomarker for the identification of Alzheimer disease using artificial neural networks as the classification algorithm. This approach could be used to try to objectively differentiate between patients with AD and control patients.

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P0463 / #1432

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

CHARACTERISING PARKINSONIAN EYE MOVEMENTS: NOVEL APPROACHES USING MACHINE LEARNING

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Aims: Objectives There is no objective diagnostic test for neurodegenerative disorders such as Parkinson's disease (PD). As saccadic eye movements are fast, non-fatiguing, and can be measured objectively and non-invasively, they are a promising candidate for quantifying motor and cognitive dysfunction in PD, as well as other neurological conditions. In this study, we evaluate the latency (reaction time), damping (resistance to oscillation), and amplitude of saccades in patients with Parkinson's disease and healthy controls. We also develop machine learning approaches to differentiate between patient groups using the raw saccadic data.
Methods: Two saccadic tasks were performed by a group of PD patients with mild to moderate disease and an age-matched healthy control group, participating in the Oxford Quantification in Parkinsonism (OxQUIP) study. We investigate the effects of disease status and task on the saccadic latency, damping ratio, and amplitude using generalised linear mixed models. Then, we evaluate the performance of two machine learning models (logistic regression and random forest) in a classification task to differentiate patients from controls. Finally, we introduce a proof-of-concept convolutional neural network to extract information from the raw eye position data and use this to differentiate between patient phenotypes.
Results: As well as general increases in reaction time caused by PD, the damping of saccadic eye movements was found to be task-dependent and affected by disease. The machine learning algorithms used were able to differentiate between patients and controls.
Conclusions: Future models based on those developed here have the potential to benefit the diagnosis of movement disorders, monitoring of disease progression, and evaluation of candidate treatments.

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POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

REDUCED IRON LEVELS IN SUPERFICIAL WHITE MATTER IN ALZHEIMER'S DISEASE

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Aims: Superficial white matter (SWM), defined as the thin white matter layer between the cortical gray matter and deep white matter (DWM), contains intracortical connections facilitated by short U-fibers. Several imaging and histological studies revealed increased iron levels in the SWM in health and disease. In Alzheimer's disease (AD), a general increase of brain iron in specific regions is observed. However, little is known about iron in SWM in AD. On the other hand, damaged SWM is linked to AD-related cognitive impairment. In this work, we investigated the iron content in the SWM in the human brain.
Methods: We performed histological staining and magnetic resonance imaging (MRI) to visualize iron in the frontal lobe of *post mortem* brain tissue of three neuropathologically assessed AD cases and one control case. Quantitative MRI was performed using a gradient echo sequence to map R_2* relaxation. Histological staining was done with diaminobenzidine-enhanced Turnbull blue.
Results: The histological evaluation revealed a higher iron staining in U-fibers and a lower staining in DWM of the control compared to all AD cases. In line with histology, MRI showed higher R_2* values, indicating higher iron content, in SWM of the control compared to the AD cases. In DWM, R_2* was lower in the control compared to the AD cases.
Conclusions: In conclusion, our results indicate an iron reduction in the SWM of AD cases, while, an overall increase of brain iron in AD is known from other studies. The reduced iron content might be explained by an iron shift from the U-fibers into DWM structures. Further studies are needed to assess the function and the role of SWM and its iron content in the human brain and in the context of AD.

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P0465 / #612

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PROTEOPHENES – AMINO ACID FUNCTIONALIZED THIOPHENE-BASED FLUORESCENT LIGANDS

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Aims: The development of small fluorescent ligands identifying protein aggregates associated with Alzheimer's disease (AD) and Parkinson disease (PD) is of great importance. Recently, luminescent conjugated oligothiophenes (LCO's) functionalized with amino acids, so called proteophenes, showed selectivity towards pathological proteinaceous species of amyloid beta- and tau aggregates in AD brain tissue, and the selectivity was highly dependent on the amino acid functionality and position along the oligothiophene backbone. To further develop the ligands, other molecular scaffolds are being chemically modified with various amino acids. For example, a group of thiophene based ligands denoted bi-thiophene-vinyl-benzothiazoles (bTVBTs) that displayed selective binding of tau aggregates in brain tissue with Alzheimer's disease, are further functionalized with amino acids to study the effect on binding selectivity.
Methods: New synthetic routes are being developed, to accomplish a library of thiophene-based fluorescent ligands functionalized with amino acids. The novel ligands' photophysical characteristics are being evaluated and staining experiments with brain sections from transgenic mouse models with AD- or PD pathology as well as human AD- and PD brain tissue are being performed.
Results: Synthetic routes for obtaining a library of thiophene-based fluorescent ligands functionalized with amino acids have been established. These ligands exhibit unique photophysical characteristics and identifies a variety of aggregated pathologies associated with AD and PD.
Conclusions: We foresee that our findings will give useful insight to how minor changes of the chemical structures of the ligands will influence their binding selectivity towards different pathological proteinaceous species, as well as increase the toolbox of fluorescent ligands intended for this purpose. The development of amino acid functionalized thiophene-based fluorescent ligands could aid in the chemical design of novel agents for clinical imaging of the pathological hallmarks involved in different neurodegenerative diseases.

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P0466 / #1955

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

ULTRASONOGRAPHY PATTERNS OF MUSCLE, NERVES AND MYOFASCIAL TRIGGER POINTS IN DIABETES MELLITUS AND OBESITY

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Aims: Ultrasound (US) is a valuable in detecting spasticity and myofascial trigger points (MTrP). Type 2 diabetes mellitus (T2DM) is associated with muscle wasting and posture injury altering ultrasound picture of muscle fibers in obese subjects. **The aim** was to assess neuromuscular ultrasound symptoms of unchanged muscles, TrPs in T2DM/obesity.
Methods: We included 32 overweight patients (24 females; 24–73 y.o.) with T2DM, BMI>30 and 20 normal weight patients (18–52 y.o.) as controls. Inclusion criteria: clinically diagnosed muscle pain (VAS 5-7) <1 month. All patients underwent general exam, precise physical tests, functional neuromuscular US using M-mode, elastography. We evaluated muscle thickness, CSA and motion, muscle trabecularity (visible bands/lines per cm), detecting central MtrPs (multifidus muscles) and peripheral (soleus muscles); evaluated nerve structure. Then patients received dry needling (DN) of detected MTrP under US guidance according to [EPMA J. 2012;3(1):13.].
Results: Muscle pattern in T2DM included ncreased echogenicity, more trabecular structure, enhanced network of hyperechoic bands 3-6/cm vs 5-10/cm with smaller hypoechoic areas (glycogen depos); lower motility, contractility. MTrPs in T2DM were smaller (1-2 mm vs 2-4 mm), contrast; decreased microvascularization (B flow); less sensitive; evoked longer needle grasp, less pronounced local muscle twitch response during DN, detected in US and ad oculus (in 48%). MTrPs shear wave elastography was 5.2±0.5 kPa vs 4.8±0.7 kPa in controls and decrease to 3.4±0.4 after treatment. Neuropathy was in 80 % in group 1; nerves US demonstrated decreasing of fascicles diameter from 1.9 to 1 mm after DN.
Conclusions: Neuromuscular ultrasound is effective to evaluate unchanged muscles, nerves and TrPs in T2DM/obesity, can provide predictive markers to monitor exercise programs; DN can indirectly improve muscle function and posture, has potential for beneficial modification metabolic health in longer terms.

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P0467 / #506

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

DIAGNOSTIC ACCURACY OF BLOOD-BASED BIOMARKERS FOR ALZHEIMER DISEASE: A META-ANALYSIS

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Aims: To examine the diagnostic accuracy of blood-based biomarkers for detecting Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI).
Methods: Seven electronic databases were comprehensively searched for studies evaluating the diagnostic accuracy of blood-based biomarkers for detecting AD or aMCI up to July 31, 2020. The pooled sensitivity, specificity, and the diagnostic odds ratio (DOR) were calculated using a hierarchical summary receiver operating characteristic model.
Results: A total of 17 studies (n = 2083) were included. Biomarker performance was then examined by using random-effects meta-analysis based on a hierarchical summary receiver operating characteristic model, yielding the DOR (diagnostic odds ratio), sensitivity, and specificity. In differentiating patients with AD from the controls, the DOR was 32.2 for the plasma Aβ42 (sensitivity = 88%, specificity = 81%), 29.1 for the plasma Aβ oligomer (sensitivity = 80%, specificity = 88%), and 52.1 for the plasma tau (sensitivity = 90%, specificity = 87%). For differentiating aMCI from the controls, the DOR was 60.4 for the plasma Aβ42 (sensitivity = 86%, specificity = 90%) and 49.1 for the plasma tau (sensitivity = 79%, specificity = 94%). The use of ultra-high sensitive technology explained the heterogeneity in the diagnostic performance of blood-based biomarkers (P = .01).
Conclusions: We suggest that blood-based biomarkers are minimally invasive and cost-effective tools for detecting AD; however, the evidence for detecting aMCI was still limited.

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P0468 / #396

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

RETINAL AND CHORIOCAPILLARIS VASCULAR CHANGES IN EARLY ALZHEIMER'S DISEASE PATIENTS USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Aims: Alzheimer's disease (AD) is a neurodegenerative disease characterized by ß-amiloyd deposition in the brain. There is currently an urgent need to find a simple, non-invasive and reliable biomarker for AD, especially in the preclinical and early stages of the disease. The retina shares with the brain the same embryological origins and it is affected by similar vascular changes. The purpose of this study was to analyze the characteristics of the retinal and choriocapillaris vascular structure by optical coherence tomography-angiography (OCTA) in patients with early AD.
Methods: 18 patients with MCI due to AD or early AD (study group) and 18 healthy age matched subjects (control group) were enrolled in the study. All participants underwent a full medical evaluation, a neuropsychological and functional status assessment, a neuroimaging assessment and an amyloid PET scan. Vascular risck factors were evaluated. The OCTA parameters analyzed were: the flow area of the choriocapillaris, vessel density and the foveal avascular zone.
Results: We found a significant reduction of the flow area of the choriocapillaris in the Study Group with respect to the Control Group (p-value: 0.001). A statistical trend of reduction was found in vessel density of the superficial capillary plexus in the Study Group with respect to the Control Group (p-value= 0.072). There was a reduction in vessel density of the deep capillary plexus in the Study Group, although not significant.
Conclusions: OCTA data from AD patients are measures that could be used as alternative biomarkers to those currently available, and that may allow more easily accessible diagnosis and monitoring of the disease, applicable even on a large scale. Further studies are necessary to better understand retinal and choroidal vascular changes in AD patients.

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P0469 / #2217

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

THE VALCODIS COHORT: A PROSPECTIVE STUDY OF ALZHEIMER'S DISEASE

Laura Ferré González[1], Lourdes Álvarez-Sánchez[2], Carmen Peña-Bautista[2], Inés Ferrer-Cairols[2], Lorena García-Vallés[2], Consuelo Cháfer-Pericás[2], Miguel Baquero[2]
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Aims: The VALCODIS (Valencian Cognitive Diseases Study) cohort was designed and performed at the Hospital Universitari i Politècnic La Fe (Valencia, Spain), for the Alzheimer's disease (AD) research from a cross-sectional study.
Methods: Participants in the VALCODIS cohort provided informed consent, these are patients who come to the neurology unit because they have a subjective memory complaint that they or their relatives notice. They were neuropsychologically evaluated, cerebrospinal fluid samples were obtained to determine some biomarkers (β-amyloid-42, β-amyloid-40, p-Tau, t-Tau, neurofilament light chain) and blood samples were taken to determine new potential biomarkers. In some patients, neuroimaging techniques (nuclear magnetic resonance (NMR) and/or computerized axial tomography (CAT), or Positron Emission Tomography- Fluorodeoxyglucose (PET-FDG)) were applied to obtain brain structural and functional information.
Results: A total of 850 participants aged 50 to 80 years, who were on follow up from January 2017 to September 2022 were included in the VALCODIS cohort. This cohort is mostly composed of AD patients, but also by other dementias (frontotemporal dementia, Lewy body dementia, vascular dementia) and people cognitively healthy.
Conclusions: The VALCODIS cohort represents a valuable infrastructure describing 6-year experience about early AD diagnosis. This cohort will provide a large number of patients, biologically diagnosed, as well as their demographical, clinical and biochemical data, and biological samples (blood, plasma, cerebrospinal fluid) to carry out further studies about early and specific AD diagnosis.

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P0470 / #2493

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

ALZHEIMER'S DISEASE AFFECTS THE HETEROTOPICITY OF CORTICAL REGIONS CONTROLLING EMOTIONAL, LINGUISTIC, AND MOTOR PROCESSING

Lovisa Ljungqvist Brinson[1], Diego Szczupak[1], Fernanda Meireles[2], Fang-Cheng Yeh[3], Sang-Ho Choi[1], Fernanda Tovar-Moll[2], Afonso Silva[1]
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Aims: Alzheimer's disease (AD) is a devasting form of dementia afflicting millions of individuals globally. Early detection of AD allows families and patient care teams to craft plans to manage and prevent disease progression. Previous studies have demonstrated significant structural and functional brain connectivity changes in AD patients. Here, we investigated whether AD explicitly affects the corpus callosum's connections.
Methods: We analyzed diffusion tensor imaging (DTI) of an aged cohort of 27 AD subjects and 53 healthy controls using DSIStudio to track the corpus callosum connections between the two cortical hemispheres. We segregated homotopic (HomC) from heterotopic (HetC) interhemispheric connections and quantified the heterotopicity index (HetI=HetC/(HetC+HomC)).
Results: We found that regions within the superior temporal gyrus, spanning emotional regulation, memory consolidation, and language/speech, increase their heterotopicity with AD (Fig. 1, warm colors). Additionally, areas like the postcentral gyrus, controlling sensory/motor processing and functioning specifically of the lower extremities, reduce their heterotopicity with AD (Fig. 1, cold colors).

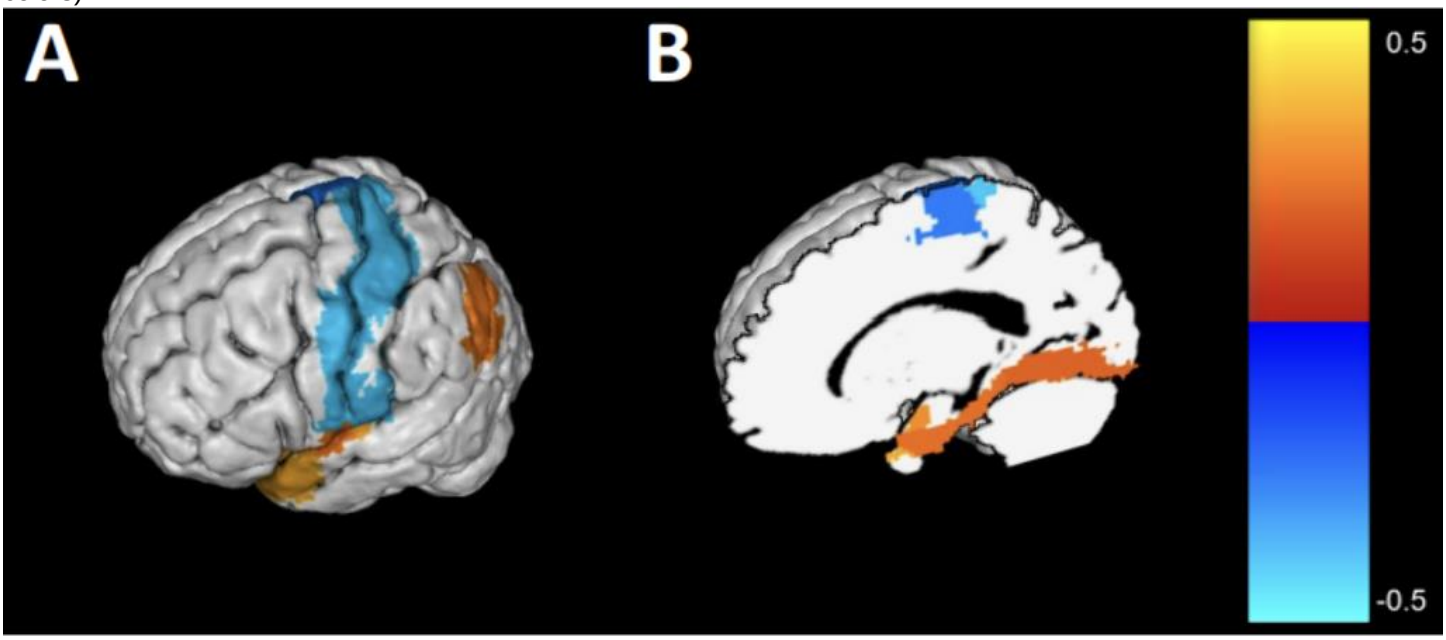

Figure 1. Statistical Populational Heterotopicity Map. Side view of the human brain depicting surface cortical regions affected heterotopically by AD: Postcentral Gyrus, Paracentral Gyrus, Angular Gyrus, Rolandic Operculum, Superior Temporal Pole, and Heschl Gyrus - A). Cross-section of cortical regions affected heterotopically by AD: Postcentral Gyrus, Paracentral Gyrus, Lingual Gyrus, Parahippocampal Gyrus, Superior Temporal Pole, and Amygdala- B). Cold colors indicate lower heterotopicity while warm colors indicate higher heterotopicity in AD subjects relative to controls.

Conclusions: Here, we propose the heterotopicity index as a potential non-invasive biomarker of AD, allowing patient care teams to design early treatments to prevent further cognitive decline. Future studies will investigate larger cohorts' heterotopicity in AD populations to expand our understanding of how these findings correlate to their clinical cognitive assessment.

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P0471 / #2290

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

OPEN SOURCE SOFTWARE FOR 3D DENDRITIC SPINES SEGMENTATION AND CLUSTERIZATION

Ekaterina Pchitskaya[1], Peter Vasiliev[1], Vyacheslav Chukanov[1], Ilya Bezprozvanny[1,2]
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Aims: Dendritic spines are small protrusions from dendrite membrane, forming the vast majority of excitatory synaptic inputs in neurons. They are characterized by various shapes, which is constantly changing. Dendritic spines morphology is altered in neurodevelopmental and neurodegenerative disorders, is changing during learning process, drug administration and other external stimulus. Classification into predefined morphological groups is a widely used approach to analyze dendritic spines morphology, where spines are divided into fixed categories such as thin, mushroom, and stubby spine. Usually performed semi-manually this approach tends to be biased, and contrast with the observation that dendritic spine shapes present a continuum rather than clearly separated classes, supported by recent investigations. To this reason reliable method to assess and explore dendritic spines morphology is under urgent need.
Methods: To address this issue, we developed free available open-source software written in Python language to segment dendritic spines from 3D confocal dendritic images, extract the wide spectrum of their morphological features and perform classification and clusterization.
Results: We offering automatic classification tool based on machine learning algorithm, which is learned to classify spines into mentioned above categories basing on the consensus made by manual spines labeling by 8 different experts. This approach allows to reduce biases and labor costs. Clusterization tool presented by k-means and DBSCAN algorithms with two different quality metrics used to determine appropriate cluster number. In addition, we developed qualitatively new non-numerical metric to describe dendritic spine shape – chord histogram, which consists of randomly build chords (the line connecting two surface points of any object) in dendritic spines volume.
Conclusions: Developed software can be used and updated to current needs by various experimenters due to the open source code.

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P0472 / #493

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

BALANCE AND GAIT ARE IMPAIRED IN PEOPLE WITH PARKINSON'S DISEASE WHO HAVE REM SLEEP BEHAVIOR DISORDER (RBD) COMPARED TO PEOPLE WITHOUT RBD

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Aims: As cholinergic neurons of the pedunculopontine nucleus (PPN) have been implicated in the control of both Rapid Eye Movement (REM) atonia and the regulation of locomotor patterns, here we sought to investigate if people with Parkinson`s disease and sleep behavior disorder (PD+RBD) have worse balance and gait impairments compared to those without RBD (PD-RBD).
Methods: We recruited 47 individuals with idiopathic PD (15 with RBD). RBD was either confirmed by medical history or assessed with the Mayo Sleep questionnaire. Subjects wore 3 inertial sensors attached to both feet and the lumbar region for gait and balance tasks. The gait task involved a 2-minute walk test down a 10-m walkway with 180-degree turns (single task and dual-task with counting back by 3s). The balance tasks had subjects stand for 30 s with eyes open with feet-together on firm and then foam surface.
Results: Medio-lateral root mean square (RMS) postural sway while standing on the foam surface was significantly larger in PD+RBD (0.13±0.05) compared to PD-RBD (0.10±0.03; $p<0.05$). Stride time variability during gait was also significantly larger in PD+RBD (10.13±7.34) compared to PD-RBD (6.85±3.83; $p<0.05$). Despite worse balance and gait in the RBD group, the groups did not differ in the MDS-UPDRS Motor Score or MoCA.
Conclusions: The co-existence of RBD and balance and gait difficulties may reflect progressive involvement of common brainstem networks in people with PD.

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P0473 / #1384

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

ASSOCIATION BETWEEN METABOLIC RISK FACTORS AND CORTICAL GLIAL REACTIVITY IN CLINICALLY UNIMPAIRED ELDERLY INDIVIDUALS

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University of Turku, Turku University hospital, Turku Pet Centre, Turku, Finland

Aims: Metabolic risk factors are associated with an increased risk for dementia, but less is known about their associations with glial reactivity or beta-amyloid accumulation. We evaluated if metabolic risk factors *i.e.,* insulin resistance, obesity, serum cholesterol values or high sensitivity C-reactive protein (representing low-grade inflammation) associate with glial reactivity or beta-amyloid accumulation in the brain measured by positron emission tomography (PET), and if these associations are modulated by *APOE4* gene dose in clinically unimpaired elderly individuals.
Methods: Sixty individuals (21 *APOE4-/-*, 20 *APOE4-/+* and 19 *APOE4+/+*) with a mean age of 67.7 years (SD 4.7), of which 63% were females were included. All underwent [^{11}C]PK11195 PET (targeting 18kDa translocator protein, TSPO) and [^{11}C]PIB PET (targeting beta-amyloid). [^{11}C]PIB standardized uptake value ratios and [^{11}C]PK11195 distribution volume ratios were calculated for a cortical composite region of interest. Fasting blood samples were collected, body mass index (BMI) measured, and homeostasis model of insulin resistance (HOMA-IR) was calculated. Associations were evaluated with linear models adjusted for age and sex both in the whole population and stratified according to *APOE4* gene dose.
Results: Higher HOMA-IR (standardized beta 0.42, p=0.002) and BMI (standardized beta 0.27, p=0.048) were associated with higher cortical composite [^{11}C]PK11195 binding in the whole population. Voxel-wise analyses indicated that this association was mainly present in the parietal cortex. Higher HOMA-IR was associated with higher [^{11}C]PIB binding, but only in *APOE4* homozygotes (standardized beta 0.44, p=0.02). No associations were found for other metabolic variables.
Conclusions: Insulin resistance and obesity seem to be associated with cortical glial reactivity in clinically unimpaired individuals. *APOE4* genotype might modulate the association between insulin resistance and beta-amyloid accumulation in the brain.

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P0474 / #1161

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

UTILIZING HETEROGENOUS KNOWLEDGE NETWORK TO PREDICT PROGRESSIVE SUPRANUCLEAR PALSY DIAGNOSIS

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Aims: Electronic Medical Records(EMR) provide extensive longitudinal data that can be utilized to better understand disease. We aim to leverage clinical data combined with knowledge-guided embeddings on a heterogenous knowledge network, Scalable Precision Medicine Open Knowledge Engine(SPOKE), to provide clinical and biological insight into progressive supranuclear palsy(PSP) diagnosis.
Methods: PSP patients were identified based on UCSF's Memory and Aging Center diagnoses, and controls without dementia were sampled from the rest of the UCSF EMR. All clinical features (conditions, diagnoses, abnormal measures) were taken before time 0, defined as the first diagnosis for PSP and 6 months before last visit day for Controls, and mapped to SPOKE entry points (SEPs). Knowledge-guided patient network signatures (SPOKEsigs) were created based upon clinical concept network embeddings as described in [1]. Random forest(RF) classification models were implemented on SPOKEsigs created -3years, -1years, and 0 days from time 0. Models were evaluated based on AUROC/AUPRC and top important features are interpreted based upon the shortest path to PSP node(DOID:678) in SPOKE.
[1]Nelson et al. JAMIA(2022). doi:10.1093/jamia/ocab270
Results: 98 PSP patients were identified, and Controls were sampled with 1:2 ratio from remaining 823k patients. RF models performed with AUROC/AUPRC at -3, -1, and 0 years of 0.68/0.40, 0.69/0.60, and 0.87/0.73, respectively. Top SEP features include muscle weakness, muscle stiffness, Parkinson's disease, and dyskinesia. Shortest path networks for top features to PSP node pass through movement-related symptoms, to drugs, genes, and pathways that lead to PSP related anatomy and diagnoses (Figure
1).

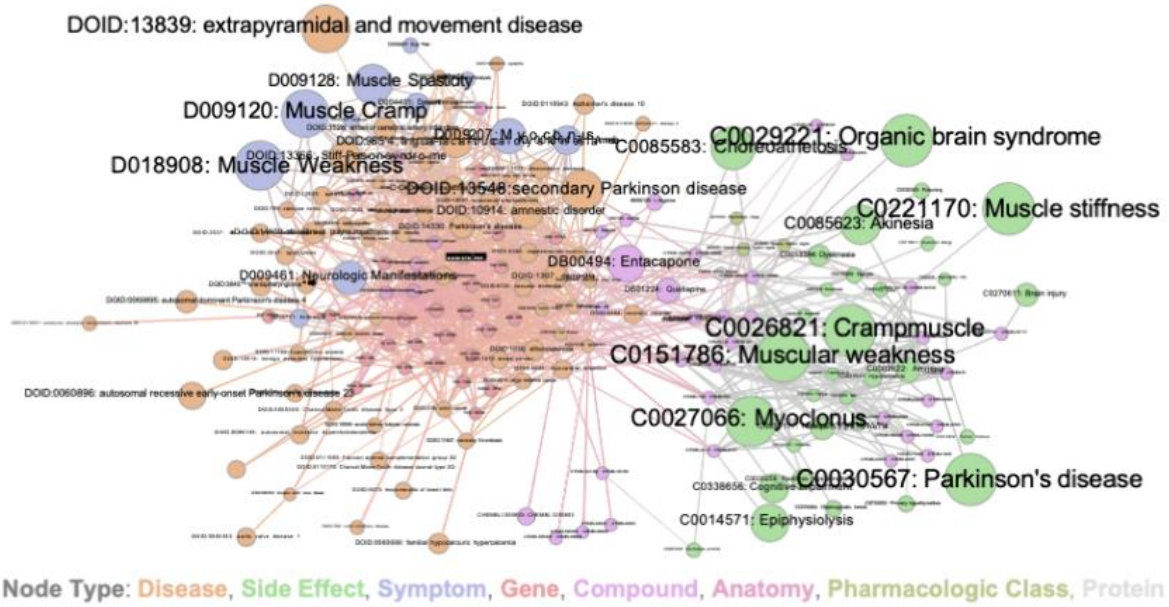

Figure 1: SPOKE networks of shortest paths from top RF nodes to PSP node. Node size = feature importance, node color = node type.

Conclusions: Utilizing SPOKE networks in conjunction with rich EMR data can help provide clinical-molecular insight that link multiple known and novel clinical features to a PSP diagnosis that can be used to predict the condition before diagnosis.

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P0475 / #2121

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

HARMONIZED DTI INDICES DIFFER BETWEEN STAGES OF PREDEMENTIA COGNITIVE IMPAIRMENT

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Aims: Longitudinal ComBat harmonization is a new tool to correct for scanner effects on longitudinal data. This study aims to assess if longitudinal, harmonized DTI indices differ between different stages of cognitive impairment.
Methods: 256 subjects from the Dementia Disease Initiation cohort (DDI) (55 healthy controls (HC), 24 healthy controls with not normal cognitive testing, 76 subjects with subjective cognitive decline (SCD) and 101 with mild cognitive impairment (MCI) at baseline) were scanned. 160 subjects had longitudinal data available, resulting in a total of 469 examinations. MRI was acquired on 5 different scanners (Philips Achieva 3.0T, Philips Ingenia 1.5 and 3.0T, Siemens Skyra 3.0T and Siemens Prisma 3.0T). DTI indices were computed using TBSS, part of FSL, and the 20 JHU white matter (WM) tracts were analysed. Longitudinal ComBat harmonization was performed in R, with age, gender, time, *APOE-ε4* status, the CSF biomarkers Aβ42, CSF p-Tau and CSF t-Tau below or above cut-off at baseline, and staging at baseline as covariates. A mixed linear model was used to evaluate DTI index difference between staging groups, with the same covariates as in the ComBat analysis.
Results: On average, L1, RD and MD increase in the patient population compared to HC, while FA decreases. For several WM tracts, these differences were statistically significant (p <0.05) (see Fig1).

TRACT	Hemisphere	FA	MD (E^{-03} mm^2s^{-1})	AxD(E^{-03} mm^2s^{-1})	RD (E^{-03} mm^2s^{-1})
Anteriorthalamicradiation	L		HC-MCI (p = 0.006)	HC-MCI (p=0.001)	
	R		HC-MCI (p=0.029)	HC-MCI (p=0.031)	
Corticospinaltract	L		HC-MCI (p=0.002) HC-SCD (p=0.019)	HC-MCI (p=0.001)	HC-SCD (p=0.017)
	R		HC-MCI (p=0.002) HC-SCD (p=0.015)	HC-MCI (p=0.002)	HC - SCD (p=0.032)
Cingulumcingulategyrus	L		HC-MCI (p=0.039)		HC - MCI (p=0.037)
	R	HC-MCI (p=0.024)	HC-MCI (p=0.011)		HC-MCI (p=0.004)
Cingulumhippocampus	L	HC-SCD (p=0.028)	HC-MCI (p=0.029)		HC-MCI (p=0.016) HC-SCD (p=0.040)
Forcepsmajor			HC-SCD (p=0.037)		
Inferiorfrontooccipitalfasciculus	L		HC-MCI (p=0.012) HC-SCD (p=0.044)	HC-MCI (p=0.010)	HC-MCI (p=0.041)
	R		HC-MCI (p=0.001) HC-SCD (p=0.024)	HC-MCI (p=0.006)	HC-MCI (p=0.005) HC-SCD (p=0.039)
Inferiorlongitudinalfasciculus	L		HC-MCI (p=0.003) HC-SCD (p=0.037)	HC-MCI (p=0.003)	HC-MCI (p=0.012) HC-SCD (p=0.038)
	R	HC-SCD (p=0.041)	HC-MCI (p=0.004) HC-SCD (p=0.026)	HC-MCI (p=0.011)	HC-MCI (p=0.008) HC-SCD (p=0.020)
Superiorlongitudinalfasciculus	L		HC-MCI (p=0.007)	HC-MCI (p=0.001)	
	R		HC-MCI (p=0.020)	HC-MCI (p=0.003)	
Uncinatefasciculus	L		HC-MCI (p=0.023) HC-SCD (p=0.030)	HC-MCI (p=0.016)	
	R		HC-MCI (p=0.035)		
Superiorlongitudinalfasciculustemp	R		HC-MCI (p=0.043)	HC-MCI (p=0.005)	

Conclusions: Differences between MCI/SCD subjects and healthy controls were found in several WM tracts, which suggests that DTI can be used in multi-site studies on longitudinal WM tract changes in early-stage of cognitive impairment.

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P0476 / #1353

POSTERS: A04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

INSULIN RESISTANCE, ALZHEIMER'S BIOMARKERS AND COGNITION: CROSS SECTIONAL AND LONGITUDINAL RELATIONSHIPS IN THE AUSTRALIAN IMAGING, BIOMARKER AND LIFESTYLE STUDY OF AGEING.

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[1]Curtin University, Curtin Medical School, Bentley, Australia, [2]Curtin University, Curtin Health Innovation Research Institute, Bentley, Australia, [3]Edith Cowan University, Centre For Precision Health, Perth, Australia, [4]Edith Cowan University, Collaborative Genomics And Translation Group, Joondalup, Australia, [5]Edith Cowan University, School Of Medical And Health Sciences, Joondalup, Australia

Aims: Alzheimer's Disease (AD) and Type 2 Diabetes (T2D) are chronic diseases that share several pathological mechanisms including insulin resistance. T2D is a modifiable risk factor for AD, though when in the progression of AD pathology insulin resistance has its greatest impact remains undetermined. In cross-sectional analysis, we have previously shown that insulin resistance is associated with reduced in cognitive function and increased CSF total tau (tTau) and phosphorylated tau (pTau). The relationship with CSF tTau and CSF pTau was moderated by CSF amyloid-beta 42. The aim of this study was to determine if a relationship existed between insulin resistance and changes in cognition over time.
Methods: The relationships between insulin resistance (measured using HOMA-IR) and cognitive function across 6 domains were investigated in cognitively normal adults of the Australian Imaging Biomarker and Lifestyle (AIBL) study using linear mixed modelling. We also determined whether sex or amyloid-beta burden influence this relationship.
Results: HOMA-IR alone showed limited influence on longitudinal changes in cognition. Following sex stratification, males show significantly lower cognition at baseline compared to females. Males with high HOMA-IR have a steeper decline in cognition over time compared to high HOMA-IR females. Amyloid-beta stratification revealed that amyloid-beta positive individuals have steeper decline in cognitive function, and those with High HOMA-IR, a steeper decline in attention over time.
Conclusions: Overall, the findings suggest that baseline insulin resistance alone does not impact cognition over time, but interacts with key AD pathologies to promote dysfunction in certain cognitive domains.

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P0477 / #2782

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

THE ALZHEIMER'S DISEASE SEQUENCING PROJECT – FOLLOW UP STUDY (ADSP-FUS): INCREASING ANCESTRAL DIVERSITY IN ALZHEIMER'S DISEASE (AD) GENETICS RESEARCH

Brian Kunkle[1], Pedro Mena[2], Kelley Faber[3], Larry Adams[2], Jovita Inciute[1], Patrice Whitehead[1], Tatiana Foroud[3], Dolly Reyes-Dumeyer[4], Amanda Kuzma[5], Yuk Yee Leung[6], Adam Naj[7], Eden Martin[8], Clifton Dalgard[9], Gerard Schellenberg[10], Li-San Wang[10], Badri Vardarajan[4], Richard Mayeux[11], Jeffery Vance[2], Michael Cuccaro[2], Margaret Pericak-Vance[2]

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Aims: A major goal of the National Institute on Aging (NIA)'s ADSP initiative is to fully reveal the genetic architecture of Alzheimer's disease (AD)/AD and related dementias (ADRD) across diverse ancestral populations. The projects upcoming phase, ADSP- FUS 2.0, *The Diverse Population Initiative*, focuses on expansion of Hispanic/Latino (HL) individuals and individuals of African and Asian ancestry populations.
Methods: ADSP-FUS cohorts consist of studies of AD, dementia, and age-related conditions. Clinical classifications (AD, dementia, and cognitively intact) are assigned based on standard criteria and derived from clinical measures and history. DNA is prepared and allocated for WGS at designated NIA sequencing centers. All raw sequence data is transferred to the Genome Center for Alzheimer's Disease (GCAD) for processing and harmonization following QC analysis. Analysis-ready genotype and sequence data along with clinical data are housed at the NIA Genetics of Alzheimer Disease Data Storage Site (NIAGADS), which stores, manages, and distributes ASDP data to AD researchers worldwide.
Results: The ADSP-FUS initiatives intend to sequence over 100,000 individuals from diverse ancestries, with the goal of obtaining sample sizes large enough to achieve statistical power for rare variant analyses in the largest US populations. Over 50,000 samples have been ascertained. Recently formed initiatives such as the Asian Cohort for Alzheimer's disease (ACAD) and Recruitment and Retention for AD Genetic Cohorts in the ADSP (READD-ADSP) are recruiting Asian American, Hispanic/Latino American, African American and African participants in an effort to help the ADSP reach target sample sizes.
Conclusions: This genomic resource is crucial to expanding our knowledge of potential genetic risk and protective variants for AD across all populations with the hope of developing new therapeutic or prevention strategies that benefit everyone.

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P0478 / #1541

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

EVALUATION OF SHORT TANDEM REPEAT GENOTYPING AND IMPUTATION IN ALZHEIMER'S DISEASE USING WHOLE-GENOME SEQUENCING

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Aims: Despite their low price, SNP genotyping arrays fail to explain the majority of heritability for many complex traits. Part of the "missing heritability" may originate from more complex genomic variants, such as short tandem repeats (STRs). Whole genome sequencing (WGS) can be used to directly genotype STRs, although it is financially and computationally more costly. An alternative approach using imputation of STRs into SNP array data was recently described by Saini et al. (Nat Commun 9, 4397, 2018). Here we aim to compare the efficiency of STR imputation and direct STR genotyping from WGS.
Methods: We performed WGS for 214 samples (from the NIMH AD Genetics Initiative). As a reference dataset 118 WGS files from the European Genome-Phenome Archive were obtained (EGAS00001002462). STR calling was performed using GangSTR, ExpansionHunter, and ExpansionHunter Denovo (EHdn) tools. STR imputation was carried out as described in Saini et al. To assess the effect of marker density on STR imputation, four different SNP sets, based on commonly used SNP arrays (Exome, Global Screening, Infinium Omni2.5, and Infinium Omni5 arrays) were extracted from WGS data.
Results: In total 589,159 STR regions were called from the WGS data, 93,932 of which are confirmed by EHdn. Emulated SNP sets were extracted successfully with ranges of marker density between 240,000-4,300,000 variants. STR imputations are currently ongoing and will be compared to the WGS-called STR genotypes.
Conclusions: To the best of our knowledge, our work represent the first independent evaluation of performing STR imputations from SNP data. While the specific performance evaluation is still in progress and will be presented at the meeting, this method is promising to add a new genomic dimension to the plethora of existing GWAS data.

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P0479 / #1567

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

COPY NUMBER VARIATION IN THE UK BIOBANK: A FOCUS ON MENDELIAN ALZHEIMER'S DISEASE GENES

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Aims: Compared to single-nucleotide polymorphisms, copy number variants (CNVs) are relatively poorly characterized genetic elements in the context of neurodegenerative diseases. To address this, we used UK Biobank whole-genome genotyping data to detect CNVs genome-wide in 438,149 participants.
Methods: Using Affymetrix Power Tools and PennCNV we focused this analysis on the identification of CNVs (duplications and heterozygous deletions) overlapping all three of the Mendelian Alzheimer's disease (AD) genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*). Mutations in these genes are a known cause of early-onset AD, however, only duplications of *APP* and deletions within *PSEN1* have been previously reported in AD. We visualized the detected CNV events by evaluating the B-allele frequency and log R ratio of the raw genotyped data; we also consulted sample-matched whole-genome sequencing data for corresponding changes in genome coverage as a technical replication.
Results: We identified expected results such as large duplications across chromosome 21 in individuals diagnosed with Down's syndrome (with or without AD). More strikingly, we also identified two individuals with large chromosome 21 duplications spanning *APP* and no record of Down's syndrome or AD to date.
Conclusions: Together with previous reports, these results question the penetrance of *APP* duplications and are the first exploration of CNVs overlapping *PSEN1* and *PSEN2* in the context of AD in a large population cohort. By characterizing the landscape of *APP*, *PSEN1* and *PSEN2* copy number variation, we explore how these key loci may be further involved in disease.

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P0480 / #1390

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

THE ROLE OF SHORT TANDEM REPEATS IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) occurring before the age of 65 years is often designated as early onset Alzheimer's disease (EOAD) and accounts for approximately 5-10% of all AD cases. Knowledge of EOAD genetics is limited to rare mutations in *APP, PSEN1,* and *PSEN2* leaving many EOAD cases without obvious genetic cause. One such cause could be elicited by short tandem repeats (STR), which represent repetitive elements in the human genome with motif sizes from 1-9bp. In this study, we used whole-genome sequencing to perform genome-wide STR profiling in order to identify expansions with a putative pathogenic role in EOAD.
Methods: We analyzed 216 DNA samples (from 75 EOAD families (173 AD cases, 43 within family controls) collected as part of the NIMH AD Genetics Initiative. All samples underwent PCR-free paired-end whole genome sequencing (2x150bp) on a NovaSeq6000 (Illumina) instrument. Subsequently, WGS data were analyzed via a customized bioinformatic pipeline using a combination of publicly available STR detection tools followed by prioritization of candidate STRs based on an in-house algorithm.
Results: In total, 198 samples passed QC and could be assessed by STR profiling. In addition to identifying a C9orf72 expansion in three families and a known AD mutation in *PSEN1* in one family, we identified AD-linked STRs located on chromosomes 2p21, 2q37.1, 5q13.2, 6q25.3, 8p23.1, 8q12.3, 8q24.22, 12q24.33, 16q24.3. All STRs segregated with disease and were absent from 118 controls generated in a separate project.
Conclusions: Thus far, our study has highlighted several promising STR expansions potentially involved in EOAD pathogenesis. We are currently extending the WGS approach to 122 samples from 48 additional families. At the meeting we will report up-to-date results from our project using all 320 WGS samples.

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P0481 / #2062

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

PRESENILIN 2 SER130LEU MUTATION ASSOCIATED TO FAMILIAL LATE-ONSET ALZHEIMER'S DISEASE AND CEREBRAL AMYLOID ANGIOPATHY IN SICILY

Chiara Cupidi[1], Francesco Calì[2], Rosalia Coppola[1], Mirella Vinci[2], Antonino Musumeci[2], Rosanna Galati[2], Pierpaolo Alongi[3,4], Luigi Grimaldi[1]
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Aims: To report the association of Presenilin 2 (PSEN2) Ser130Leu mutation to late-onset Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) with proven amyloid deposition in a Sicilian family.
Methods: The proband underwent clinical and neuropsychological assessment, brain MRI and brain Florbetaben-PET for amyloid. Clinical diagnosis was made according to McKhann criteria for possible AD and to Boston criteria 2.0 for probable CAA. A NGS gene panel comprising 57 known genes associated to dementia was used for genetic screening on genomic DNA from peripheral blood.
Results: Familial history revealed late-onset AD in four of seven siblings and late-onset psychosis in the father suggesting an autosomal dominant transmission. The proband experienced a slowly progressive memory impairment and disexecutivesymptoms at age 73. Neuropsychological assessment confirmed AD-type cognitive profile. Brain MRI showed an old right parieto-occipital lobar hemorrhage, multiple cerebral microbleeds, compatible with CAA, and diffuse cortical atrophy including mesial temporal lobes. Florbetaben-PET showed amyloid deposition in the left hemishere, mainly in temporal lateral cortex, precuneus/posterior cingulate cortex and parietal lobules, suggesting AD pathology. Genetic screening found the PSEN2 Ser130Leu heterozygous mutation.
Conclusions: The PSEN2 Ser130Leu mutation has been described in four unrelated late-onset AD patients with a predicted deleterious effect on protein function. However, it is currently classified as not pathogenic because neither significant effect on Aß-protein levels was found in cellular models nor cerebral amyloid pathology was investigated in mutated patients. We report a late-onset AD family in which this mutation is associated to both AD and CAA, sharing the same Aß-protein-mediated pathogenic pathway. Moreover, amyloid deposition was proven in the PSEN2 Ser130Leu carrier proband by molecular neuroimaging. These findings might suggest a role of PSEN2 SER130Leu in AD pathogenesis and in amyloidopathies at large.

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P0482 / #1183

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

CLASSIFICATION OF SORL1 VARIANT PATHOGENICITY IN ALZHEIMER'S DISEASE PATIENTS.

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Aims: Rare missense variants in the *SORL1* gene have been identified as strong risk-increasing factors in Alzheimer's Disease (AD). Current approaches to identify these variants usually rely on generic *in silico* variant pathogenicity-prediction algorithms. Here, we aimed to design a new variant classification strategy that adds in-depth knowledge of SORLA structural folding and function to the variant risk prediction.
Methods: We identified rare *SORL1* missense variants (MAF<1%) in a combined sample of whole exome sequencing data from the ADES and ADSP consortia comprising 18,959 cases & 21,893 controls after quality control. We classified variants into Loss-of-Function (LoF) or missense variants. Missense variants were further classified into likely pathogenic, uncertain significance and likely benign based on an in-depth evaluation of the structure of protein functional domains and predicted pathogenicity of the variant (REVEL algorithm). Each variant class was associated with AD using logistic regression models and stratified by *APOE* ε4 status.
Results: LoF variants were associated with 15.45 fold (95%CI=[6.74-35.44], p=3.66x10^{-20}) increased risk for AD. The 'likely pathogenic' group demonstrated a high burden for AD (OR=6.65, 95%CI=[4.13–10.7], p=1.44x10^{-20}). Notably, variants that disrupt calcium cages in the CR domain (p=*4.62x10^{-05}*) or the YWTD-motif in the YWTD domain(p=*0.002*) were observed in cases only. The 'uncertain significance' variants had a considerably lower effect on AD (OR=1.55, 95%CI=[1.22–1.96], p=1.44x10^{-20}) and the 'likely benign' group was not associated with AD (OR=1.14, 95%CI=[0.91–1.43], p=0.251). Importantly, LoF or likely pathogenic variant carriers had, on average, a similar age at AD onset. When stratifying by *APOE* ε4 status, the additive effect exerted by *SORL1* variants was similar in the different *APOE* groups.
Conclusions: Our classification model is able to successfully identify likely pathogenic *SORL1* variants, to improve the identification of patients with possible *SORL1*-associated-AD.

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P0483 / #1277

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

MUTATION ANALYSES OF DISEASE CAUSING GENES IN PATIENTS WITH EARLY ONSET FORMS OF NEURODEGENERATIVE DISORDERS

Vilmantas Giedraitis[1], María Pagnon De La Vega[1], Rosemarie Brundin[1], Lars Lannfelt[1], Malin Löwenmark[1], Martin Ingelsson[1,2,3], Lena Kilander[1]
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Aims: Studies on familial forms of neurodegenerative disorders provide important knowledge of underlying disease mechanisms. For Alzheimer's disease (AD) and frontotemporal dementia, pathogenic mutations can be found in several genes. Here, we aimed at investigating the presence of mutations in a clinical cohort of patients with early onset dementia.
Methods: Patients diagnosed with early onset or familial forms of dementia were included. In the first screening 102 patients were analyzed by targeted exome sequencing. In an upcoming analysis 48 new patients will be screened using whole exome sequencing.
Results: On the first set of DNA samples we have completed the analyses of all coding exons in eleven known dementia genes (*PSEN1*, *PSEN2*, *APP*, *MAPT*, *APOE*, *GRN*, *TARDBP*, *CHMP2B*, *TREM2*, *VCP* and *FUS*). In *PSEN1* we found two previously described pathogenic mutations (P264L and M146V). The P264L mutation was detected in two siblings with AD with age at onset of 40-50 years. The M146V mutations was identified in an AD patient with age at onset of about 30 years. We also identified an *APP* mutation leading to a six amino acid intra-amyloid β deletion. This *Uppsala APP mutation* causes an aggressive form of familial AD and its pathogenic effects have been described by us in detail. Furthermore, we found several potentially pathogenic mutations in *PSEN2*, *FUS, MAPT* and *GRN* genes. For the new analyses, also genes associated with dementia diseases in large genome wide association studies are investigated.
Conclusions: Screening for mutations in disease causing genes can aid in the clinical diagnosis and enable us to discover pathogenic mechanisms that can be targeted by novel therapeutic strategies.

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POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

PATHOGENIC MUTATIONS IN CSF1R AND ABCD1 GENE IN A PATIENT WITH EARLY ONSET DEMENTIA WITH PARKINSONISM

Gabriela Novotni[1], Nikolina Tanovska[1], Ivan Barbov[1], Antoni Novotni[2]
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Aims: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare autosomal dominant genetic disease due to mutations in CSF1R gene, with complex underlying mechanisms that lead to white matter damage. On the other hand, ABCD1 gene mutations have been found to cause another rare genetic disease- X-linked adrenoleukodystrophy. Both these conditions are characterized by progressive development of white matter changes and consequent varying degrees of cognitive and movement problems.
Methods: A case study discussing the coexistence of two pathogenic mutations in CSF1R gene and ABCD1 gene respectively in a 46-year-old male with early onset and rapid progressive cognitive decline resembling frontotemporal dementia and parkinsonism is presented.
Results: The disease history is presented followed by the diagnostic work-up.
A 46 year-old male, developed a severe dementia within less than a year. Ten months after the initial cognitive symptoms, movement problems occurred, presented with L-dopa non-responsive parkinsonism.Three years after the initial symptom onset, the patient is bedridden with severe swallowing difficulties and emotional incontinence.
The white matter changes on the repeated brain MRI scans suggested a leukodystrophy pattern which led to the genetic testing. Using NGS (Next Generation Sequencing) two pathogenic mutations were found in CSF1R and ABCD1 that could possibly explain the clinical syndrome. Having plasma levels of very long-chain fatty acids (VLCFA) within referent range, puts weight on the ALSP diagnosis.
Conclusions: Genetic testing should be listed in the diagnostic work-up when evaluating an early onset, rapid progressive dementia associated with atypical parkinsonism.Having these rare genetic conditions coexisting in a same patient is a rarity of its own that rises diagnostic, therapeutic, and academic dilemmas.

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P0485 / #2541

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

HEREDITARY AND GENEOLOGICAL CHARACTERISTICS OF PARKINSON'S DISEASE DEPENDING ON THE CLINICAL FORMS

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Aims: Study of the genetic characteristics of Parkinson's disease and their role in early detection of the disease
Methods: To achieve the goal of the study, 106 patients with various forms of PD were enrolled. The age of patients in the main group was from 18 to 70 years, and the average was 56.04±8.9. The average duration of the disease is 5.56±6.2 years. 55(51.8%) of the examined patients in the main group were men and 51(48.2%) were women.
Results: PD is considered a genetic degenerative disease and can be passed from one generation to another in an autosomal dominant or autosomal recessive type, and often occurs sporadically. The results obtained on the basis of genetic and anamnestic data showed that 21 patients (19.8%) were autosomal dominant, 38 patients (35.8%) were autosomal recessive, and 47 patients (44.8%) were known to meet sporadically. At the next stage, we analyzed the types of breeding according to the clinical forms of the disease. It was found that 18 (85.7%) patients with autosomal dominant type had akinetic-rigid form, and 3 (14.3%) suffered from tremor form. It was found that 21 (55.2%) patients with autosomal recessive type had tremor and 17(44.8%) had mixed PD. It was found that 17 (36.1%) of the sporadic patients had tremors and 30 (63.9%) had mixed forms. It should be emphasized that in the autosomal-dominant type, the rpoband male, the female patient, and the proband female were bred from the male patient.
Conclusions: The type of reproduction of PD is closely related to the clinical forms of the disease, the akinetic-rigid form is more autosomal-dominant, the tremor form is relatively autosomal recessive, and the mixed form can be reproduced almost uniformly from generation to generation.

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P0486 / #2601

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

THE MISSENSE VARIANT OF GENOME-WIDE SIGNIFICANT LOCI IN CHROMOSOME 14 IS CRITICAL FOR LONG-TERM VISUOSPATIAL MEMORY PERFORMANCE

Junwoo Park[1], Sarang Kang[1], Jungsoo Gim[1,2], Sunjae Lee[3], Seok-Jun Kim[1], Ha Suk Kim[4], Jang Jae Lee[1], Kyu Yeong Choi[1], Kun Ho Lee[1,2]
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Aims: The Seoul Neuropsychological Screening battery (SNSB) is the widely-used comprehensive test battery for the cognitive function of Korean speakers. Yet its widespread usage in Korea, the impact of genetic variants on SNSB is poorly understood. To elucidate this research concern, we conducted a genome-wide association study (GWAS) on genotype data to investigate associations with neuropsychological tests.
Methods: Over 10,000 subjects enrolled in Gwangju Alzheimer's and Related Dementia cohort undergo cognitive assessment with SNSB with follow-up diagnosis. SNSB contains five cognitive domains; attention, language, visuospatial functions, memory, and executive functioning. We used the latest SNSB screening results from 2,055 subjects with matching DNA samples and defined diagnostic information. Subject genotype data were acquired using Affymetrix® Axiom KORV1.0 and imputed with HRC panel V.1.1. SNPs with minor allele frequency<1%, call rates<95%, HWE p-value $<1\times10^{-6}$ were excluded from analysis. We performed linear regression with raw test scores and 10 million imputed genotype variants with PLINK software. Age, sex, education level, and the first four PCs were adjusted as covariates.
Results: The missense variant of the genome-wide significant (GWS) loci on chromosome 14 showed substantial associations in RCFT delayed recall (1.71×10^{-11}) and K-MMSE total score (4.14×10^{-9}).
Conclusions: The missense variant on chromosome 14 may effectively predict overall cognitive dysfunction and long-term visuospatial memory loss, which are the testing domains of MMSE and RCFT. Additional analyses on protein structure and in-vivo studies are required to thoroughly investigate the functional effects of the missense mutation. Since RCFT delayed recall also showed significant associations with CSF phospo-Tau level (Seo et al., 2021), the identified GWS variant may indicate neurodegeneration in Tauopathy and AD.

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P0487 / #2749

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

POLYGENIC RISK CORRESPONDS TO NEUROAXONAL DAMAGE IN OLD-AGED ADULTS WITH IMMINENT ALZHEIMER'S DISEASE.

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Aims: Establishing valid blood-based diagnostic strategies is a precondition for successful prevention and early therapeutic intervention in Alzheimer's Disease (AD). This study aimed at evaluating the predictive value of plasma Neurofilament light chain (NfL) and polygenic risk score (PRS) for the development of AD in a prospective study over 7.5 years.
Methods: 144 healthy 75-year-old participants from the Vienna-Transdanube-Aging (VITA) longitudinal cohort study were tested for: 1) neuroaxonal damage by single molecular array plasma NfL levels at baseline, 30-, 60- and 90-months. 2) Individual risk for sporadic AD, as estimated by PRS, calculated from genome-wide association study (GWAS) data. 3.) Presence of AD-dementia after 90 months.
Results: 19 participants developed AD after 90 months. Plasma NfL increased significantly over 90 months in all participants (AD: $p<0.0001$; non-AD: $p=0.002$). In the AD group baseline NfL plasma levels correlated with PRS ($r=0.47$, $p=0.044$). This relationship was not observable in the non-AD group ($r=-0.14$, $p=0.11$; Fisher's r-to-z: $z=2.45$, $p=0.014$).
Conclusions: Our data suggest that individuals at increased genetic risk for sporadic AD might particularly benefit from assessing plasma NfL as diagnostic marker.

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P0488 / #535

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

GENETIC ARCHITECTURE OF PLASMA ALZHEIMER DISEASE BIOMARKERS

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Aims: Case-control genome-wide association studies (GWAS) have identified many risk loci for Alzheimer disease (AD) but require large sample sizes and identify variants with small effect sizes. We aim to leverage new assays in plasma for Aβ, tau, p-tau and NFL as informative endophenotypes for AD to increase statistical power. This will allow us to identify novel variants and provide information about biological mechanisms.
Methods: Plasma Aβ40 (n=1,467), Aβ42 (n=1,484), Tau (n=504), p-tau181 (n=1,079) and NfL (n=2058) levels were obtained for individuals from the Knight-ADRC (MAP), the Alzheimer's Disease Neuroimaging initiative (ADNI) and the Human Connectome Project (HCP). GRCh38 aligned GWAS and sequencing data is also available from these samples. We performed linear regression to determine single nucleotide polymorphisms (SNPs) associated with these plasma AD biomarkers. Additional post GWAS analyses, including functional annotation, gene-set analyses, colocalization, and overlap with CSF biomarkers and the latest AD risk GWAS (Bellenguez et al., 2022).
Results: We found several genome-wide significant hits, including *APOE* associated with Plasma Aβ42, tau, p-tau, and NfL. Fine mapping highlighted nine genes near our top hits. All but one has been previously investigated in relation to AD. Analysis of overlap between plasma, CSF and AD risk finds minimal overlap for regions outside of APOE, indicating that larger studies are needed.
Conclusions: This represents the largest GWAS for plasma AD biomarkers measured with the novel and more powerful assays. Previous studies using CSF biomarker levels as quantitative traits identified novel genes implicated in AD risk, onset, and progression. This study finds APOE to have a pervasive influence on plasma biomarker levels, but no novel findings could be found. Larger studies of more plasma biomarkers are needed to improve detection of associations to AD.

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POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

DETERMINING HOW A KLOTHO GENETIC VARIANT SUPPRESSES APOE4 RISK USING NOVEL MOUSE MODELS

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Aims: Apolipoprotein E4 (APOE4), a common variant of *APOE*, is a major genetic risk factor for late-onset Alzheimer's disease (LOAD), but APOE4 carriers do not always develop LOAD. Several large-scale genetic studies have identified a common haplotype of the aging factor *klotho* that modify disease risk in APOE4 carriers. In humans, *klotho* harbors two common missense variants (*rs9536314*, p.F352V; *rs9527025*, p.C370S) that define the *klotho* V/S (KL-V/S) haplotype, which is protective against LOAD in APOE4 carriers, and the *klotho* F/C (KL-F/C) haplotype, which is not. We sought to understand this genetic interaction using novel mouse models.
Methods: We replaced the native mouse haplotype with protective KL-V/S and common KL-F/C haplotypes using CRISPR/Cas9. To validate the effects of these *klotho* haplotypes on klotho secretion, soluble p-KL serum levels of young mice were compared using ELISA. We also measured p-KL in eight month old amyloidogenic *App*^{SAA} mutant mice, which have amyloid plaques in the brain.
Results: Secreted p-KL was decreased in KL-F/C mice harboring the novel mouse risk haplotype when compared to B6 controls and KL-V/S mice. In contrast, KL-V/S mice showed no significant differences in soluble p-KL serum levels when compared to B6 controls. Secreted p-KL levels in KL-V/S mice were significantly elevated when compared to the *App*^{SAA} mice, whereas KL-F/C mice showed similar levels to the aged *App*^{SAA} model.
Conclusions: Taken together, these data suggest the native mouse *klotho* allele acts similarly to the protective KL-V/S haplotype, while the KL-F/C haplotype leads to lower secreted klotho and potentially greater disease risk. These models are therefore suitable to elucidate how *klotho* variants protect from LOAD pathologies, and will enable detailed studies of how this protection is specific to the APOE4 genotype.

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P0490 / #552

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

INVESTIGATING THE OVERLAP BETWEEN IMMUNE CELL COMPOSITION IN HEALTHY ADULTS AND NEURODEGENERATIVE DISEASES BY GENOME-WIDE ASSOCIATION ANALYSES

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Aims: Recent work has shown that the immune system plays a crucial role in various non-immunological human diseases, including Alzheimer's Disease (AD) and Parkinson's Disease (PD). In this context, genome-wide association study (GWAS) data offer valuable insights to further elucidate the involvement of the immune system in these diseases. This study aims to identify genetic factors determining immune cell type distributions in blood and to assess whether these play a role in risk for AD and PD.
Methods: Fluorescence-activated cell sorting was performed in PBMCs in 483 healthy individuals from the Berlin Aging Study II. Using these data, we performed GWAS on 92 different immune cell types using linear regression models. Furthermore, we constructed polygenic scores (PGS) based on the largest available GWAS for AD and PD and assessed these for association with immune cell distributions. For comparison, we also constructed PGS from recent COVID-19 GWAS results. To further characterize the PGS results we performed GREML and Mendelian Randomization (MR) analyses.
Results: GWAS on immune cell type proportions revealed 20 different loci that showed genome-wide significant association ($p<5.0E-8$) in several immunologically plausible genes. For instance, CD4+ memory stem T cells were associated with rs12257092 in exon 11 of the *FAS* gene ($p=1.55E-10$). The COVID-19 PGS was significantly associated with early-differentiated CD4+ and CD8+ T-cells (at FDR=1%). PGS analyses for AD and PD GWAS data as well as GREML and MR analyses are currently ongoing.
Conclusions: Our primary GWAS analyses suggest that genetic factors impact immune cell compositions in healthy individuals. First PGS analyses point at a shared genetic basis between immune cell distributions and COVID-19 predisposition. At the meeting, these analyses will be extended by also including GWAS data for AD and PD.

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P0491 / #2267

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

CORRELATION OF POLYGENIC RISK SCORES WITH ALZHEIMER'S DISEASE NEUROPATHOLOGY, T-CELL TRANSCRIPTOMICS, AND DISEASE TRAITS

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Aims: We calculated polygenic risk scores (PRSs) for a variety of disease traits from subjects in the Religious Orders Study/Rush Memory and Aging Project (ROSMAP). We searched for connections between PRSs and transcriptomic data from four T-cell subtypes.
Methods: We used whole-genome sequencing data from ROSMAP participants to calculate PRSs for 20 traits across four trait categories: immune function, neurodegenerative disease, autoimmune disease, and psychiatric disorders. We tested the predictive value of the PRS for Alzheimer's disease (AD) against clinical and pathological traits. We correlated PRSs for 20 traits with T-cell transcriptomic data. We then compared PRS-associated genes across traits and cell types, using gene set enrichment analysis to detect biological processes significantly represented by PRS-associated genes.
Results: The maximum predictive value of the AD PRS was 75.94%. PRS distributions for subjects with a clinical or pathological diagnosis of AD were significantly different than those from control subjects, and the AD PRS correlated significantly with quantitative neuropathological traits such as plaque and tangle burden. Over 13,000 genes from T-cell transcriptomic data were associated with the PRS for at least one trait, with some overlap across traits and cell types. For most autoimmune and neurodegenerative disease traits analyzed, CD4+ T-cell subtypes were more likely to yield positive PRS-gene associations, while CD8+ T-cell subtypes more commonly showed genes whose expression was inversely related to the PRS.
Conclusions: PRSs are becoming a widely utilized tool for their diagnostic and prognostic predictive value, as well as their potential for patient stratification in precision medicine. Our research lends insight into potential biological mechanisms behind PRS-disease associations for a variety of disease traits that implicate adaptive immunity.

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P0492 / #2411

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

LONGITUDINAL MODELING FOR SINGLE NUCLEOTIDE POLYMORPHISM ASSOCIATION WITH ALZHEIMER'S DISEASE

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Aims: Robust associations between genetic traits and neurodegenerative pathologies have been established thanks to the advent of GWAS. Meta-analysis incorporating tens of thousands of subjects allowed to discover hundreds of genetic loci associated with the diagnosis of diseases such as Alzheimer's Disease. Our aim is to identify associations between SNPs and longitudinal features of the disease progression, such as speed of progression, feature-specific dynamic patterns, etc. A finer understanding of the link between SNPs and disease progression could help design new polygenic risk scores, targeting not the diagnosis, but e.g. progression speed, hence allowing for higher-powered clinical trials for instance.
Methods: We developed and validated a new statistical model that extracts interpretable progression parameters for patients from a longitudinal cohort. Our model is able to link time-independent covariates — such as SNP arrays — to dynamic aspects of the disease such as progression speed for each monitored biomarker, disease onset-time, progression patterns, etc. We applied our method to observational cohorts from the Alzheimer's Disease Neuroimaging Initiative (ADNI) effort. We modeled a multivariate progression profile that included both the evolution of cognitive neuropsychological assessments and the dynamics of imaging biomarkers (brain volumes, tau and Abeta loads). We pre-selected the SNPs that we included in our analysis from a published GWAS.
Results: Our results suggest that multiple profiles of SNP coexist even among the top-associated SNPs of GWAS (some are linked mainly with onset-time, while others show a strong association with the disease dynamics for either all or a particular subset of features).
Conclusions: We proposed a model to link individual SNP to dynamic aspects of the disease, and examined some SNPs associated with AD diagnosis, which suggested new kinds of associations based on disease dynamics.

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P0493 / #529

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

CEREBRAL PERFUSION IN ALZHEIMER'S DISEASE PATIENTS CARRYING RISK ALLELE IN BIN1 GENE

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Aims: Common genetic polymorphisms in the gene *BIN1* (Bridging Integrator-1) are the second strongest risk factors in Alzheimer's disease (AD) following *APOE-e4* allele, both in terms of the p-values and the odds ratio conferred. AD patients carrying risk allele in *BIN1* also present with high levels amyloid and phosphorylated tau levels in the brain, and faster clinical progression – the only gene out of ~40 AD risk genes to show association with both, AD biomarkers and progression. The highest expression of *BIN1* is in the muscle cells, including vascular smooth vessels, followed by brain. In this study we set out to assess if AD patients carrying the BIN1 risk associated SNP (single nucleotide polymorphism) rs6733839 show altered regional cerebral blood flow estimated using early frame florbetapir positron emission tomography (PET) data.
Methods: We used clinical and imaging data at baseline prior to randomization from AD patients from the following AD clinical trials, a total of 523 patients diagnosed with mild-AD.

The Alzheimer's disease clinical trial name and the number of patients used in the study

Clinical Trial (ClinicalTrials.gov ID)	n (FLORBETAPIR-PET)
NAVIGATE-AD(NCT02791191)	187
DAYBREAK(NCT02783573)	336

Cerebral perfusion standardized uptake value ratio (SUVR) was measured in a composite neocortical region with respect to pons plus vermis as a reference. We then utilized EMMAX (Efficient Mixed-Model Association eXpedited) method to test for association using an interaction model of perfusion rate with three principal components and the risk allele in the SNP rs6733839.
Results: The risk allele in the SNP rs6733839 failed to show statistically significant association with cerebral blood perfusion as estimated using early frame florbetapir PET.
Conclusions: Our results suggest that changes in vasculature is not a pathogenic mechanism due to BIN1 risk variants leading to AD.

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P0494 / #863

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

IDENTIFYING ALZHEIMER'S DISEASE AND RELATED DISORDERS PATHOGENIC MUTATIONS CARRIERS IN THE UK BIOBANK WHOLE-EXOME SEQUENCING

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Aims: 1. Objectives The aim of this study was to identify carriers of rare monogenic mutations associated with early-onset Alzheimer's disease (EOAD) or related disorders in the UK Biobank. This provides a reference set of variants to identify individuals who should be removed from late-onset-AD (LOAD) genome-wide association studies (GWAS).
Methods: 2. Methods Mutations on *PSEN1*, *PSEN2, APP,* and *MAPT* genes were extracted from whole-exome sequencing data of ~470,000 individuals. All variants within these genes were extracted and annotated with VEP (Ensembl Variant Effect Predictor) using the ClinVar plugins. By using the proxy phenotype of subjects with an affected 1st degree relative, odds ratios (OR) adjusted for ancestry, age, sex, and APOE-ε2 and APOE-ε4 dosages were calculated. Variants with "pathogenic" status linked to AD or related disorders on Alzforum were selected, and additional mutations were identified based on support in the existing literature. Demographics and family history of carriers are provided in **Tables 1-4.**
Results: 3. Results We found carriers of known pathogenic *PSEN1, APP,* and *MAPT* mutations in UK Biobank. No mutations on *PSEN2* passed the filtering process. Five additional mutations on *PSEN1* and one on *APP* that were not listed as known pathogenic on Alzforum were identified. They were found in at least one affected carrier or a carrier with family history of dementia and had CADD scores > 20.

Table 1. Pathogenic variants identified on *APP* in UKB WES 470K. All variants within these genes were extracted and annotated with VEP (Ensembl Variant Effect Predictor) using the ClinVar plugins. Variants with ClinVar "pathogenic" status linked to a neurodegenerative disease in these genes were selected and their carrier details were annotated. Evidence of pathogenic status was also checked in the Alzforum mutations library. Demographics are reported as follows: AgeSex*APOE* (e.g. 40M33 means 40 years old male ε3ε3). Additionally, family history of dementia is reported as MAD (maternal AD) or PAD (paternal AD), or SAD (sibling AD). If the family member is deceased, age at death is reported in parentheses; -9 represents missing information.

GENE	HGVSP	RSID	CONSEQUENCE	CADD	OR	P	AD DEMOGRAPHICS	CN DEMOGRAPHICS
APP	p.L723P	rs63751122	missense	31.0	51.7308	0.0875		55F33 – MAD (59)
APP	p.V717I	rs63750264	missense	25.3	87.7299	$1.04x10^{-2}$	59M33 – MAD (62) 54F33	50M33 – MAD (47)
APP	p.E693Q	rs63750579	missense	31.0	20.9341	0.188		72M23 – PAD (66)

Table 2. Pathogenic variants identified on *MAPT* in UKB WES 470K. All variants within these genes were extracted and annotated with VEP (Ensembl Variant Effect Predictor) using the ClinVar plugins. Variants with ClinVar "pathogenic" status linked to a neurodegenerative disease in these genes were selected and their carrier details were annotated. Evidence of pathogenic status was also checked in the Alzforum mutations library. Demographics are reported as follows: AgeSex*APOE* (e.g. 40M33 means 40 years old male ε3ε3). Additionally, family history of dementia is reported as MAD (maternal AD) or PAD (paternal AD), or SAD (sibling AD). If the family member is deceased, age at death is reported in parentheses; -9 represents missing information.

GENE	HGVSP	RSID	CONSEQUENCE	CADD	OR	P	AD DEMOGRAPHICS	CN DEMOGRAPHICS
MAPT	p.R5L	rs63750959	missense	24.3	1.89	0.577		52F34 – MAD (73) 58M33, 63M33, 46M23, 69M33
MAPT	p.G55R	rs1012826460	missense	25.1	8.07	4.59×10^{-2}		51M33 – PAD 63F34 – MAD 51M23, 55M34, 47F33
MAPT		rs1568327531	splice donor	34.0	2.49	0.458		63M33 – MAD (82) 65M23, 46M34
MAPT	p.Q336R (p.Q671R)	rs63750573	missense	23.3	14.9	3.58×10^{-2}		60F33 – PAD (67) 66F34 – MAD (95) 44M33
MAPT	p.R406W (R741W)	rs63750424	missense	29.8	14.3	6.48×10^{-6}	62M44 – PAD (69) 72F33, 64F22, 67M23	52F33 – PAD (66) 50M34 – PAD (78) 56F33 – PAD (70) 56F23 – PAD 63M33, 55F33, 56M34, 73F33, 46F33, 63M33

Table 3. Pathogenic variants identified on *PSEN1* in UKB WES 470K. All variants within these genes were extracted and annotated with VEP (Ensembl Variant Effect Predictor) using the ClinVar plugins. Variants with ClinVar "pathogenic" status linked to a neurodegenerative disease in these genes were selected and their carrier details were annotated. Evidence of pathogenic status was also checked in the Alzforum mutations library. Demographics are reported as follows: AgeSex*APOE* (e.g. 40M33 means 40 years old male ε3ε3). Additionally, family history of dementia is reported as MAD (maternal AD) or PAD (paternal AD), or SAD (sibling AD). If the family member is deceased, age at death is reported in parentheses; -9 represents missing information.

GENE	HGVSP	RSID	CONSEQUENCE	CADD	OR	P	AD DEMOGRAPHICS	CN DEMOGRAPHICS	OTHER DEMENTIA
PSEN1	p.A79V	rs63749824	missense	27.1	8.20	3.30×10^{-3}		59M33 – PAD 57M33 – PAD (78) 53M33 – PAD 62M34 – PAD (-9) 57F33, 54M33, 67M34	68F24 – unspecified, MAD (70) 72F34 – MCI
PSEN1	p.I143F	rs63750322	missense	26.8	22.7	0.177		55M34 – MAD (60)	
PSEN1	p.A246E	rs63750526	missense	26.0	48.7	4.32×10^{-2}	62M33 – MAD (50)	51M33 – MAD (57)	
PSEN1	p.L262V		missense	24.5	25.9	0.159		55F34 – MAD (78)	
PSEN1	p.R269H	rs63750900	missense	29.3	8.03	1.36×10^{-3}	68F33	63F34 – MAD (70) 53M33 – PAD (75) 56M34 – MAD (65), PAD (72) 61M23 – PAD (73) 56F33, 56M33	72F33 – vascular 61M33 – unspecified 77M33 – vascular 81F33 – vascular

Table 4. Novel pathogenic variants identified on *PSEN1* and *APP* in UKB WES 470K. All variants within these genes were extracted and annotated with VEP (Ensembl Variant Effect Predictor) using the ClinVar plugins. Variants with ClinVar "pathogenic" status linked to a neurodegenerative disease in these genes were selected and their carrier details were annotated. Evidence of pathogenic status was also checked in the Alzforum mutations library. Demographics are reported as follows: AgeSex*APOE* (e.g. 40M33 means 40 years old male ε3ε3). Additionally, family history of dementia is reported as MAD (maternal AD) or PAD (paternal AD), or SAD (sibling AD). If the family member is deceased, age at death is reported in parentheses; -9 represents missing information.

GENE	HGVSP	RSID	CONSEQUENCE	CADD	OR	P	AD DEMOGRAPHICS	CN DEMOGRAPHICS	KNOWN PATHOGENIC MUTATIONS
PSEN1	p.L435I		missense	29.3	11.9	$3.76x10^{-2}$	75F34 – MAD (65) 70M44 - SAD	56M33 – MAD 60F24	L435F
PSEN1	p.M457V	rs1430581353	missense	24.2	41.3	$3.94x10^{-2}$	66M34 – MAD	70F34 – MAD (76) 53M33 – MAD (75)	
PSEN1	p.G378A	rs63750323	missense	28.6	7.59	0.110	75M34 - SAD	63M23 – MAD 74M34 – MAD (87) 74F34, 59F33	G378E G378V
PSEN1	p.F175S	rs63750771	missense	25.4	5.69	0.219	68F34	58F34	
PSEN1	p.P264R		missense	28.7	8.26	0.361	69F34		P264L
APP	p.I716M		missense	20.0	21.8	0.105		60M34 – MAD (73) 60M34 – MAD (78)	I716F

Conclusions: 4. Conclusions Our study provides a list of pathogenic variants occurring in the largest population-based exome sequencing cohort. This list helps identify individuals with likely EOAD and flags them for exclusion from LOAD GWAS. We also identify five *PSEN1* variants and one *APP* variant that merit further investigation.

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P0495 / #2383

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

OVERESTIMATED ALZHEIMER'S DISEASE PREDICTION USING POLYGENIC RISK SCORE DERIVED FROM SUMMARY STATISTICS

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Aims: Polygenic risk score (PRS) is often derived from summary statistics, from which the independence between discovery and replication sets cannot be monitored. Prior studies, in which independence is strictly observed, report a relatively low gain from PRS in binary traits. We hypothesize that the independence assumption may be compromised when using the summary statistics, and suspect an overestimation bias in the predictive accuracy.
Methods: We consider the task of Alzheimer's disease (AD) prediction across genetics datasets, including the International Genomics of Alzheimer's Project (IGAP), AD Sequencing Project (ADSP), and Accelerating Medicine Partnership - Alzheimer's Disease (AMP-AD). PRS is computed from either sequencing studies for ADSP and AMP-AD (denoted as rPRS) or the summary statistics for IGAP (sPRS). Two variables with the high heritability in UK Biobank, hypertension, and height, are used to derive an exemplary scale effect of PRS. The expected performance of sPRS is computed for AD prediction.
Results: Using ADSP as a discovery set for rPRS on AMP-AD, ΔAUC and ΔR2 (performance gains in AUC and R2 by PRS) record 0.069 and 0.11, respectively. Both drop to 0.0017 and 0.0041 overlapping subjects are removed from AMP-AD. sPRS is derived from IGAP, which records ΔAUC and ΔR2 of 0.051±0.013 and 0.063±0.015 for ADSP and 0.060 and 0.086 for AMP-AD, respectively. On UK Biobank, rPRS performances for hypertension assuming a similar size of discovery and replication sets are 0.0036±0.0027 (ΔAUC) and 0.0032±0.0028 (ΔR2). For height, ΔR2 is 0.029±0.0037.
Conclusions: Considering the high heritability of hypertension and height, sPRS results of AD are inflated. The higher performances relative to the size of the discovery set were observed in several PRS studies. For sPRS, potential duplications should be carefully considered within the same ethnic group.

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P0496 / #1978

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

ALZHEIMER GENETIC RISK LOCI AFFECT DISTINCT NEUROPATHOLOGICAL PROCESSES

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Aims: Neurodegenerative brain diseases (NBDs) ultimately result in loss of brain volume and subsequent cognitive decline. However, in the elderly brain, many underlying pathologies can be observed. In Alzheimer's disease, tau neurofibrillary tangles (NFT) and amyloid plaques are considered the main hallmarks. Neuropathologically, a myriad of different features can be observed in the brain of AD patients. These features are not exclusive to AD but do occur to a certain extent in many other NBDs. To investigate the genetic underpinnings of these neuropathological features, we extracted DNA from a cohort of 369 post-mortem brains of NBD patients and non-diseased controls with detailed neuropathological characterization. We then investigation the association between the genetic risk loci and several neuropathological phenotypes.
Methods: Genotyping of 85 genetic loci, previously found to be associated with AD, is ongoing using an in-house developed oxford nanopore technologies (ONT) multiplex assay, allowing simultaneous sequencing of all variants on an ONT Flongle platform. After sequencing, base- calling, alignment to Hg38 and variant calling are performed followed by QC on the data. Association testing on a subset with complete genotype information (n= 192) was done using linear regression in PLINK.
Results: Regression analysis revealed association between genetic risk loci and granulovacuolar degeneration, Hirano bodies, cerebral amyloid angiopathy, Braak NFT stage and the phases of amyloid plaque pathology. For each of these neuropathological phenotypes, significant and nominally significant associations were discovered.
Conclusions: We found significant and nominally significant associations between several known AD risk loci and neuropathological features, possibly highlighting biological pathways involved in formation of these features. Our ongoing work is currently focusing on increasing our sample size to further validate the associations we discovered.

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P0497 / #1061

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

GWAS FOR THE TAILS OF THE INSULIN DISTRIBUTION IN EUROPEAN CHILDREN IDENTIFIES GENOTYPES ASSOCIATED WITH DEMENTIA PHENOTYPES

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Aims: Objectives: Previous results from a Swedish cohort of middle-aged women showed a U-shaped relationship between fasting serum insulin and incident dementia (1). We aimed to perform genome-wide association (GWA) analyses for fasting serum insulin in European children with focus on variants associated with the tails of the insulin distribution. (1) Mehlig et al., Neurology 91(5):e427-e435 (2018)
Methods: Genotyping was successful in 2833 children from 7 European countries 2-14 years old at insulin measurement. Because levels vary during childhood analyses were based on pre-selected age- and sex-specific percentiles of fasting insulin modelled by logistic regression. Additive genetic models were adjusted for age, sex, BMI, year, country, and principal components to account for ethnic heterogeneity. We used quantile regression to examine how associations with specific variants varied across the insulin spectrum.
Results: GWA analyses of the tails of the insulin distribution identified several variants that were located on genes previously associated with both insulin and Alzheimer's disease (AD). One variant associated with the 85th insulin percentile was located on the *SLC28A1* gene previously linked to AD and type 2 diabetes (rs2122859, p-value = 4 10^{-8}). Two variants associated with the 15th insulin percentile were located on *RBFOX1* (rs2109059, p = 10^{-6}) and *SH3RF3* (rs36197836, p = 4 10^{-6}), genes linked to brain amyloidosis and late-onset AD, respectively. Quantile regression showed large variability in effect size across the insulin spectrum for these variants.
Conclusions: Our approach identified variants that were associated with the tails of the insulin spectrum only. Future analyses should investigate whether variants associated with low insulin values are associated with different dementia phenotypes than those associated with hyperinsulinemia and diabetes.

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P0498 / #321

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

IDENTIFICATION OF PATHWAYS ENRICHED IN ANIMAL MODELS OF ALZHEIMER'S DISEASE USING SYSTEM BIOLOGY

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Aims: Alzheimer's disease is the most prevalent neurodegenerative disorder and accounts for the majority of people diagnosed with dementia. We used RNA Sequencing data to perform enrichment analysis of Alzheimer's disease mouse model to find the pathways containing genes which are overly expressed. We presented this approach to infer genes over expression in various biological pathways
Methods: We searched for Alzheimer's disease data set of Mus musculus on GEO, retrieved the processed data file, which consisted of 53710 genes, normalization of data performed using R studio packages. From which 670 differentially expressed genes were identified. Upregulated genes i.e. 39 genes were input to enrichment analysis tool, significantly enriched 10 genes in reactome were then searched for corresponding pathways.
Results: From the present study, we have identified ten genes in Reactome database which are: TTR, SCARNA8, SNORA33, COL11A2, SNORA57, BGLAP, SNORA52, SNORA81, SNORA23, SNORD17, LARS2 that were found to be significantly enriched in human biological pathways. We also found ttr which codes for Transthyretin gene overly expressed in the neuronal system. Tetramer dissociation and partial unfolding leads to the formation of aggregates and amyloid fibrils.
Conclusions: Therefore, it may be concluded that the genes identified in the present study using Over-representation analysis approach, have been implicated to be involved in pathophysiology of Alzheimer's disease.

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P0499 / #2118

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

A GENOME-WIDE ASSOCIATION STUDY IN PERUVIANS SUGGESTS NEW RISK LOCI FOR ALZHEIMER DISEASE

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Aims: Increasing racial/ethnic diversity in genetic studies is critical for defining the genetic architecture of Alzheimer disease (AD). Amerindian (AI) populations are substantially underrepresented in AD genetic studies. The Peruvian (PE) population, with up to ~80% of AI ancestry, provides a unique opportunity to assess the role of AI ancestry in AD. We performed the first genome-wide association study (GWAS) in the PE population to identify novel AD susceptibility loci and characterize the known AD genetic risk loci in the PE population.
Methods: The PE dataset includes array-genotype and phenotype data from 550 individuals (168 cases; 382 controls), all imputed to the NHLBI TOPMedv5 haplotype reference panel. We performed genome-wide association analyses using the SAIGE software with a generalized linear mixed-model. The model included genotype, sex, age, and principal components (population substructure) as fixed effects and a genetic relationship matrix as a random effect.
Results: We identified the *APOE* gene as a genome-wide significant with an effect size comparable to the effect size found in non-Hispanic white (NHW) populations (*OR=3.7(3.0-4.5),pv=6.6x10^{-11}*) (GIF=1.02). In addition to *APOE*, one additional known AD loci, *BIN1* (*pv=0.04*), showed nominal significance. Variants at four additional loci reached suggestive significance (*P<5x10^{-5}*): *NFASC* (pv=4.6x10^{-7}) on chromosome 1, *ALPP* (pv=7.9x10^{-6}) on chromosome 2, *STK32A* (pv=1.5x10^{-7}) on chromosome 5, *DGKB* (*pv=1.3x10^{-5}*) on chromosome 7, and *KDM4C* (*pv=7.1x10^{-7}*) on chromosome 9. Follow-up ancestry-aware analysis at the *DGKB* (Diacilglicerol kinase beta) locus showed increased AI ancestry among the risk allele carriers.
Conclusions: The high frequency of the risk allele in AI ancestry increased the power to detect association and suggests that the signal at the *DGKB* locus was driven by the AI ancestry emphasizing the importance of incorporating ancestry-aware approaches into gene discovery.

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P0500 / #610

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: AGING

SUBSET-BASED META-ANALYSIS OF ALZHEIMER'S DISEASE AND LONGEVITY

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Aims: Ageing is the largest risk of developing late-onset Alzheimer's disease (AD). Both longevity and AD have a polygenic architecture and *APOE* is the only gene repeatedly associated with them. In this study we aimed to investigate for common pleiotropic effects among the two traits and better understand the underlying biological pathways.
Methods: We utilised the publicly available AD summary statistics data by Kunkle et al. (2019) (N=63,926) and data from individuals surviving at or beyond the age corresponding to the 90th survival percentile by Deelen et al. (2019) (N=36,746). We estimated the genetic correlation between the two traits using the LD Score regression (LDSC) and meta-analysed the data using a technique called association analysis based on subsets (ASSET). After meta-analysis, SNPs showing effects in opposite directions were considered as significant when their $p_{ASSET} \leq 5e\text{-}08$, and the association in both traits reached nominal significance of $p<0.05$. Independent signals were identified after linkage disequilibrium (LD)-clumping the results with $r^2<0.1$ within 1000-kb window.
Results: LDSC identified a negative, non-significant correlation between AD and longevity (r_g =-0.18, p=0.16). ASSET identified 431 possible pleiotropic risk loci shared between AD and longevity resulting in 26 independent associations. The majority (19/26) was mapped to chromosome 19 and the *APOE* region with rs28399637 showed the strongest association (p_{ASSET}=1.58e-122). The rest of the pleiotropic SNPs were mapped to *HBEGF* (rs1116803, p_{ASSET}=4.41e-09), *MS4A3* (rs583296, p_{ASSET}=3.35e-11), *CR1* (rs2093761, p_{ASSET}=4.14e-15), *BTNL2* (rs4335021, p_{ASSET}=3.55e-08), *BIN1* (rs6733839, p_{ASSET}=3.16e-28), *SPI1* (rs67472071, p_{ASSET}=1.19e-11) and *CD2AP* (rs9395288, p_{ASSET}=2.66e-09).
Conclusions: Our findings suggest that some variants associated with AD-risk may affect longevity either by modifying the onset of AD or through their effect on other age-related diseases. Better understanding of how the brain ages can aid in developing interventions to address AD.

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P0501 / #1920

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: AGING

FRAILTY SYNDROME IN AUTOSOMAL DOMINANT ALZHEIMER DISEASE BY PSEN1- E280A VARIANT

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Aims: To characterize the frailty status based on its cognitive status in individuals of the largest known Autosomal Dominant Alzheimer's Disease (ADAD) kindred by the PSEN1-E280A variant.
Methods: A cross-sectional study of patients with mild cognitive impairment (MCI) or dementia due to the PSEN1-E280A variant. All the participants underwent a complete assessment that included a standardized clinical examination, neuropsychological evaluation, nutritional assessment, and functional scales.
Results: 111 participants underwent the study. 45.9% were males, with a median of 50 years of age. The most frequent comorbidity was hypertension. Twenty-five individuals have MCI and eighty-six dementia, 10 have fragile and 28 prefragile status. The risk of malnutrition was identified in 48 individuals. 18,9% of participants have polypharmacy, and only 11 individuals have fallen in the last year. No significant difference was seen between the variables.
Conclusions: Frailty is a frequent syndrome in ADAD; both clinical conditions may generate a worse health-related status, such as undernutrition, hypertension, and more severe disease.

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P0502 / #699

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: AGING

ASSOCIATIONS BETWEEN NON-APOE AD-PRS AND DEMENTIA-RELATED MRI MEASURES IN A POPULATION-BASED SAMPLE FOLLOWED BETWEEN AGE 70 AND 75

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Aims: Studies of the relation between genetic risk factors for Alzheimer's disease (AD) and structural magnetic resonance imaging (MRI) measures of relevance for dementia in population-based samples followed over time are limited. The aim of the present study is to investigate such associations among individuals recruited from the general population and examined at age 70 and 75.
Methods: Participants included in the study (n=752) were born 1944 and belong to the Gothenburg H70 Birth Cohort Studies, which are epidemiological studies of older individuals within Gothenburg, Sweden. The participants underwent MRI scanning and blood sampling for DNA extraction. Genetic analyses were performed with the Neurochip (GWAS-array from Illumina). Potential associations between genetic risk for AD (i.e. polygenic risk score (PRS) for AD) and MRI measures were investigated with linear regressions adjusted for sex.
Results: based on cross-sectional analyses at age 70 show associations, in the expected direction, between a non-*APOE* AD-PRS and hippocampal volume (p=0.01) and an AD signature of cortical thickness including mean isthmus cingulate, posterior cingulate, and precuneus thickness (p=0.02). No association was seen with another AD signature of cortical thickness including mean entorhinal, inferior temporal, middle temporal, and fusiform thickness. None of the MRI measures were associated with *APOE* e4 carriership.
Conclusions: Our results indicate that genetic risk for AD beyond *APOE* seem to be associated with brain measures of relevance for dementia among 70-year olds from the general population. Analyses of data from the age 75 examination will reveal valuable information about these associations over time.

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P0503 / #2039

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: AGING

PREDICTING DEMENTIA IN DIABETES PATIENTS FROM BIOLOGICAL AGE ESTIMATED USING DEEP LEARNING IN RETINAL SCREENING PHOTOGRAPHS

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Aims: Biological age may be a more clinically valuable independent predictor of age-related diseases than chronological age. As the retina is a conveniently imaged biological surrogate of the brain, we aimed to determine whether AI-estimated biological age using retinal photographs can independently predict future dementia in patients with type 2 diabetes (T2D).
Methods: A deep learning model was applied to 102,082 diabetes retinal screening photographs from 8,506 patients with T2D in the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) bioresource to predict age at each photograph date. The predicted age difference (PAD) was calculated as the difference in years between predicted and chronological age for the earliest available (baseline) photograph for each patient. Using our previously validated electronic medical record linkage approach we determined incident all cause dementia in GoDARTS. Multivariate Cox regression was used to evaluate the association between PAD, ApoE4 status and dementia outcome adjusted for chronological age.
Results: Among the 8,506 individuals with baseline PAD available, 1,018 developed dementia during a median of 13 years follow-up. In a multivariate Cox model including chronological age, PAD significantly increased the risk of developing dementia per PAD year (HR = 1.031, 95%CI = 1.014 – 1.048, p = 0.0003), independently of ApoE4 status (HR = 2.169, 95%CI = 1.892 – 2.486, $p < 2e^{-16}$). However, PAD did not significantly increase the prediction with ApoE4 status (AUC = 0.6543 for ApoE4 status, compared to 0.6549 for PAD and ApoE4 status).
Conclusions: Retinal biological age, defined by PAD, is a significant independent predictor of future all cause dementia in patients with T2D. However in this study, PAD does not appear to significantly improve prediction beyond ApoE4 status and chronological age.

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P0504 / #2256

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

LEAD EXPOSURE IN A KNOCK-IN MOUSE MODEL OF ALZHEIMERS DISEASE PATHOLOGY SUGGESTS AN UNEXPECTED MECHANISM FOR COGNITIVE IMPAIRMENT

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Aims: Objectives: Exposure to lead (Pb) is a major public health problem that could occur through contaminated air, food, or water. Although Pb has long been known to be neurotoxic in children, recent research indicates that cumulative, low-level Pb exposure likely drives age-related neurologic dysfunction in adults, and has been linked to an increased risk of late-onset Alzheimer's disease (AD). It has been proposed that Pb exposure may increase the risk of AD via altering the expression of AD-related genes and, possibly, activating the molecular pathways underlying AD-related pathology.
Methods: Methods: We exposed APPxPS1 knock-in (KI) mice and wild type (WT) controls to 0.2% Pb acetate in drinking water for 3 months. Expression of AD-related genes was determined by qRT-PCR, amyloid pathology was measured by ELISA, and AD-protein levels were obtained by immunoblot. Cognitive performance was evaluated by Morris Water Maze (MWM).
Results: Results: Pb exposure caused significant cognitive dysfunction, but this was not related to an increase in amyloid pathology, or to changes in the expression of common AD-related genes. In spite of this finding, the effect on cognitive dysfunction was only observed in the KI mice, and not in the WT controls, suggesting that the effect may be mediated through another aspect of the AD-related mutations.
Conclusions: Conclusions: It is widely believed that Pb exposure is unrelated to AD; our data indicate that this belief may stem from a narrow prior focus on AD hallmarks such as plaques and tangles, and that the reality may be far more subtle. Our data imply that Pb exposure requires AD-related vulnerability in order to affect cognitive function, but that the AD pathology itself need not necessarily worsen. Funding provided by NIEHS (ES024158).

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P0505 / #1215

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

POST-TRAUMATIC STRESS AND COGNITIVE IMPAIRMENT: A SINGLE-SAMPLE MENDELIAN RANDOMIZATION STUDY OF WORLD TRADE CENTER RESPONDERS

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Aims: Trauma-related stress is a health risk factor as it undermines the body's physiologic response to situational demands, leading to diminished cognitive ability and dysregulated immune functions that increase the risk of disease. The terrorist attacks that occurred on 9/11/2001, traumatized many survivors and first responders. Tens of thousands of people experienced this trauma but vary in the duration and intensity of exposure, as well as subsequent experience of cognitive impairment and symptoms of post-traumatic stress disorder (PTSD). The present study tested the putatively causal link between persistent symptoms of PTSD and the precipitously high incidence of cognitive impairment in World Trade Center (WTC) responders.
Methods: A single-sample Mendelian randomization study was conducted in a large (n = 3992) longitudinal sample of WTC responders to test whether the effect of PTSD on the hazard rate of cognitive impairment is consistent with a cause-effect relation. Consistent with current recommendations, we implemented a variety of robust methods to evaluate the consistency of estimates across different analytic routines, including 2-Stage least squares, adjusted 2-stage least squares, adjusted 2-stage LIML, 3-stage FIML, 3-stage with bootstrapping, and 3-stage MCMC.
Results: First-stage results provide evidence for the predictive validity of the genetic instrument for PTSD, supporting the relevance criterion of a valid instrument. Moreover, the genetic instrument for PTSD was not predictive of cognitive impairment, supporting the exclusion criterion, while a genetic instrument for Alzheimer's Disease was predictive of cognitive impairment. Second-stage results indicate that a causal pathway between PTSD and cognitive impairment cannot be ruled out after controlling for potential genetic confounds.
Conclusions: Findings suggest that persistent symptoms of PTSD may be a cause of a heretofore unknown disease arising independently from Alzheimer's disease though having similar cognitive symptomatology

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P0506 / #1301

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

IMPACT OF MOOD DISORDER HISTORY AND BONE HEALTH ON COGNITIVE FUNCTION AMONG HEALTHY AGEING MEN

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Aims: Poor cognitive function, a major disabling condition of old age, is often considered a prodromal feature of dementia. High mortality and the lack of a cure for dementia have necessitated a focus on the identification of potentially modifiable risk factors. Some of the mental and physical health conditions such as mood disorders and bone loss have been previously linked with poor cognition although their combined effect remains largely unknown. Considering the multifactorial nature of dementia pathology, we investigated whether a joint excess effect (i.e. interaction) exists between mood disorders and bone loss in predicting cognitive function in a population-based sample of men.
Methods: Four hundred and forty-two male participants were drawn from the Geelong Osteoporosis Study and cognitive function was assessed via the CogState Brief Battery that measured cognitive performance across four domains. Mood disorders and hip bone mineral density (BMD) were evaluated using a semi-structured clinical interview and dual energy x-ray absorptiometry, respectively. Linear regression analyses were conducted to investigate whether a lifetime history of a mood disorder, hip BMD or two-way interaction effects between them is associated with overall cognitive function and cognitive performance in the individual domains.
Results: Both mood disorder history and increasing BMD showed a positive association with poor overall cognitive performance, while they negatively impacted each other's association with cognitive function.
Conclusions: The findings lend support to the hypothesis that mood disorders and hip BMD can impact each other's association with cognitive function and these interactions should be accounted for in establishing risk factors. These potentially modifiable risk factors may enable the identification of high-risk groups for whom early interventions can be made before irreversible neurological damage occurs.

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P0507 / #1572

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

EXPLORING THE RELATIONSHIP BETWEEN GENETIC VARIATION IN AQUAPORIN-4, SLEEP AND ALZHEIMER'S DISEASE PHENOTYPES.

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Aims: The Aquaporin-4 protein (encoded by the *AQP4* gene) has an important role in the glymphatic system, which is one suggested mechanism by which amyloid-β is cleared from the brain during sleep. Our group has reported previously on the moderating effects of genetic variants within *AQP4* and sleep on cortical amyloid-β burden. This study aimed to extend this analysis and assess associations with additional downstream AD phenotypes using both cross-sectional and longitudinal data.
Methods: Participants of the Australian Imaging, Biomarker and Lifestyle (AIBL) Study of Ageing with available genetic, brain imaging and cognitive data were included for analysis in the current study. Genetic variants within the *AQP4* gene were extracted from genome wide genotyping assays, and sleep measures were calculated using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Analyses involved assessing whether variants within *AQP4* moderated the relationship between sleep and AD phenotypes including cortical amyloid-β, brain volume and cognition cross-sectionally and longitudinally.
Results: A number of variants within *AQP4* significantly moderated associations between sleep measures, including sleep latency and disturbance and AD phenotypes, including cortical amyloid-β accumulation and brain volume atrophy.
Conclusions: The results of this study confirm our previous findings and suggest that interactions between *AQP4* genotypes and sleep measures are associated with additional AD phenotypes included brain volume and cognition. Further, associations were observed when assessing both cross-sectional and longitudinal data. While there is a growing body of literature supporting the role of sleep and risk for AD, there is still significant inter-individual variability in its effectiveness. The findings here suggest that genetics will be important to consider when recommending sleep-based interventions in AD.

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P0508 / #2156

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

GENETICALLY DETERMINED ASTHMA, BUT NOT ALLERGIC RHINITIS AND ECZEMA, IS ASSOCIATED WITH A SLIGHTLY REDUCED RISK OF ALZHEIMER'S DISEASE: A TWO-SAMPLE MENDELIAN RANDOMIZATION

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Aims: Several observational studies have suggested an association between the atopic disorders and the risk of Alzheimer's disease (AD). However, current research results are inconsistent. A causal association between atopic disorders and the risk of AD cannot be established.
Methods: In these two-sample Mendelian randomization (MR) analysis, instrumental variables (IVs) from the genome-wide association study (GWAS) for three types of atopic disorders (asthma, allergic rhinitis, and eczema) from European participants were applied to explore the relationship with AD through five methods (inverse-variance weighted, MR egger, weighted median, simple mode, weighted mode), accompanied by multiple pluripotency and heterogeneity tests.
Results: The two-sample MR analysis revealed that asthma was associated with lower risk of AD through the IVW method (OR: 0.995; 95% CI: 0.991–0.998; P = 0.002), weighted median (OR: 0.995; 95% CI: 0.990–0.999; P=0.002), and weighted mode (OR: 0.992; 95% CI: 0.986–0.999; P=0.025). However, no statistical differences were detected by MR egger and simple mode. In addition, there was no evidence for the causal effect of allergic rhinitis and eczema on the risk of AD. There were no obvious heterogeneities and horizontal pleiotropy in the causal effect of three types of atopic disorders on AD through Cochran's Q statistic, intercept of MR Egger regression and MR pleiotropy residual sum and outlier (MR-PRESSO) test. Meanwhile, leave one-out analysis showed all SNPs contributing to consistent causal estimate.
Conclusions: Taken together, this study demonstrated a genetic association between asthma and reduced AD risk, but not allergic rhinitis and eczema. Future studies should focus more on the effects of long-term use of drugs for atopic disorders on the risk of AD.

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P0509 / #628

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

ANTIMONY MAY IMPAIR COGNITIVE FUNCTION IN OLDER ADULTS: EVIDENCE FROM THE HEALTHY AGEING AND BIOMARKERS COHORT STUDY (HABCS) IN CHINA

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Aims: We aimed to explore the association of Sb exposure with cognitive impairment among older adults.
Methods: Data was from a prospective cohort of the Healthy Ageing and Biomarkers Cohort Study from 9 longevity areas selected by the Chinese Society of Gerontology. A total of 1333 participants aged 65 and older (mean age: 78.8±9.1) were recruited and followed up from 2017/18 to 2020/21. Blood and urine samples were collected from each participant, and the concentrations of blood Sb (B-Sb) and urine Sb (U-Sb) were measured by inductively coupled plasma mass spectrometry. Cognitive function was assessed via a validated Mini-Mental State Examination. Cox proportional hazards models were performed to explore the association of Sb exposure with cognitive impairment. Restricted cubic splines were used to flexibly model the association of the Sb with cognitive function.
Results: During 4972.1 person-years follow-up, 241 incident cognitive impairments were documented. After adjusting for potential covariates, each e-fold increase in U-Sb adjusted for creatinine (Ucr-Sb) was associated with a 53.7% increased risk of cognitive impairment [hazard ratio (HR)=1.537, 95% confidence interval (95% CI): 1.205-1.961]. Compared with the low group (<0.10 μg/L), the HR (95% CI) of cognitive impairment in the high group (≥0.19 μg/L) was 2.363(1.472-3.792). The results remained robustness in B-Sb. For each increased in e-fold of B-Sb, the risk of cognitive impairment in the older adults increased by 52.6% (HR=1.526, 95%CI: 1.093-2.131). Restricted cubic splines showed a linear and monotonic association between Sb and risk of cognitive impairment.
Conclusions: Sb was considered to be a risk factor for cognitive impairment in Chinese older adults. Reducing Sb exposure may reduce the population burden of future cognitive impairment, especially in areas with high Sb contamination.

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P0510 / #2270

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

THE ASSOCIATION OF JOB CHARACTERISTICS WITH COGNITION AND CSF MARKERS OF ALZHEIMER'S DISEASE: A MULTIDIMENSIONAL OCCUPATION SCORE AS NOVEL INDICATOR OF COGNITIVE RESERVE

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Aims: Cognitively stimulating occupations have been linked with good cognition in older ages. It remains unclear whether occupational demands are associated to underlying pathological processes of Alzheimer's disease (AD). We aimed to investigate the relation of a large spectrum of work characteristics to cognition to establish a multidimensional occupation score (MOS) and to examine whether AD pathology mediates the association between MOS and cognition.
Methods: Professions from patients (Memory Clinic, Ulm University) were unraveled for 246 occupational characteristics using the Occupational Information Network (O*Net Online). The MOS was created in a training sample (N=338) and independently validated (N=283). Aβ42 and tau was determined in CSF by routine assays. For constructing and validating the MOS we applied multiple linear regression (covariates age, sex, and Apolipoprotein E status). Mediation analysis assessed relation of AD pathology as link between MOS and cognition.
Results: The 10% most predictive descriptors included in the MOS mostly entail physical work demand as negative ($\beta s \leq -0.18$, $ps \leq 0.01$) and cognitive work demand as positive predictors of cognition ($\beta s \geq 0.18$, $ps \leq 0.01$). The MOS itself showed a positive association to cognitive performance ($\beta=0.255$, $p<0.001$, 95%CI [0.162,0.348]) and in the validation sample, the MOS significantly predicted cognition ($\beta=0.164$, $p=0.008$, 95%CI [0.044, 0.284]). In mediation analysis, no indirect link between the MOS and cognition via AD pathology was discovered, neither via tau ($\beta=-0.001$, n.s.) nor via Aβ42 ($\beta=-0.018$, n.s.) indicating no significant mediating role of AD pathology between MOS and cognition.
Conclusions: We found a positive association between occupational cognitive demand and cognition in older age. The created MOS significantly predicted cognitive performance. Moreover, AD pathology did not mediate the association between occupation score and cognition. Our data suggest that working conditions may be a protective factor against dementia.

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P0511 / #2412

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: METABOLIC AND CARDIOVASCULAR

THE DIAGNOSIS OF CARDIOVASCULAR DISEASES IN DEMENTIA PATIENTS IN AUSTRIA- AN EPIDEMIOLOGICAL CASE-CONTROL STUDY

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Aims: Studies have shown that cardiovascular diseases promote the onset and progression of dementia. In this retrospective case-control study, we investigated whether cardiovascular disease (myocardial infarction, stroke or intracranial haemorrhage) was diagnosed more frequently in dementia patients than in a non-demented control group.
Methods: National social insurance data from dementia patients and a matched control population were used for this analysis. These data included information on whether the following conditions were listed as the main diagnosis in the discharge letter: Myocardial infarction (I20*, I21*), intracranial haemorrhage (I60*, I61*, I62*) or stroke (I63*, I64*, I65*, I66*, I69*).
Results: Overall, 116655 dementia patients and an equal number of non-demented controls were included in this analysis. A total of 1100/116655 (0.9%) dementia patients and 3162/116655 (2.7%) controls were diagnosed with myocardial infarction ($p<0.001$). Cerebral ischaemia was diagnosed in 2877/116655 (2.5%) dementia patients and 4409/116655 (3.8%) controls ($p<0.001$). A diagnosis of intracranial haemorrhage was made in 0.4% (499/116655) of dementia patients and in 1.1% (1258/116655) of the control patients ($p<0.001$). During the observation period, significantly more dementia patients than patients in the control group were hospitalised at least once (97727/116655, 83.8% vs. 67740/116655, 58.1%; $p<0.001$).
Conclusions: Although dementia and cardiovascular disease have overlapping risk factors, which would suggest that demented patients are at higher risk for myocardial infarction, stroke, and intracerebral haemorrhage, in our cohort all three diseases were diagnosed significantly less frequently in dementia patients than in controls. Dementia patients are admitted to hospital more often, but seem to be discharged with other diagnoses, which could mean that cardiovascular disease is underdiagnosed in this patient cohort.

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P0512 / #928

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

GENETIC SUSCEPTIBILITY TO HSV-1 INFECTION AND THE RISK OF ALZHEIMER'S DISEASE

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Aims: The aim of this project was to estimate the potential effect of cold sores on Alzheimer's disease using genetic variants.
Methods: We created a polygenic risk score for susceptibility to cold sores using summary statistics from a GWAS study on 25,108 cases with cold sores and 63,332 controls. Three other candidate genes associated with frequency of cold sores were identified: IFLN4 rs12979860-T, CSSG-1 rs10446073-T and TLR3 rs3775291-T. The genetic markers were coded additively as having 0,1 or 2 copies of the effect allele. The associations between the PRS, IFNL4, CSSG-1, TLR3 and AD risk were modeled in an independent nested case-control sample with individual level data. The first five principal components were included as covariates to control for genetic ancestry.
Results: A total of 297 cases and 297 controls passed quality control. The mean age was 75 years and 76 % were female. The OR for AD per 1 SD increase in genetically predicted cold sores was 1.02 (95 % CI [confidence interval] 0.86 - 1.21, p = 0.82). In the whole sample, the IFNL4 T allele was associated with increased risk of AD (OR 1.23, 95 % CI 1.03-1.47, p = 0.019). The CSSG-1 T allele was associated with increased AD risk in *APOE*e4 non-carriers (OR 1.95, 95 % CI 1.06-3.60, p = 0.03)
Conclusions: In conclusion, two genetic markers previously linked to cold sore frequency were associated with increased AD risk. On the contrary, the PRS for genetic liability to cold sores was not associated with AD. This could be due to a lack of association between cold sores and AD, or that the genetic variants included in the PRS were only weakly correlated to the exposure of interest.

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P0513 / #1342

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

LONGITUDINAL EFFECTS OF HERPESVIRUSES ON SEVEN COGNITIVE ASSESSMENTS IN THE HEALTHY ELDERLY

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Aims: Herpesviruses have been proposed to be involved in Alzheimer's disease (AD) development as potentially modifiable triggers of AD pathology, and may also possibly be involved in early cognitive decline. The objective was to investigate cross-sectional and longitudinal associations between herpes simplex virus (HSV)-1 and seven cognitive assessments in relation to *APOE4*, anti-cytomegalovirus (CMV) IgG, anti-HSV IgM, and anti-herpes virus treatment among elderly Swedes.
Methods: The study included 849 participants in the population-based PIVUS cohort. Presence of antibodies in sera at 70 years was determined using enzyme-linked immunosorbent assay. Anti-herpes prescriptions were collected from medical records. Mini-mental state examination (MMSE), trail-making test (TMT), and the seven min screen including subscales were used to assess cognitive performance at ages 75 and 80 years. The research questions were investigated using linear mixed effects models.
Results: Anti-HSV-1 IgG was associated with poorer performance on MMSE, TMT-A, TMT-B, and seven min screen at 75 years ($p = .033$, $p = .022$, $p < .001$, and $p = .004$, respectively). HSV-1 was also associated with worse verbal fluency ($p = .002$) and Benton temporal orientation ($p = .042$), but not with enhanced cued recall or clock drawing. The rate of cognitive decline was slow and did not differ with HSV-1 carriage. Anti-CMV IgG was not cross-sectionally associated with cognition, but anti-CMV IgG carriers declined more in performance on TMT-B than non-carriers over time. Anti-HSV IgM and anti-herpes virus treatment were not associated with cognition among HSV-1 carriers.
Conclusions: These findings indicate that HSV-1 is linked to poorer cognition also among cognitively healthy elderly, including memory, executive function, verbal fluency, and temporal orientation impairment. This finding provides further insight into possible prodromal AD pathological processes.

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P0514 / #2515

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

TESTING THE KNOWLEDGE OF ALZHEIMER'S DISEASE VIA AN INTERVENTION STUDY AMONG COMMUNITY HEALTH SERVICE CENTER STAFF IN JIAXING, CHINA

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Aims: This study aimed to investigate the knowledge status of Alzheimer's disease (AD) among community health service center (CHSC) staff in Jiaxing, China, and to compare the effects of online with offline training.
Methods: A total of 763 people from 12 community health service centers were investigated using a self-created general situation questionnaire and the Alzheimer's Disease Knowledge Scale (ADKS). Among the participants, 261 people who were willing to receive training were randomly divided into two groups according to the institution in which they worked to receive online or offline training, respectively.
Results: The average ADKS score was 19.77, and the awareness rate was 65.92%; the results for every field were as follows: treatment and management (81.32%); life impact (77.76%); disease course (75.23%); assessment and diagnosis (68.94%); risk factors (65.05%); symptoms (57.90%); caregiving (44.06%). Education and profession had impacts on the total ADKS scores ($P < 0.05$). A total of 261 people participated in the training, and there were significant differences in ADKS scores before and after training ($P < 0.05$). Before the training, there was no significant difference in ADKS score between the two groups; after the training, either ($P > 0.05$). There were significant differences in the ADKS scores after training in both groups ($P < 0.05$).
Conclusions: Community health service center staff in Jiaxing had limited knowledge of AD, particularly in the "symptom" and "caregiving" dimensions. One instance of training on AD-related knowledge to some degree helped to improve this but still fell short of meeting the national requirements. No significant differences were found between offline and online training effects.

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P0515 / #2606

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

SUMMARY OF BRAIN DONATION AND BRAIN BIO-REPOSITORY - EXPERIENCES OF SNUH BRAIN BANK

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Aims: Here, we introduce Seoul National University Hospital Brain Bank (SNUHBB) with our repositories, including human dural-fibroblast culture, neural progenitor cell culture, and frozen and FFPE brain tissues.
Methods: All autopsies were performed within 24 hours of death. After removing the whole brain, the left brain was immediately fixed in 10% formalin solution. After the right brain was slabbed to a 1cm thickness, some regions (Midbrain, Hippocampus, etc.) were collected for OCT-embedded block or formalin fixation. The remaining slabs were snap-frozen in LN2, and then sealed, and stored at -80℃. On day 7th, the formalin-fixed left brain was cut into 1cm slabs and continuously fixed in formalin. On day 21th, a comprehensive gross examination was performed. A portion of the fresh dura mater was used for fibroblast culture. Fresh subventricular zone was sampled for neural progenitor cell culture. Most neuropathological examinations of the brain follow previous guidelines of neurodegenerative diseases using immunohistochemical biomarkers.
Results: From 2015 to October 2022, there were 827 brain donation applicants before death (M:F=391:437) in SNUHBB. Those in their 60s were the most (n=243, 29.4%). From 2014 to October 2022, the number of brain samples donated by autopsy was 124. The median age of the brain donors was 71.5 years and the median postmortem interval of the autopsy was 9.5 hours. The most common neuropathological diagnosis including mixed pathologies was Lewy body disease (n=18, 15.3%), Vascular brain injury (n=17, 14.4%), and Alzheimer's disease neuropathologic change (n=12. 10.2%). Brain tissue has been distributed for over 20 domestic collaborative studies so far.
Conclusions: The Brain Bank is an essential institution for identifying the characteristics of brain diseases based on accurate neuropathological diagnosis and providing brain tissue to the research field.

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P0516 / #2648

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

INVESTIGATION OF APOLIPOPROTEIN E GENE AND LIPID PROFILE IN SYRIAN ALZHEIMER'S PATIENTS

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Aims: In Syria, there are no studies about apoE polymorphism and the levels of lipid profile in Alzheimer's patients. So that, there is an urgent need to more studies related to this field. The fact that the pathophysiological alterations associated with Alzheimer's disease begin several years before the appearance of clinical cognitive complaints. Thus, it's necessary to determine biomarkers that help in early AD diagnosis
Methods: We investigated in this study the distribution of ApoE ε4 genotype and the plasma levels of total cholesterol (TC) and LDL in two groups represent Syrian population; Alzheimer's patients (AD group, n=33) and in cognitively normal participants (CN group, n=11).
Results: The genotypes of ApoE observed in the study samples were only two types; Ɛ3/Ɛ3 and Ɛ3/Ɛ4. The distribution of ApoE Ɛ3/Ɛ4 genotype for AD patients was estimated 15.15% ($p > 0.05$, OR: 1.786), and this value was higher than value estimated for CN individuals, and the distribution of ApoE Ɛ3/Ɛ3 genotype for AD patients was 84.85%.Allele Ɛ4 frequency was higher in AD than in CN ($P > 0.05$, OR: 1.721). Furthermore, plasma levels of TC and LDL were significantly higher in AD patients than in cognitively normal participants (P=0.026- OR:1.029 and P=0.000099-OR:1.029, respectively).
Conclusions: This preliminary study on Syrian Alzheimer's patients showed that the percentage of Ɛ3/Ɛ4 genotype falls within the specified range by international studies carried out on Alzheimer's patients (3.8% - 64.7%), and demonstrated that the elevated TC and LDL blood levels may correlate with AD, and measuring lipid plasma levels could be an indicator as risk factor to AD.

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P0517 / #1372

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

LINKAGE OF A MEMORY CLINIC-BASED COHORT AND BIOBANK WITH REGISTER-BASED DATA FOR RESEARCH ON COGNITIVE DECLINE AND DEMENTIA

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Aims: To create a resource for longitudinal population-based research on cognitive decline and dementia by combining several data sources.
Methods: The GEDOC study has been based at the memory clinic at the Karolinska University Hospital in Stockholm, Sweden since 1992. The study enrolls patients at their initial clinical work-up for dementia and includes participants who at baseline are diagnosed with dementia due to Alzheimer's disease or other causes, mild cognitive decline, or subjective cognitive decline. Data on clinical assessments, cognitive tests, lab tests and neuroimaging reports from the memory clinic were retrieved from digital medical records and associated hospital systems that have been in use comprehensibly since the early 2000's. The data were processed for further linkage with longitudinal data in the Swedish Dementia Register, and the National Patient and Causes of Death Registers.
Results: Of about 13,000 participants in total, data for 10,373 individuals and 52,046 memory clinic visits between September 1998 and January 2022 were retrieved (median 3 visits/participant). Imaging reports were retrieved for 3,264 participants. Lab tests for up to 44 different biomarkers were retrieved for 5,590 individual participants and 11,612 sample occasions. Apolipoprotein E (ApoE) genotype was retrieved for 3,178 participants, whereof 36.6% were heterozygous and 10.2% were homozygous for ε4.
Conclusions: Although data from the hospital systems were retrieved in mostly unstructured text form and required considerable and challenging processing to enable linkage with national registers and eventual analyses, it is feasible to use the GEDOC study for population-based research on cognitive decline and dementia.

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P0518 / #933

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

PSEN1/SLC20A2 DOUBLE MUTATION CAUSES EARLY ONSET ALZHEIMER'S DISEASE AND PRIMARY FAMILIAL BRAIN CALCIFICATION CO-MORBIDITY

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Aims: Primary familial brain calcification (PFBC) and early onset Alzheimer's disease (EOAD) are often caused by Mendelian mutations. While PFBC is characterized by widespread symmetrical brain calcifications, less severe calcifications are also found in Alzheimer's disease. However, nothing is known about a potential interaction of pathogenic mechanisms causing the two diseases.
Methods: Whole exome sequencing, florbetabene-PET, fluordeoxyglucose-PET, CSF analysis, neurological examination and serial neuropsychological assessment was performed on a patient with suspected PFBC. cMRI and targeted genetic testing was performed on three children.
Results: We detected a loss-of-function mutation in *SLC20A2* in a patient with asymmetric tremor, early onset dementia and severe brain calcifications including the hippocampus. Neuropsychological testing demonstrated progressive deficits in temporomesial and frontotemporal circuits. Surprisingly, both CSF β-amyloid parameters and FBB-PET suggested cortical β-amyloid pathology. Genetic re-analysis of exome sequences revealed an additional missense mutation in *PSEN1*. Two children younger than 30 years carried the *SLC20A2* mutation and had mild calcifications.
Conclusions: Here we describe the first patient with both genetic PFBC and genetic EOAD. The clinical syndrome pointed to additive but not synergistic effects of the respective two mutations. The hippocampal calcifications may be the combined result of PSEN1-linked pathology and a predisposition for brain calcifications due to the *SLC20A2* mutation. We also provide MRI-based evidence for the formation of PFBC calcifications decades before onset of disease.

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P0519 / #114

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

CAUSAL ASSOCIATIONS BETWEEN PLASMA PROTEIN LEVELS AND ALZHEIMER DISEASE

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Aims: The aim of this study was to infer causal relationships between protein levels measured in blood and the risk of late-onset Alzheimer disease (AD).
Methods: Two-sample Mendelian randomization (MR) was used to infer the causal effect of protein levels on AD risk. Summary statistics from genome-wide association studies (GWAS) for 4,907 SomaScan aptamers (measuring 4,719 proteins) from Ferkingstad et al. (2021) in 35,559 Icelanders (average age = 55±17years), and for AD GWAS from Bellenguez et al. (2022). Instruments for exposures were selected at $p < 5x10^{-8}$ and $p < 5x10^{-6}$ thresholds respectively for the main and sensitivity analyses. Instruments were pruned for linkage disequilibrium ($r^2 < 0.0001$) to ensure selection of independent instruments. Because *APOE* is highly pleiotropic and exposure effect size is hypothesized by MR not to be larger than the outcome (Steiger filtering), thus variants within ±1MB from *APOE* were removed in the MR-analysis. Two tests were considered: Inverse-Variance-Weighted and Weighted-Median, which allows robust MR estimates even when some invalid instruments are included.
Results: Among known AD-GWAS genes, TREM2, PILRA, ACE, CR1, and BIN1 protein levels were associated with AD. Proteins without prior AD-GWAS links were also found to be associated with AD including: PPBP, NRP2, AZGP2, and TNFSF13B/BAFF (**Figures 1&2**). Interestingly, APOE and KLOTHO levels were not associated with AD (**Figures 3&4**), though increased APOE level significantly associated with increase AD risk when including cis-*APOE* variants at $p < 5x10^{-6}$ (**Figure 5**).

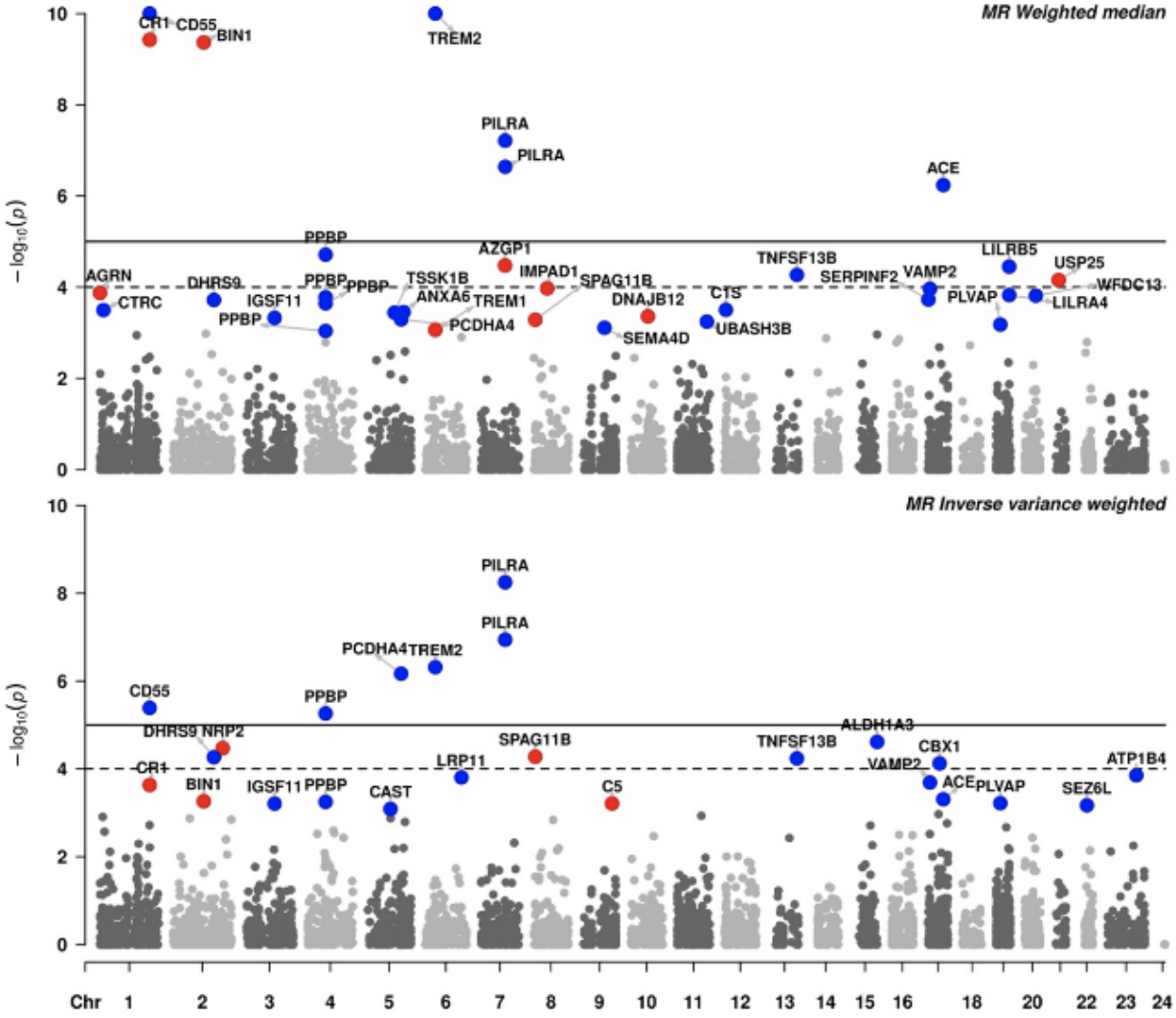

Figure 1. Manhattan plots per aptamer/gene showing the significance of two MR tests: Weighted Median (top), Inverse Variance Weighted (bottom) with independent genetic instruments selected in the exposure GWAS at $p < 5x10^{-8}$. Solid line represents the Bonferroni corrected significance threshold $p < 10^{-5}$ accounting for the number of tested aptamers, dotted line corresponds to $p < 10^{-4}$, and all annotated proteins passed the suggestive threshold $p < 10^{-3}$. Proteins colored in red have increased level associated with increased AD risk, while proteins in blue have increased level associated with decreased AD risk.

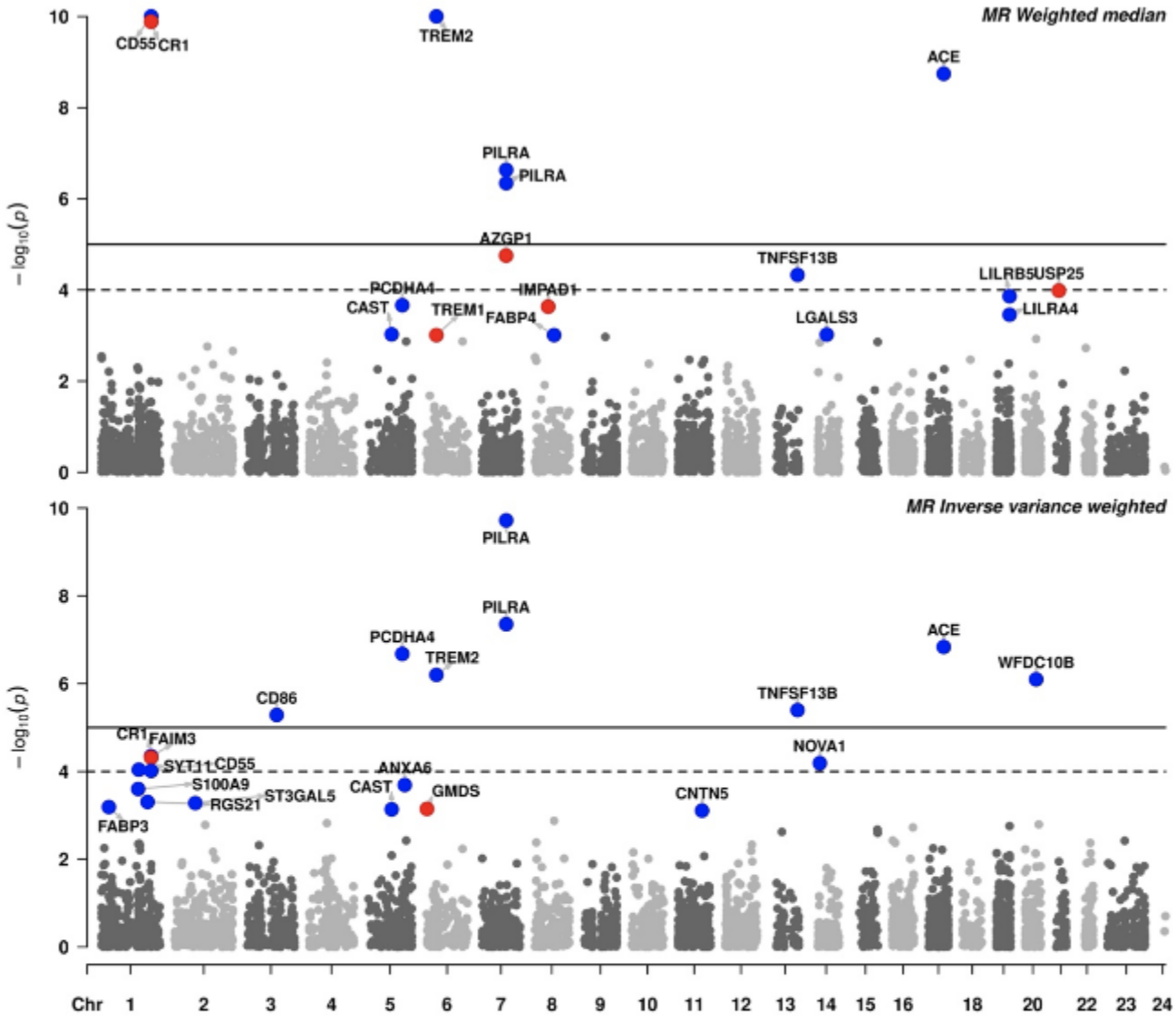

Figure 2. Manhattan plots per aptamer/gene showing the significance of two MR tests: Weighted Median (top), Inverse Variance Weighted (bottom) with independent genetic instruments selected in the exposure GWAS at $p < 5x10^{-6}$. Solid line represents the Bonferroni corrected significance threshold $p < 10^{-5}$ accounting for the number of tested aptamers, dotted line corresponds to $p < 10^{-4}$, and all annotated proteins passed the suggestive threshold $p < 10^{-3}$. Proteins colored in red have increased level associated with increased AD risk, while proteins in blue have increased level associated with decreased AD risk.

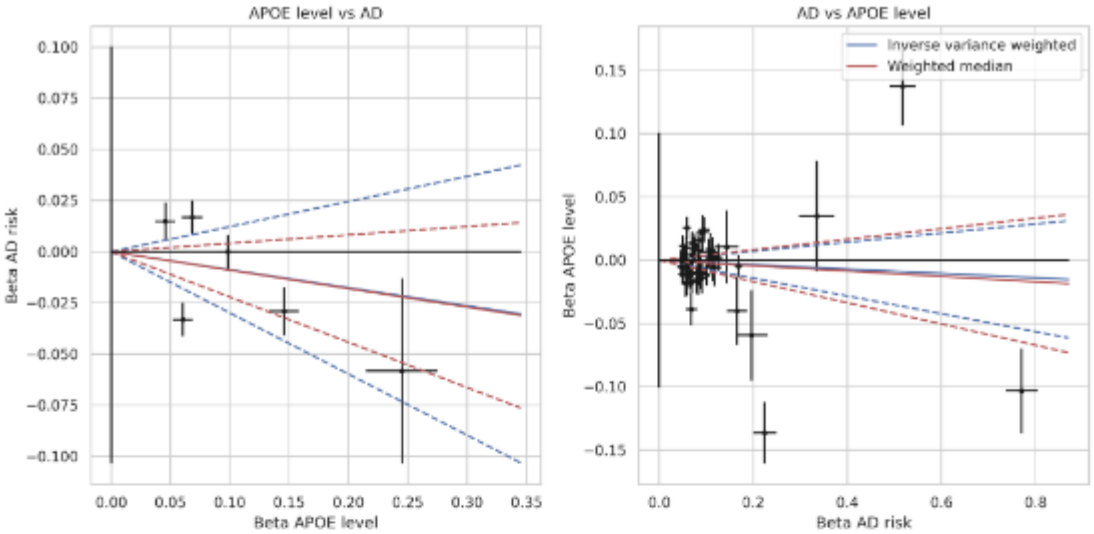

Figure 3. Bidirectional Mendelian Randomization for APOE level and AD with independent genetic instruments selected in the exposure GWAS at $p < 5x10^{-8}$. Left panel shows the forward MR association with APOE level as exposure and AD risk as outcome; right panel shows the reversed MR association with AD risk as exposure and APOE level as outcome.

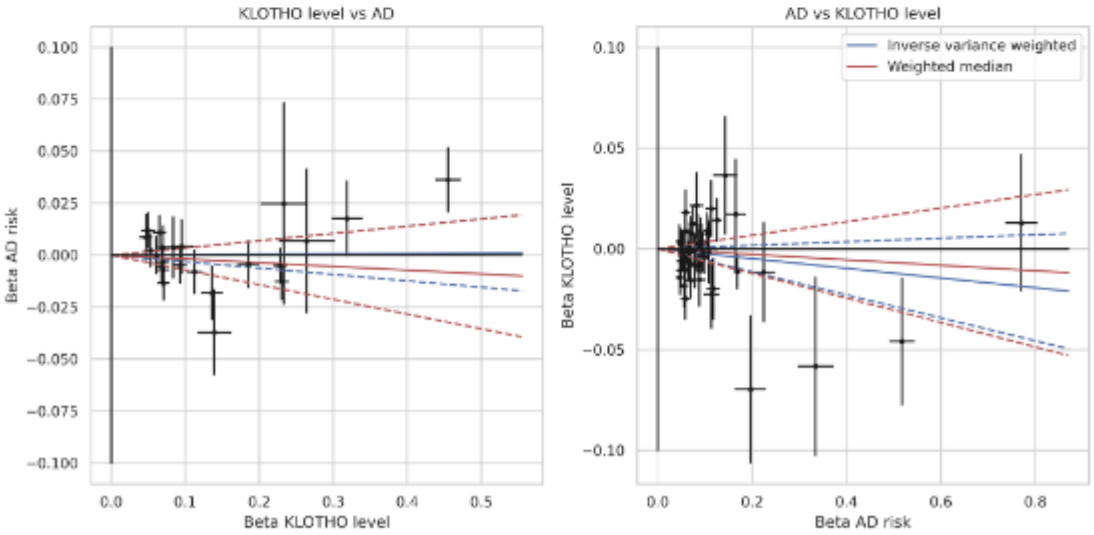

Figure 4. Bidirectional Mendelian Randomization for KLOTHO level and AD with independent genetic instruments selected in the exposure GWAS at $p < 5x10^{-8}$. Left panel shows the forward MR association with KLOTHO level as exposure and AD risk as outcome; right panel shows the reversed MR association with AD risk as exposure and KLOTHO level as outcome.

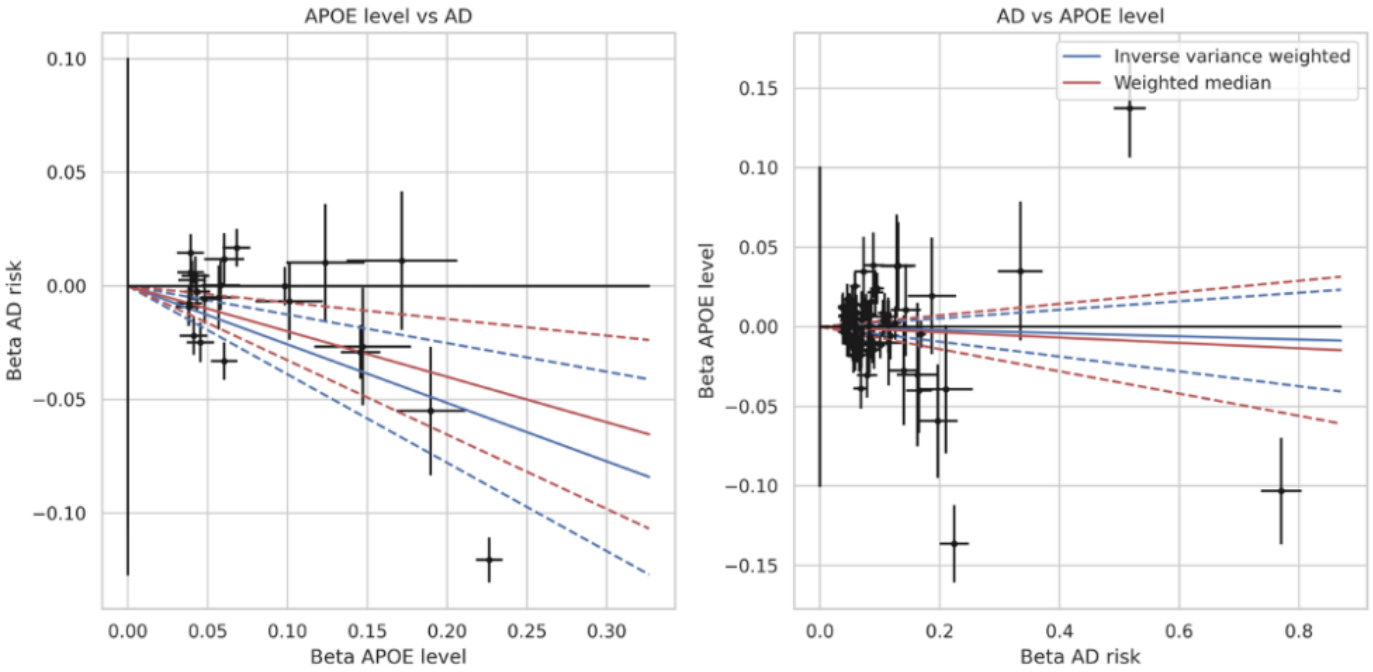

Figure 5. Bidirectional Mendelian Randomization for APOE level and AD with independent genetic instruments selected in the exposure GWAS at $p < 5x10^{-6}$. Left panel shows the forward MR association with APOE level as exposure and AD risk as outcome; right panel shows the reversed MR association with AD risk as exposure and APOE level as outcome.

Conclusions: Our study informs the directionality of association between certain plasma protein levels and AD risk, and prioritizes candidate proteins to be considered for AD drug development.

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P0520 / #2448

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

LATE-ONSET MYOCLONIC EPILEPSY AND ITS IMPACT ON DOWN SYNDROME WITH ALZHEIMER DISEASE

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Aims: Late onset myoclonic epilepsy (LOMEDS) seems to be an important comorbidity in elderly patients with Down syndrome (DS) who exhibit Alzheimer disease (AD). In fact, seizures may interact with AD evolution with possible acceleration of cognitive decline. However, few studies have examined the characteristics and treatment of this entity. Our aim is to better define LOMEDS in DS with AD.
Methods: We present 8 patients 4 men/ 4 women) with DS plus AD who developed myoclonic seizures or generalized tonic-clonic seizures. In-all cases, clinical, neuroimaging and electroencephalographic (EEG) studies were performed
Results: The mean age of SD patients when first seizure occurred was 54.9±5.2 years (age at onset of AD 53.4±3 1 years, mean duration of AD 1.6±3.4 years). In seven cases, AD progressed quickly after the onset of epilepsy -seizures appeared with mean duration of AD 3 years-; in the other one, seizures preceded AD 10 years. Six cases showed slowing of brain activity with theta and delta rhythms in EEG, whereas inter-critical generalized poly spike waves were observed in five patients. In all cases, cerebral cortical atrophy was found in neuroimaging studies. Five patients responded well to levetiracetam, in two cases lamotrigine and valproate were effective and in other two a combination of levetiracetam with valproate and clonazepam, respectively, was required. Five patients died (median age 57.8±3 3 years, mean duration of seizures 2.5±0 5 years).
Conclusions: The increase of life expectancy in DS has led to a better knowledge about late onset complications related to DS, such as AD and LOMEDS. This study supports LOMEDS is associated with a poor prognosis due to the worsening of cognitive impairment albeit good antiepileptic response in SD plus AD.

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P0521 / #756

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

MACHINE LEARNING TO IDENTIFY VARIABLES TO PREDICT MORTALITY RISK AFTER DEMENTIA DIAGNOSIS: A LONGITUDINAL COHORT STUDY

Shayan Mostafaei[1], Minh Tuan Hoang[1], Pol Jurado[1], Hong Xu[1], Lluis Zacarias-Pons[2], Maria Eriksdotter[1], Saikat Chatterjee[3], Sara Garcia-Ptacek[1]
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Aims: Using ML algorithms, our objective was to identify the most important variables for mortality after dementia diagnosis in the Swedish Registry for Cognitive/Dementia Disorders (SveDem).
Methods: From SveDem, 28,023 dementia-diagnosed patients are included for our study. Sixty variables were considered as potential predictors of mortality risk, such as, demographics, mini-mental state examination (MMSE) score, time from referral to initiation of work-up, time from initiation of work-up to diagnosis, dementia medications, comorbidities, and some specific medications for chronic comorbidities (e.g., cardiovascular disease). We apply sparsity-inducing penalties for three ML algorithms and identify the important variables to predict mortality risk. Area-under-ROC curve (AUC) measure is used to evaluate predictive power of the algorithms.
Results: A support-vector-machine with an appropriate sparsity penalty provides accuracy=0.7077, AUC=0.7375, sensitivity=0.6436, and specificity=0.740. Across three ML algorithms, a majority of the identified twenty variables agreed with literature and with our previous studies in SveDem. We also found new variables which were not previously reported in literature in association with mortality in dementia. Performance of basic dementia diagnostic work-up, time from referral to initiation of work-up, and time from initiation of work-up to diagnosis are elements of the diagnostic process which were identified by the ML algorithms and warrant future attention. For prediction of time to death, the CoxBoost model identified fifteen variables: highly important variables were age at diagnosis, MMSE score, sex, BMI and Charlson Comorbidity Index (CCI) with selection scores as 23%, 15%, 14%, 12% and 10%, respectively.
Conclusions: Sparsity-inducing ML algorithms in association with clinical characteristics and demographic data can provide good predictions of death risk and time to death. Therefore, ML methods could be used as a complement to traditional statistical methods.

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P0522 / #1553

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

OLIGODENDROCYTE ENRICHED HUMAN SPHEROIDS FOR GENOMIC REGULATORY ARCHITECHTURE STUDIES IN ALZHEIMER'S DISEASE

Aura Ramirez[1], Jihanne Shepperd[1], Maria Muniz[1], Liyong Wang[1], Wanying Xu[2], Fulai Jin[2], Anthony Griswold[1], Juan Young[1], Derek Dykxhoorn[1], Jeffery Vance[3]
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Aims: Despite their prominence, oligodendrocytes have been less studied in AD research than other cell types. Further, as we increase diversity in AD research, characterization of ancestry-related chromatin and genomic regulatory architecture is needed. Here we utilize induced pluripotent stem cells (hiPSC) to evaluate the regulatory architecture from AD patients and unaffected controls with Amerinidian (AI) and African (AF) ancestry.
Methods: hiPSC lines derived from AD patients or non-cognitively impaired controls with >96% of either AI, AF or EU global ancestry were differentiated using a multi-stage protocol that promotes the development of oligodendrocytes in neural spheroids. After inducing terminal differentiation and enrichment of oligodendrocyte populations in the last stage of the protocol, cells were collected and lysed to isolate nuclei for multiomic profiling of the transcriptome and epigenome using single nuclei ATAC and RNA-seq. Additionally, we harvested these neural spheroids to study enhancer-promoter interactions using Hi-C analyses.
Results: We identified oligodendrocyte lineage cells at different stages of development ranging from dividing cells with transcriptional profiles consistent with those of oligodendrocyte precursor cells (OPC) to mature myelinating oligodendrocytes. We compared the oligodendrocyte subclusters across ancestries and cases versus controls to characterize the genomic landmarks and signatures associated with AD related GWAS hits. Astrocytes and neurons were also derived within our 3D spheroids allowing us to study ancestry-related cell type specific changes in regulatory architechture.
Conclusions: Our results provide a closer look into oligodendrocyte chromatin structure and gene regulation in the context of AD in an ancestry-specific manner. These results offer new insights into the genomic regulatory architecture of a previously overlooked cell lineage that constitutes a major population in the central nervous system and is compromised during AD in terms of abundance and function.

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P0523 / #604

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

ESTIMATING TRANSITION PROBABILITIES ACROSS THE ALZHEIMER'S DISEASE CONTINUUM USING A NATIONALLY REPRESENTATIVE REAL-WORLD DATABASE IN THE UNITED STATES

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Aims: This study aimed at estimating the probabilities of clinical transitions between disease states and impact of selected covariates.
Methods: We developed a mixed-effects, five-state Markov model using a Bayesian approach to estimate the transition probabilities across the AD severity stages, adjusted for five baseline covariates, among patients from the Health and Retirement Study (HRS). HRS surveys a nationally representative random sample bi-annually. MCI and AD severity states were defined using the modified telephone interview on cognitive status (TICS-m).
Results: A total of 11,292 AD patients was analyzed. Within 1 year from the initial state, the probability of transition from initial to next AD state was greater in earlier disease: 14% from MCI to mild AD and ~5% from mild to moderate AD, but <1% from moderate to severe AD. After 10 years, the probability of transition to the next state was markedly higher for all states, but still greater in earlier disease: 29% from MCI to mild AD, 23% from mild to moderate AD, and 6% from moderate to severe AD. Males, older patients, those with lower years of education, without employment or staying in a nursing home were identified as patients suffering a higher risk of deterioration ($p < 0.01$ for all covariates).
Conclusions: This analysis shows that the risk of severity progression is greater in earlier AD states, increases over time, and is higher in patients who are male, older, with fewer years of education, unemployed or in a nursing home at baseline.

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P0524 / #609

POSTERS: A05.I. GENETICS, EPIDEMIOLOGY: OTHER

ASSESSING OUT-OF-POCKET EXPENSES AND INDIRECT COSTS OVER THE ALZHEIMER'S DISEASE CONTINUUM IN THE UNITED STATES

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Aims: To describe out of pocket (OOP) and indirect healthcare spending among patients with Alzheimer's disease (AD) by severity stages in a representative sample of the US population.
Methods: Data from the Health and Retirement Study (HRS) were analyzed over the period of 1994-2018. Mild cognitive impairment (MCI) and AD severity stages were ascertained using the modified telephone interview of cognitive status (TICS-m). OOP for hospital, nursing home, outpatient surgery, and other health services were assessed. Indirect costs included unpaid caregiving services and employer-based missed workdays and early retirement. Sensitivity analyses were performed by varying assumptions of caregiver employment, missed workdays, and early retirement.
Results: MCI and AD patients were 67.8±10.7 and 80.9±9.3 years old, 55.7% and 63.3% female, and 28.3% and 0.9% employed, respectively. MCI and AD prevalence was 42.99% and 3.23%, respectively. OOP increased with AD severity, ranging from $450 in mild to $866 in severe AD per patient per month (PPPM) and was higher in MCI ($553) than mild AD. Indirect costs (PPPM) to employers were similar across MCI and AD severities ($181-$226). Costs from unpaid caregiving increased by disease severity, from $86 in MCI to $1190 in severe AD. Total OOP and indirect costs increased by disease severity, from $864 in MCI to $2237 in severe AD. Sensitivity analysis assuming non-working caregivers and zero costs to employers decreased the OOP and indirect costs by 23-34%. OOP were higher in privately insured patients ($p<0.01$), or with higher income ($p<0.01$).
Conclusions: This study shows that OOP and indirect costs increase with AD severity, and OOP increase with higher income in the US.

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P0525 / #2710

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

DISECTING THE ROLE OF APP AS A SOLUBLE LIGAND AND/OR AS SYNAPTIC ADHESION MOLECULE

Marija Banicevic[1], Zvi Menahem[1], Laura Keppler[1], Ritu Rajender[2], Stefan Kins[2], Christian Buchholz[3], Ulrike Müller[1]
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Aims: In addition to its fundamental role in the pathogenesis of Alzheimer's disease, the amyloid precursor protein (APP) has essential physiological functions at the synapse. Both transmembrane APP signalling and secreted APP ectodomain fragments are required for normal PNS and CNS function. APP-mediated synaptic adhesion is important during synaptogenesis. However, proteolytic cleavage of cell surface APP leads to APPsalpha secretion, which has been shown to support both structural and functional synaptic plasticity. Our goal is to understand the interdependence and regulation of these processes at the synapse.
Methods: To this end, we generated APP variants that are either deficient in synaptic adhesion or secretion of the large APP ectodomain. APPdeltaE1 lacks the major domain responsible for trans-dimerization and synaptic adhesion. APPd8 harbours a deletion encompassing the alpha-secretase cleavage site. The deleted region was replaced by a stretch of 8 aspartate residues (D8) to increase electrostatic repulsion of ADAM10. In APPdeltaS622 both the alpha- and beta-secretase sites were deleted.
Results: AAV9 based expression vectors encoding these APP variants were produced and used for the transduction of primary cortical neurons of APP-knockout mice. Western blot analysis of neurons expressing either APPd8 or APPdeltaS622 indicated that secretion of APPs was almost completely abolished in neuronal cultures. To analyze these secretion-deficient APP variants in vivo, AVVs will be stereotactically injected into the hippocampus of APP/APLP2 deficient mice (NexCre cDKOs). In addition, we intend to study whether APP variants may rescue functional impairments of these mice including reduced spine density and synaptic plasticity.
Conclusions: These APP variants are important tools to unravel the role of APP as a soluble ligand and/or as synaptic adhesion molecule in vivo.

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P0526 / #2504

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

APP AND ITS ADAPTORS FE65/L1 REGULATE ACTIN CYTOSKELETON DYNAMICS IN GROWTH CONES AND DENDRITIC SPINES

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Technical University of Kaiserslautern, Human Biology And Human Genetics, Kaiserslautern, Germany

Aims: Important insights into the physiological functions of the APP family have been gained by analyzing mouse mutants. APP/APLPs KO mice exhibit defects in neuronal migration, dendritic branching, and synaptic plasticity. Interestingly, many of those phenotypes are also found in Fe65/L1 KO mice, suggesting a common functional pathway. We hypothesize that these different impairments are caused by alterations of actin dynamics.
Methods: We used a variety of different methods, including dye-fillings and morphological analysis of hippocampal neurons, cell fractionation, live cell imaging of actin cytoskeleton, and FRAP analysis. Furthermore, we performed rescue experiments with APP/Fe65 deletion constructs and knockdowns of putative actin regulators interacting with Fe65.
Results: Our data show that both Fe65 and APP KO mice exhibit reduced neuronal outgrowth and a decrease of mature spines. Furthermore, loss of function of Fe65 and APP causes a stabilization of actin fibers, resulting in reduced growth cone and dendritic spine dynamics. Moreover, rescue experiments with different Fe65 and APP mutants clearly demonstrate that the interaction of APP and Fe65 is required for control of actin dynamics. Consistent with this, cell fractionation and immunocytochemical studies showed that APP is required to recruit Fe65 to the plasma membrane. Finally, using reverse and forward genetic approaches we elucidated how APP and Fe65 regulate actin cytoskeleton dynamics.
Conclusions: Our studies suggest that APP/APLPs recruit members of the Fe65/L1 family and modulators of actin dynamics to certain sites in the plasma membrane that are required for destruction of existing and de novo formation of actin filaments. This likely explains the diverse phenotypes observed in APP and Fe65 KO animal models, including changes in neuronal growth and structural synaptic plasticity.

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P0527 / #446

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

LACK OF APLP1 LEADS TO SUBTLE ALTERATIONS IN NEURONAL MORPHOLOGY BUT DOES NOT AFFECT LEARNING AND MEMORY

Susanne Erdinger[1], Irmgard Amrein[2], Michaela Back[3], Jakob Von Engelhardt[3], David Wolfer[2], Ulrike Müller[1]
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Aims: For the etiology of Alzheimer's disease, the amyloid precursor protein APP is a key player. Its physiological functions, however, are still being uncovered. APP is a member of a small gene family that also includes the synaptic adhesion proteins APLP1 and APLP2, which are closely related to APP. While APP and APLP2 are widely expressed, APLP1 expression is only detected in the nervous system. Previous genetic studies, including combined knockouts of several family members, pointed towards a unique role for APLP1, as only APP/APLP1 double knockouts proved viable.
Methods: Here, we studied brain and neuronal morphology of APLP1 single knockout (KO) animals, which had not yet been examined in detail. Moreover, we analyzed neuromotor behavior and studied the performance of APLP1 mice in various paradigms of learning and memory.
Results: At the macroscopic level, APLP1-KO mice show normal brain anatomy and no difference in hippocampal volume. Sholl analysis of hippocampal CA1 pyramidal cells indicated subtle alterations in dendritic complexity, but normal spine density. The behavioral studies revealed in APLP1-KO mice a small deficit in motor function and slight impairments in diurnal locomotor activity, while learning and memory were not affected by the loss of APLP1.
Conclusions: In conclusion, our findings indicate that members of the APP family serve both unique and overlapping functions that should be taken into account for therapeutic treatments of Alzheimer's disease.

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P0528 / #297

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

CONFORMATIONAL MODELS OF APP PROCESSING BY GAMMA SECRETASE BASED ON ANALYSIS OF PATHOGENIC MUTATIONS

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Aims: Proteolytic processing of amyloid precursor protein (APP) plays a critical role in pathogenesis of Azheimer's disease (AD). Sequential cleavage of APP by β and γ secretases leads to generation of Aβ40 (non-amyloidogenic) and Aβ42 (amyloidogenic) peptides. Multiple familial AD (FAD) mutations in APP, PS1, or PS2 result in increased Aβ42:Aβ40 ratio in patient brains. In this study we performed molecular modeling of APP complex with γ-secretase and analyzed potential effects of FAD mutations in APP and PS1.
Methods: We noticed that all FAD mutations in APP transmembrane domain are predicted to cause an increase in the local disorder of its secondary structure. Based on structural analysis of known γ-secretase structures we proposed that APP can form a complex with γ-secretase in 2 potential conformations – M1 and M2. In conformation M1 transmembrane domain of APP forms a contact with perimembrane domain that follows the transmembrane domain 6 (TM6) in PS1 structure. In conformation M2 transmembrane domain of APP forms a contact with transmembrane domain 7 (TM7) in PS1 structure.
Results: We discovered that the mutations increase conformational flexibility of M2 and reduce the flexibility of M1. Based on the results we proposed that M2 conformation, but not M1 conformation, of γ secretase complex with APP leads to amyloidogenic Aβ42 processing of APP. Our model predicts that APP processing in M1 conformation is favored by a curved membranes, such as membranes of early endosomes. In contrast, APP processing in M2 conformation is likely to be favored by a relatively flat memranes such as membranes of late endosomes and plasma membrane.
Conclusions: Our results suggest that specific inhibitors of Aβ42 production could be potentially developed by selectively targeting M2 and not M1 conformation of γ secretase complex with APP.

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P0529 / #1765

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

ABSENCE OF RHBDL4 AFFECTS APP PHYSIOLOGY & RESCUES COGNITION IN AMYLOIDOSIS MOUSE MODEL.

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Aims: Autosomal dominant inherited mutations causatively link the amyloid precursor protein (APP) to Alzheimer's disease (AD) and one of its proteolytic cleavage products, Aβ peptides, is a hallmark of AD. Unveiling APP's functions and defining the triggers leading to Aβ production are crucial to determining the cellular conditions underlying AD. We have discovered a novel processing pathway of APP mediated by the ER resident rhomboid-like-protease 4 (RHBDL4). We have shown in HEK293T cells that RHBDL4 cleavage results in decreased total APP and Aβ. We aim to determine the physiological relevance of this pathway in a mouse model of AD.
Methods: We crossed mice expressing human APP only in neurons (hAPP J20) to RHBDL4 global knockout (KO) mice. We determined the effects of RHBDL4's absence on APP expression and amyloidogenic processing using western blot and ELISA. We assessed cognition using the Y maze and the Novel Object Recognition (NOR) test.
Results: In RHBDL4 KO x J20 mice, we found that total APP, β-CTFs and Aβ levels from brain samples were significantly increased. In contrast to our expectations, absence of RHBDL4 rescued cognition in 5 months old female double transgenic mice, implying that elevated APP and Aβ levels alone do not affect cognition at that age. Instead, we propose that RHDBL4 rescues cognition through the Wnt/β-catenin pathway whose decreased signaling has been published to underlie cognitive defects in the hAPP J20 model. Specifically, we have shown *in vitro* that RHBDL4 absence increases β-catenin protein expression, possibly hinting at a greater activation of the pathway in rescued mice.
Conclusions: Our results mirrored our *in vitro* findings and confirmed RHBDL4's relevance for APP physiology *in vivo* as well as AD pathology.

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P0530 / #900

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

IS GENETIC ROBUSTNESS INVOLVED IN ALZHEIMER'S DISEASE?

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Aims: In this study we show that genetic mutations, which introduce premature stop codons (PTC) in the amyloid precursor protein (*app)* genes, activate TA of other *app* family members in zebrafish and human neural progenitor cells (NPC).
Methods: CRISPR/Cas9 method has been used to knockout promoter region of *appb* in zebrafish to prevent expression of this gene and investigate the expression level of other App family memebers.
Results: Here we show that the TA of *appa* and *aplp2* requires degradation of mutant mRNA and does not depend on Appb protein level or translation. Using knockdown and chemical inhibition, we show that nonsense-mediated mRNA decay (NMD), involving Upf1 and combined Upf3a/Upf3b, mediates degradation of *app* family members when PTC is present as well as the normal transcripts. In addition, our data indicate that the genetic compensation is highest during early neuronal differentiation since no TA was observed in a more differentiated human neuroblastoma SH-SH5Y cell line or adult zebrafish brain
Conclusions: In conclusion, our results support that, mutations in the *app*-genes, which results the degradation of PTC-bearing mRNA, induce genetic compensation by other *app* family members through TA in zebrafish and human neuronal progenitors.

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POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

REVEALING HIDDEN SENSORIMOTOR MEMORIES IN MICE WITH AD-RELEVANT PATHOLOGY

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Aims: Alzheimer's disease is a progressive form of dementia where cognitive capacities deteriorate due to neurodegeneration. Interestingly, Alzheimer's patients exhibit cognitive fluctuations during all stages of the disease. Though it is thought that contextual factors are critical for unlocking these hidden memories, understanding the neural basis of cognitive fluctuations has been hampered due to the lack of behavioral approaches to dissociate memories from contextual-performance. Our previous work demonstrated that interleaving reinforced with non-reinforced ('probe') trials in an auditory go/no-go discrimination task, allows us to distinguish between acquired sensorimotor memories and their contextual expression.
Methods: Here, we used this approach, together with two-photon calcium imaging on behaving APP/PS1+ mice, to determine whether amyloid accumulation impacts underlying sensorimotor memories and/or contextual performance in an age dependent manner.
Results: Importantly, peripheral auditory function, measured using auditory brainstem responses, was similar between WT and APP/PS1+ mice. We found that while contextual-performance is significantly impaired in 6-8mo APP/PS1+ mice compared to age-matched controls, these animals show only minor impairments in underlying sensorimotor memories. However, 12mo APP/PS1+ mice show deficits in both domains. The impairment found in the young adults was accompanied by a reduction in stimulus selectivity and behavioral encoding in the auditory cortex of APP/PS1+ mice that was partially restored in probe trials. Ongoing analyses aim to identify whether this impairment is cortex-wide or is concentrated near Aβ plaques. These effects were recapitulated with a reinforcement learning model that accounts for contextual signal changes. Model parameters affected were those governing contextual scaling and behavioral inhibition.
Conclusions: These results suggest that Aβ deposition impacts circuits involved in contextual computations before those involved in acquiring knowledge and that neural circuit interventions (modulating inhibition) may hold promise to reveal hidden memories.

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P0532 / #2496

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

ANALYSIS AND IDENTIFICATION OF INTRA AND EXTRACELLULAR ENDOCYTOSIS MOTIFS OF APP

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Aims: The intracellular sorting, targeting and internalization of type-I transmembrane proteins, like APP is normally mediated via short amino acid sequences in the cytoplasmic domain. For APP it has been further shown that the localisation in individual compartments of the secretory pathway leads to a different processing of APP and thereby directly influences the generation of Amyloid beta (Aβ). As BACE 1 is mostly active in endosomes, the endocytosis of APP is an important step in the reduction of Aβ release. In previous studies we could show that APP endocytosis is regulated by different motifs, including the classical NPTY endocytosis motif and the basolateral sorting signal (BaSS). However, extracellular endocytosis signals have not been described yet.
Methods: Antibody uptake assays with neuronal cells to analyze the internalization rate of WT and mutant APP lacking different putative internalization signals. The amount of endocytosed protein was determined by measuring the intensity of surface protein compared to internalized protein.
Results: To understand the underlying signaling of the APP endocytosis we generated different mutants and examined their endocytosis rate. We show that APP contains, besides its cytosolic localized signals, also an external endocytosis signal which is require for efficient APP internalization. Moreover, we show that this extracellular motif is not only required for endocytosis, but is also sufficient to increase endocytosis rate of APP homologs, such as APLP1.
Conclusions: Our data will help to understand the molecular mechanisms underlying APP endocytosis. Furthermore, the extracellular endocytosis motif could be a target for antibodies or small molecules to lower APP endocytosis and in turn Aβ production.

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P0533 / #1607

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

APOE EFFECTS ON ABETA PATHOLOGY AND MICROGLIOSIS IN 5XFAD MOUSE MODEL

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Aims: Brains of AD patients are characterized by the deposition of amyloid plaques (A), neurofibrillary tau tangles (T), and neurodegeneration (N) referred to as ATN pathology. These events are invariably associated with neuroinflammation, and increasing evidence indicates a crucial role of microglia at different stages of the disease process. APOE is the major genetic risk factor of AD, with effects of APOE on AD onset and progression. However, the specific APOE contribution in progression along the ATN axis, particularly the role of APOE in amyloid induced tau pathology and downstream neuro-degeneration, remains to be understood in detail. Here, we investigate in first instance the effect of APOE deficiency on Aß pathology and microglial response.
Methods: We crossed 5xFAD with APOE+/+ and APOE-/- mice and analysed at 3 and 6 months of age. IHC and biochemical analyses were performed.
Results: APOE strongly modulates Aβ pathology affecting total Aβ load, plaque morphology and maturation of the plaques. APOE deficient mice display larger and more diffuse plaques, while dense cored plaques are decreased, indicated by ThioS staining. In addition, APOE deletion reduces overall microgliosis decreasing phagocytic microglial response along with less plaque-associated microglia.
Conclusions: We here show a crucial role of ApoE in modulating amyloid pathology, in line with previously published data. We use this model to study the underlying mechanisms of this effect in depth. Furthermore, this model provides the basis for further analysis of APOE dependent effects downstream of Aß on Tau pathology and Tau driven neurodegeneration, by further crossing this model with Tau transgenic mice. Our models are anticipated to contribute to the analysis of the role of APOE along the ATN axis.

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P0534 / #1536

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

APOLIPOPROTEIN E GLYCOFORMS IMBALANCE IN THE BRAIN OF ALZHEIMER'S DISEASE PATIENTS

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Aims: The majority of Alzheimer's disease (AD) cases are sporadic, although different genetic factors, such as the *APOE* genotype, have been associated to the illness. The ε4 allele of *APOE* significantly increases the likelihood of developing AD, reducing the age of onset. Despite a large amount of studies taking the *APOE* genotype into account, few studies have addressed the basic characterization of the apoE protein in AD, such as imbalances of different apoE species in the brain.
Methods: apoE protein levels from brain samples of control and late stage AD patients (Braak stages V-VI) with varying *APOE* genotype (ε3/3, ε3/4, ε4/4) from 2 independent collections were studied by electrophoresis/SDS-PAGE to allow the identification of single apoE species.
Results: ApoE is present in the brain as a ~36 kDa species, but also a 34 kDa species, probably representing immature glycoforms. In both collections, we observed a significant decrease in the presence of the mature 36k Da glycoforms, which completely disappeared in one collection, leading to an imbalance in the 36/34 apoE glycoform ratio. This imbalance appears to be mainly associated to the disease condition and not to the *APOE* genotype.
Conclusions: The balance of apoE glycoforms is altered in the brain of AD patients, due to a significant depletion of the mature glycoforms, which may be the functional apoE species. This altered glycosylation pattern could affect the physio-pathological role played by apoE in the Alzheimer's Disease brain. Further studies are required to determine the exact role of each of these different apoE isoforms in order to further undertsand how this imbalance may be contributing to the disease.

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P0535 / #1588

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

INTRAGENIC ELEMENTS WITHIN TOMM40 MODULATE APOE EXPRESSION IN HUMAN MICROGLIA

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Aims: We have previously shown that *APOE4* gene expression is significantly increased in brains with European local ancestry (LA) versus African local ancestry (LA) haplotypes. Using Massively Parallel Reporter Assays (MPRA), we subsequently identified in microglia and astrocytes enhancer regions lying in this LA associated with this expression difference. Here, we sought to functionally validate these enhancers in culture and further narrow the key enhancer regions, as a next step towards therapeutic intervention in *APOE4*.
Methods: Human Microglial Clone 3 (HMC3) CRISPRi/a lines were transduced using inducible dCas9-VP64 (Activator), dCas9-KRAB (Interferer) or dCas9 (control) using lentiviral vectors. We generated vectors encoding four single-guide RNAs (sgRNAs) targeting two enhancer regions (namely, B10 or B13). Additionally, we constructed alternative vectors including only 3 out of the 4 sgRNAs targeted at the B10 locus, and a non-targeting vector control bearing polyT tracts to truncate the expression of the scaffold RNAs. Each of these vectors were transduced into the HMC3 CRISPRi/a lines. Expression of the dCas9 constructs was induced using Doxycycline. RNA was extracted and the expression of *APOE* and *TOMM40* was measured by qRT-PCR.
Results: *APOE* expression significantly increased when targeting B10 or B13 with the activating dCas9-VP64. No significant changes in *APOE* expression were observed when inducing dCas9-KRAB in the HMC3 cell line. The increased expression of *APOE* was diminished when the first ~200bp of B10 were left untargeted in the dCas9-VP64 line, suggesting this area is key to modulate *APOE* expression.
Conclusions: These initial results support our previous findings that regions B10 and B13 house regulatory elements that modulate *APOE* expression and show the potential location of a ~200bp cis-active element within B10 that could be driving the modulatory effects of European LA on APOE.

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P0536 / #1915

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

IMPACT OF VASCULAR APOE EXPRESSION IN CEREBROVASCULAR FUNCTION AND AMYLOID PATHOGENESIS

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Aims: *APOE4* is the strongest genetic risk factor for Alzheimer's disease (AD), whereas *APOE2* is protective compared to the common and reference *APOE3* allele. ApoE is a lipid transporter, and each apoE isoform exhibits different biochemical properties which impact amyloid β (Aβ) metabolism, immune system and cerebrovasculature, altering isoform-specific risks towards AD. Cerebrovascular dysfunction has recently gained greater recognition as an important risk factor of cognitive impairment and AD. Vascular dysfunction disrupts homeostasis and impairs efficient removal of pathogenic components, such as Aβ. Aβ accumulation in cerebrovasculature, cerebral amyloid angiopathy (CAA), frequently co-occurs with (>80%) AD. Aβ drainage along vasculature is mediated by vascular mural cells (VMCs). Clarification on how VMC-derived apoEmodifies brain/vascular functions in the presence and absence of Aβ are essential for discriminating its protective effects against AD.
Methods: We have developed a novel conditional mouse model that specifically expresses human *APOE2*/*3/4.* Upon breeding to sm22α-Cre mice in the background of *Apoe* knockout mice, we induce VMC-apoE expression to investigate the impacts on cognition, cerebrovascular function, and blood-brain barrier integrity. In addition, we examine how apoE impacts amyloid development, CAA formation and related neuroinflammation in the presence of Aβ pathology.
Results: VMC-apoE2 has increased physical fitness and decreased lipid shuttling ability. VMC-apoE3 reduces diffuse plaque load and reduces microgliosis. VMC-apoE4 increases diffuse Aβ plaque load in the hippocampus, increased microgliosis in the cortex, and increased BBB leakage.
Conclusions: VMC-apoE redistributes Aβ into the vasculature with different impacts for each genotype. VMC-APOE2 protection could potentially be due contributions to attributes involving improved physical fitness.

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P0536a / #3144

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

SORTILIN AND APOE INTERACTIONS – A MOLECULAR PATHOLOGY OF ALZHEIMER'S DISEASE?

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Aims: Objectives
Apolipoprotein E4 (apoE4) increases the risk for Alzheimer's disease compared to isoforms apoE2 and apoE3. All three differ at merely two aa positions. The interaction of neuronal sorting receptor sortilin and apoE is important for amyloid β clearance and anti-inflammatory lipid metabolism. The latter is disrupted in the presence of apoE4 instead of apoE3. We investigate potential structural variations for the sortilin-apoE complexes with the different apoE isoforms to determine if the observed functional alterations are related to structural changes.

Methods: Initially production and purification protocols for sortilin (full-length and ectodomain) as well as the three apoE isoforms will be established. Subsequently the complex formation (stoichiometry and stability) will be biochemically and biophysically analyzed via SEC-shift assays, nanoDSF, DLS, MST, mass photometry. Finally various structures of sortilin-apoE complexes will be determined by cryo-electron microscopy.

Results: Production of apoE3 and sortilin was established in HEK-F cells. Sortilin was purified via a GFP-tag based affinity chromatography while apoE3's internal heparin-binding capacity was sufficient for affinity purification. Both proteins were further purified via size exclusion chromatography. Unfortunately, purified sortilin still entails it's propeptide, which will interfere with ligand binding. ApoE3 is purified as lipidated monomer and dimer or tetramer.

Conclusions: To perform comprehensive biochemical and structural analysis of the sortilin-apoE complex formation, further optimization of the protein purification is required. Next steps are to obtain mature and activated sortilin by furin cleavage. Further a production system for monomeric apoE3 in *E. coli* will be established in order to produce cheap non-lipidated apoE3. This will be used as control in screening experiments of the sortilin-apoE interaction. Additionally, production systems for apoE2 and apoE4 will be established in HEK-F cells and *E. coli*.

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P0537 / #1405

POSTERS: A06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: SECRETASES

QUANTITATING PRESENILIN: IDENTIFYING THE IMPACT OF PRESENILIN EXPRESSION ON GAMMA-SECRETASE ACTIVITY AND THE FUNCTIONAL IMPLICATIONS

Melissa Eccles[1,2], Amy Woodfield[1,2], Ayeisha Milligan Armstrong[1,2], David Groth[1,2], Mark Agostino[1,2,3], Giuseppe Verdile[1,2,4]
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Aims: Presenilin proteins are well established as the catalytic component of γ-secretase, and while there are overlapping functions for presenilin-1 (PS1) and presenilin-2 (PS2), several independent functions have been identified. The presenilin field does not typically directly compare PS1 and PS2 expression when investigating the functional roles of these proteins. This work developed methods to quantitate presenilin expression and utilised this to understand the comparative functional consequences of PS1 and PS2 expression.
Methods: Exogenous Myc-tagged presenilin was expressed in HEK293 presenilin knockout CRISPR cell lines to directly compare exogenous presenilin expression. A purified recombinant PS fusion protein was generated and used to quantitate endogenous presenilin-1 and presenilin-2 protein units. PS1 and PS2 were quantitated in human brain tissue, differentiated neuroblastomas, and M17-neuroblastoma and human microglia cell (HMC3) lines lacking PS1 or PS2.
Results: In HEK293 cells PS1 expression is 5.6-times higher than PS2 expression. When presenilin expression is accounted for PS1 and PS2 process equal amounts of Notch1 and PS2 processes more APP. In the frontal cortex and hippocampus of control human brains there is respectively 44.5-times and 17-times more PS1 than PS2. The ratio of PS1:PS2 protein in immortalised cell lines ranges from 0.66 in M17 to 17.6 in HMC3. In both M17 and HMC3 cell lines the loss of either PS1 or PS2 leads to significant upregulation of the alternative presenilin paralog, indeed loss of PS2 in HMC3-cells causes a 290% increase in PS1 expression.
Conclusions: We demonstrate the importance of considering PS1 and PS2 protein expression when interpreting presenilin activity and highlight the importance of quantitative characterisation of presenilin proteins when selecting experimental models to ensure effective analysis of the attributed functional roles.

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P0538 / #1423

POSTERS: A06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: SECRETASES

BIOPHYSICAL CHARACTERISATION OF WILDTYPE AND MUTANT GAMMA-SECRETASE BINDING TO SUBSTRATES ASSOCIATED WITH BETA-AMYLOID REMOVAL

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Aims: Presenilin-1 (PS1) and presenilin-2 (PS2) have well established roles in generating Aβ. As the catalytic component of γ-secretase, they also play a role in Aβ removal via regulation of Aβ degrading enzymes, Aβ phagocytosis and clearance. This work explores the specific preferences of Aβ removal associated substrates for PS1- and/or PS2-γ-secretase and investigates the effect that autosomal dominant Alzheimer's disease presenilin mutations have on substrate binding.
Methods: Well-Tempered Metadynamics (WTMetaD) was used to characterise the conformational ensembles of PS1- and PS2-γ-secretase bound to substrates associated with Aβ removal functions. Binding energy calculations were performed on low energy states identified by WTMetaD to identify substrate preference PS1- vs PS2- γ-secretase. Alchemical perturbation was performed to determine how PS mutations affected substrate binding.
Results: We show that CD44, INSR, LDLR, LRP1, LRP8, MER, RAGE, SORL1 and SORT1 preferentially bind PS1-γ-secretase, while TREM2 and VLDLR preferentially bind PS2-γ-secretase. Analysis of the effect of PS mutations on the binding of Aβ removal substrates correlates with age of onset (AOO). Mutations associated with an earlier AOO have a uniformly negative affect on substrate binding, whereas mutations that have a later AOO differentially affect substrate binding.
Conclusions: The role of the presenilin proteins, and effect of mutations, is poorly understood in the context of Aβ removal mechanisms. Our work provides a thorough understanding of the effect of wildtype and mutant presenilin proteins on the binding of Aβ removal substrates, providing the foundation for the effective design of highly specific γ-secretase modulators.

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P0539 / #1100

POSTERS: A06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: SECRETASES

EFFECT OF NICASTRIN GLYCOSYLATION ON ENZYMATIC ACTIVITY AND SUBSTRATE PREFERENCE OF GAMMA-SECRETASE

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Aims: γ-Secretase complex, the assembly of Nicastrin, Presenilin, PEN-2 and Aph-1, catalyzes the cleavage of amyloid precursor protein to generate amyloid-b peptide (Aβ), the main culprit of Alzheimer's disease. Among the γ-secretase subunits Nicastrin is the only subunit which is glycosylated and has 16 potential *N*-glycosylation sites. Our previous study using lectin resistant mutant cell line demonstrated that Nicastrin glycosylation status is critical for enzymatic activity and substrate preference of γ-secretase (*Moniruzzaman et al., Biochem. Biophys. Res. Commun.* 2018). However, it is unclear which glycosylation site is particularly responsible for γ-secretase. Here we examine which Nicastrin glycosylation sites are critical for Aβ production and Notch cleavage.
Methods: We expressed Nicastrin mutants on individual N-linked glycosylation sites in Nicastrin knockout cells generated by CRISPR Cas9 to examined Aβ production and Notch cleavage.
Results: We found that N45A and N573A mutants of Nicastrin increased C99 cleavage, compared to Notch cleavage in living cells. On the other hand, N530A mutant of Nicastrin exhibited reduction in C99 cleavage, compared to Notch cleavage in cell-based assay.
Conclusions: Therefore, mutagenesis including deeper glycobiology study will be significant to identify γ-secretase activity modulating glycosylation site of Nicastrin, and to see how AD pathology is regulated by glycosylation status of Nicastrin. We will discuss enzymatic activity and substrate preference on isolated γ-secretase comprising of these Nicastrin mutants.

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P0540 / #124

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

CROSS-TALK BETWEEN SOMATOSTATIN AND DOPAMINE RECEPTOR SUBTYPES PROMPTS STRUCTURAL ORGANIZATION OF MAPS IN AN IN-VITRO AD MODEL

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Aims: In a healthy brain, structural organization and translocation of microtubule-associated proteins (MAPs) to neurites play a critical role in neural network formation and cognition. Disrupted intra-neural localization or altered translocation of MAPs in the hippocampus and cortical neurites are associated with the clinical symptoms of Alzheimer's disease (AD). Somatostatin (SST), a growth hormone inhibitory neuropeptide, is known to impede the aggregation of amyloid beta (Aβ). Similarly, Dopamine (DA), a key neurotransmitter involved with cognition, alleviates AD pathology by restoring cortical plasticity. The Somatostatin receptor (SSTR) and Dopamine receptor (DR) families share ~30% sequence homology and form heterodimers *in-vitro*. Since hetero-oligomers create a novel receptor, pharmacological different from its native receptor, we propose that endogenous heterooligomers exist between SSTRs/DRs, which might serve as a novel therapeutic target in promoting neurite formation and structural organization of MAPs and its translocation to neurites.
Methods: The present study investigated the interaction between SSTRs and DRs by treating differentiating (using retinoic acid) human SH-SY5Y neuroblastoma cells with SSTRs and DRs-specific agonists with/without amyloid beta (Aβ). Receptor cross-talk was evaluated using double-labeled immunocytochemistry and co-immunoprecipitation.
Results: Our results indicate that MAPs organization and translocation in Aβ-treated cells were perturbed, and neurite formation was disrupted. The membrane co-localization of SSTRs/DRs was also disrupted following Aβ-treatment. In contrast, cells treated with SSTR/DR agonists displayed strong interaction between DRs and SSTRs at the membrane and prompted terminally differentiated neurites and translocation of MAPs to the distal ends of neurites. Moreover, a strong interaction observed between DRs/SSTRs and MAPs suggests its role in neuronal integrity and functionality.
Conclusions: Taken together, our study demonstrates that cross-talk between SSTRs and DRs is a prerequisite in ameliorating Aβ-induced MAP disorganization and disrupted neurite formation.

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Alzheimer's and Parkinson's Diseases
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March 28 - April 1, 2023 | Gothenburg, Sweden

P0541 / #2628

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

AB EFFECT ON NEURONAL-LIKE CELLS' METABOLIC PROFILE

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Aims: A key player in Alzheimer´s disease (AD) pathogenesis is the Aβ peptide, which tends to aggregate into oligomers and fibrils, and finally senile plaques; a major hallmark in AD brains. This peptide is extremely toxic to neurons, triggering several mechanisms, that ultimately induce neuronal death. In addition, brain metabolic alterations are linked to disease pathogenesis. In this work, the effect of Aβ in the metabolic profile of two neuronal-like cell lines was analyzed using Fourier Transform Infrared (FTIR) spectroscopy.
Methods: Human neuroblastoma cell line SH-SY5Y and mouse neuroblasts N2a were treated with 10 µM of Ab_{25-35} peptide for 48 h. After treatment, cells were detached, and aliquots containing $1x10^5$ cells were prepared. After centrifugation, cell pellets were immediately frozen until FTIR analysis. Prior to analysis, pellets were resuspended in PBS and FTIR spectra was acquired. Data was analyzed by Partial Least Squares (PLS) multivariate analysis or using univariate approaches for the calculation of peak areas associated with fingerprint region (1200-900 cm^{-1}), a spectral region associated, among other metabolites, to carbohydrates and nucleic acids.
Results: Preliminary PLS analysis of the fingerprint region showed a clear discrimination between the spectra of control and Aβ-treated cells. Analysis of the peak areas of this spectral region also showed significant differences between the two groups.
Conclusions: Aβ peptide similarly altered the spectroscopic profile of the two neuronal-like cell lines, particularly in the fingerprint region, supporting the contribution of this peptide to AD metabolic pathogenesis. This work was funded by Instituto de Biomedicina (iBiMED) under Grant UIDB/04501/2020 and UIDP/04501/2020; MV is supported by the individual PhD grant UI/BD/151354/2021

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POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

AGE, SEX, AND LIPID METABOLISM INTERSECT TO ELICIT COGNITIVE DECLINE IN A MOUSE MODEL OF ALZHEIMERS DISEASE

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Aims: Objectives: We sought to compare how age and sex interact with lipid metabolism in N5 TgCRND8 mice, our sexually dimorphic AD model of Ab deposition devoid of a-syn pathology to elicit cognitive decline.
Methods: Methods: We used unbiased lipidomic approaches employing nanobore high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (nLC-ESI-MS/MS) coupled to ion mobility and novel bioinformatic pathway and machine learning analysis approaches to map sex-specific network disruptions at 2, 4 and 6 months of age in plasma and temporal cortex. We linked these changes to performance in a panel of behavioural tests (nest building, Y-maze, and Morris Water Maze). We then tested whether dietary intervention would alter lipid compositions and delay behavioural phenoconversion
Results: Results We quantified and characterized the phospholipid and sphingolipid compositions differentially disrupted in plasma and brain of male and female mice of each genotype. We identified defining changes in metabolism that differentially associated with cognitive decline and pathology in either sex. We further show that critical lipid indicators of disease are constellations of lipids differentially modified by diet in male and female mice to change behavioral outcome.
Conclusions: Conclusions: Ceramide, glycerophosphocholine, and glycerophosphoserine metabolism is differentially disrupted in a sexually dimorphic mouse model of AD and can be modulated by diet to change rate of behavioural phenoconversion.

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POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

WEIGHTED KEY DRIVER NETWORK ANALYSIS OF GENES AND THEIR INFLUENCE ON ALZHEIMER'S DISEASE ENDOPHENOTYPES

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Aims: The TaRget Enablement to Accelerate Therapy Development for AD (TREAT-AD) consortium is missioned to provide tools to the Alzheimer's research community for the discovery of novel therapeutics. Here we provide networks summarizing Alzheimer's disease (AD) endophenotypes and a ranking of genes based on their network causality in driving that endophenotype.
Methods: Biological domain (biodomain) networks are networks of genes associated with AD which are then clustered further into subnetworks based on Gene Ontology terms (GO terms) to correspond with AD endopehotypes. We used gene scores based on genetics and multi-omics as the basis for weighting the biodomain networks for the weighted Key Driver Analysis (wKDA) algorithm from the Mergeomics R package. The biodomain networks share genes, but GO terms are mapped to specific biodomains, thus one can interrogate a biodomain network to determine the influence a particular gene has on every other biodomain.
Results: Analysis of the lipid metabolism biodomain network yielded the genes CRK and KL as potential therapeutic targets. CRK and KL had elevated impacts in the autophogy and immune response biodomains. CRK also had elevated impacts in the vasculature biodomain. The expectation is that modulations of CRK or KL in the lipid metabolism network would have the largest cross-network effects in the aforementioned biodomains.
Conclusions: Using wKDA to identify causal genes of the lipid metabolism AD endophenotype network suggests that genes CRK and KL should be targeted in the lipid metabolism pathway for pharmacological interventions in AD, and the downstream impacts of this targeting will be most strongly impact autophagy, immune response and vasculature biodomains. Makinen V, Le Shu, Zhao Y, Kurt Z, Zhang B, Yang X (2022). *Mergeomics: Integrative network analysis of omics data*. R package version 1.24.0.

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POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

HETEROGENEITY OF APOER2 ISOFORMS IN THE HUMAN ALZHEIMER'S DISEASE BRAIN AND THEIR CELLULAR AND FUNCTIONAL IMPLICATIONS

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Aims: The two largest risk factors for Alzheimer's disease (AD) are age and the ε4 allele of apolipoprotein E (*APOE*). APOE is involved in neuronal lipid homeostasis and is known to bind to transmembrane lipoprotein receptors such as APOER2. Recent studies have implicated alternative splicing defects in AD and other neurodegenerative diseases. One such splicing defect lies within exon 18 in *APOER2*, where AD individuals demonstrate less exon 18 inclusion. Due to *APOER2*'s high degree of cassette exon splicing events and enrichment in the brain, we hypothesized that alternative splicing of *APOER2* may be altered in AD brains, and these unique isoforms might impact cellular changes and affect synaptic function.
Methods: To profile the entire *APOER2* transcript, we used single molecule long-read RNA sequencing from the hippocampus and parietal cortex of three human female control and three female Braak stage IV AD brain tissue. Individual exon frequencies were further analyzed through quantitative PCR. Additionally, we examined novel *APOER2* isoforms at the cellular level to determine cell-surface expression and effects on synaptic function.
Results: Our data indicates *APOER2* is dysregulated in both individual exon alternative splicing and full-length transcripts in the hippocampus and parietal cortex of AD brains compared to control. We also found different combinations of *APOER2* splicing events give rise to changes in cell-surface expression that may affect synaptic function.
Conclusions: We found alternative splicing events in *APOER2* are altered in AD patients and serve a critical role in cell-surface expression which may affect ligand binding, such as to APOE, and neuronal function. We conclude that atypical alternative splicing of *APOER2*, in neurodegeneration could provide key insight into the association between APOE genotype and AD.

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POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

AN INTEGRATIVE MULTI-OMICS APPROACH REVEALS MOLECULAR SIGNATURES ASSOCIATED WITH AGE AND HIGH-FAT DIET IN MOUSE MODELS OF ALZHEIMER'S DISEASE

Ravi Pandey[1], Kevin Kotredes[2], Dylan Garceau[2], Annat Haber[1], Kamil Borkowski[3], Siamak Mahmoudiandehkordi[4], Ananth Shantaraman[5], Duc Duong[5], Nicholas Seyfried[5], Rima Kaddurah-Daouk[4], Michael Sasner[2], Gareth Howell[2], Adrian Oblak[6], Bruce Lamb[6], Greg Carter[1,2]
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Aims: Alzheimer's disease (AD) is a complex, multifactorial pathology with high heterogeneity in biological alterations. Our understanding of cellular and molecular mechanisms from disease risk variants to various phenotypes is still limited. Therefore, it is required to integrate the information from multiple data modalities for thorough exploration of endophenotype networks, biological interactions related to disease and thus accelerate our understanding of heterogeneity in Alzheimer's disease.
Methods: In this study, we performed multi-level omics in a cohort of mouse models expressing humanized Abeta and two genetic risk factors (APOE4 and Trem2*R47H) at multiple ages for both sexes. Data from multiple omics platforms (transcriptomics, proteomics, and metabolomics) were analyzed at single-omic level as well as integrated in an unbiased fashion, considering interaction between modalities using multi-omics factor analysis (MOFA). We also systematically aligned multimodal mouse data to relevant human studies cohort.
Results: Multi-omics integration identified major dimensions of heterogeneity explaining the variance within the cohort and differentially associated with age, sex, and high fat diet. Enrichment analysis of genes and protein associated with these dimensions were significantly enriched for multiple AD-related processes. Specifically, dimensions associated with age and diet related heterogeneity exhibited overrepresentation of immune response and metabolic processes as well as increased levels of long-chain acylcarnitine's and reduced levels of spermidine in aged and high-fat diet fed AD mouse models similar to human AD.
Conclusions: We identified axes of variation within a cohort of LOAD mouse models using integrative multi-omics approach. Our analysis revealed multiple interaction between distinct multi-omics molecular signatures associated with Alzheimer's disease. In this study, we highlighted that assembling multi-omics measurements reveal interrelated pathway alternations in AD and its ability to identify biomarkers combinations that may be used in clinical practice.

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POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

MIRNOME-WIDE DIFFERENTIAL EXPRESSION ANALYSES IN ENTORHINAL CORTEX OF ALZHEIMER'S PATIENTS AND CONTROLS HIGHLIGHT SEVERAL NOVEL MIRNAS

Marcel Schilling[1], Valerija Dobricic[1], Janina Fuß[2], Soeren Franzenburg[2], Laura Parkkinen[3], Christina Lill[1,4,5], Lars Bertram[1,6]
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Aims: Post-transcriptional regulation has been implicated in Alzheimer's disease (AD) pathogenesis. Micro RNAs (miRNAs) are post-transcriptional regulators that are highly expressed in brain tissue. Still, previous studies have been limited in both the number of samples and/or the number of molecules assayed to reliably assess the potential involvement of miRNAs in AD. To this end, we compared miRNA expression using RNA sequencing in brain tissue extracted from 174 AD patients and aged control individuals.
Methods: Entorhinal cortex (EC) samples were collected from 90 AD patients (61 to 95 years) and 84 healthy controls (41 to 100 years). Total RNA was extracted and small-RNA-sequencing libraries prepared and sequenced at ~2.3M reads/sample on average. MiRNAs were quantified using miRDeep2 and compared between cases and controls using DESeq2, adjusting for potential confounding factors. Additionally generalized linear models were fit to identify miRNAs differentially expressed with respect to Braak-staging
Results: We detected > 600 miRNAs expressed in EC, about one third of which had been previously assessed by the ROS/MAP project (Patrick et al. 2017). For the majority of those, miRNA expression levels show a high correlation ($r = 0.698$, p-value < 2.2e-16). Leveraging our entire data set, we found > 20 miRNAs significantly differentially expressed between AD cases and controls and over twice as many associated with Braak staging While several differentially expressed miRNAs were already previously reported (*e.g.* miR-129-3p and miR-195-5p) our study highlights numerous novel miRNAs not previously linked to AD.
Conclusions: Our study provides the largest differential miRNA-expression analysis in terms of miRNAs assayed and one of the largest in terms of sample size. Mapping the target mRNAs of these miRNAs holds promise in leading to a better understanding of AD pathogenesis.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

IDENTIFICATION OF EPIGENETIC BIOMARKERS FOR COGNITIVE DECLINE USING LONGITUDINAL GENOME-WIDE DNA METHYLATION PROFILES

Jan Homann[1,2], Yasmine Sommerer[2], Valerija Dobricic[2], Valentin Vetter[3], Sandra Düzel[4], Ulman Lindenberger[4], Ilja Demuth[3], Christina Lill[1], Lars Bertram[2]
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Aims: A substantial portion (>60%) of Alzheimer's disease (AD) variance is explained by genetic factors but it is becoming increasingly clear that other mechanisms like epigenetics make substantial contributions. We determined epigenetic trajectories using genome-wide DNA methylation (DNAm) data generated at two timepoints (~7.5 years apart) from whole blood samples of ~1,050 healthy probands (age at baseline >60 years) of the Berlin Aging Study II (BASE-II). The main aim of our study is to identify DNAm signatures that are predictive of a later cognitive decline in study participants.
Methods: Genome-wide DNAm profiling was performed via the Human MethylationEPIC array (Illumina, Inc) and resulting DNAm data were processed using in-house computational pipelines. Cognitive testing was performed at both time points using four tests of episodic memory performance, analyzed individually and combined. DNAm profiles were used as independent variables in the context of an epigenome-wide association study (EWAS) to predict cognitive performance using linear models. DNAm-based "polyepigenetic scores" (PES) were calculated to compare our results with those from other groups.
Results: Genome-wide DNAm profiles from two timepoints are available for 1,019 individuals. First analyses utilized a recently proposed principal components (PC) based algorithm to estimate DNAm telomere length (DNAmTL) from genome-wide DNAm data. In these analyses we observed the expected highly significant difference in DNAmTL between T0 und T1 (*P*-value = 1.23E-83), suggesting that the generated longitudinal DNAm profiles are suitable for the envisioned EWAS analyses, which are still ongoing at the time of writing.
Conclusions: We generated a unique dataset of >1000 aged individuals with longitudinal data on both the cognitive as well as DNAm domains. At the meeting we will provide a detailed summary of the EWAS analyses on cognitive decline in these samples.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

LIQUID BIOPSY AS A SOURCE OF EPIGENETIC BIOMARKERS FOR ALZHEIMER DISEASE'S PATIENTS

Monica Macias[1,2], Blanca Acha-Santamaria[2], Idoia Blanco-Luquin[2], Miren Roldán[2], Javier Sánchez Ruiz De Gordoa[1,2], Jon Corroza[1], Mikel San Martín[1], Sara Zueco[3], Carolina Cabello[1,2], Elena Erro[1,2], Ivonne Jericó[1,2], Maite Mendioroz[1,2]
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Aims: In recent years, new DNA methylation variants have been reported in genes biologically relevant to AD in human brain tissue samples. However, this AD-specific epigenetic information remains locked in the brain tissue and, therefore, undetectable while the patient is alive. Hence, we explored the feasibility of employing liquid biopsy techniques to detect methylation differences in cell-free DNA (cfDNA) from plasma of AD patients and controls.
Methods: We selected 81 AD patients (79±7 years) and 105 cognitively healthy controls (78±7 years) with no significant differences in age or gender. cfDNA was isolated from 2 mL plasma by using QIAmp Circulating Nucleic Acid Kit (Qiagen) and bisulfited converted. We analyzed cfDNA methylation of *SPAG6*, a gene involved in neurogenesis previously reported as differentially methylated in hippocampus of AD patients, at three individual cytosine-guanine dinucleotides (CpGs) by pyrosequencing (Qiagen). Mann-Whitney U tests were performed with IBM SPSS v20.
Results: cfDNA could be readily isolated from AD patients and controls. We observed significant higher *SPAG6* cfDNA methylation levels in all individual CpG assayed and in average in AD cases compared to controls ($p<0.05$).

***SPAG6* methylation median % (IQR)**	**AD patients**	**Controls**	**P value**
CpG1	12.7 (6.9-21.1)	8.6 (0.14.8)	0.001
CpG2	14.1 (7.7-21.3)	11.4 (4.7-16.7)	0.029
CpG3	11.7 (3.6-15.5)	7.9 (0-12.9)	0.024
Average	13.4 (7.9-18.1)	10.4 (5.6-15.5)	0.008

Table 1. Percentage of cfDNA methylation of *SPAG6* from AD patients and controls. Data are expressed as median and interquartile range (IQR).

Conclusions: These results suggest that liquid biopsy technique would provide access to this brain information in a non-invasive way during patients'lifetime. The isolation of cfDNA from plasma of AD patients may constitute a source of potential epigenetic biomarkers to aid AD clinical management.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

GENOME-WIDE MENDELIAN RANDOMIZATION ANALYSES PINPOINT SEVERAL ALZHEIMER'S AND PARKINSON'S GWAS LOCI POTENTIALLY ACTING VIA DNA METHYLATION

Olena Ohlei[1], Yasmine Sommerer[1], Jan Homann[1,2], Laura Deecke[1,2], Valentin Vetter[3], Ilja Demuth[3], Marcel Schilling[1], Valerija Dobricic[1], Laura Parkkinen[4], Christina Lill[1,2,5], Lars Bertram[1,6]
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Aims: Recent genome-wide associations studies (GWAS) in Alzheimer's disease (AD) and Parkinson's disease (PD) have identified a large number of risk variants, but their functional effects on pathogenesis are still largely unknown. To close this gap, we created a genome-wide map of single nucleotide polymorphisms (SNPs) determining DNA methylation (DNAm) variation, so called methylation quantitative trait loci (meQTL). Next, we used Mendelian randomization (MR) to assess the connection between AD/PD predisposition and DNAm using associated SNPs as instrumental variables.
Methods: Genetic (Global Screening Array) and DNAm (MethylationEPIC Array) data were generated from whole blood (n=1058) and buccal (n=837) DNA specimen collected from probands of the Berlin Aging Study II. Matrix-eQTL software was used to generate genome-wide maps of meQTL effects. To test for associations between traits and DNAm levels we applied the summary data–based Mendelian randomization (SMR) approach. Significant SMR signals were tested for heterogeneity, assessed for replication in brain tissue (n=142), and validated using small-scale MR methods .
Results: Our meQTL GWAS analyses tested approximately 6 million SNPs for association with ~750,000 CpG probes. We identified between 15 and 11 million genome-wide significant ($p < 10^{-14}$) SNP-CpG pair associations in each tissue. More than 500 SNP-CpG pairs in more than two dozen known GWAS genes for AD and PD were highlighted as genome-wide significant by SMR. A substantial fraction of these SNP-CpG pairs also showed nominal significant SMR effects in brain.
Conclusions: The results of our study suggest that several known AD and PD GWAS loci may act by affecting DNAm levels. Our study provides a comprehensive list of these genes to help prioritize future functional studies in AD and PD.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

BULK TISSUE- AND CELL-TYPE-SPECIFIC PROFILING IMPLICATES A ROLE FOR EPIGENETIC DYSREGULATION IN THE DORSAL RAPHE NUCLEUS OF ALZHEIMER'S DISEASE PATIENTS

Renzo Riemens[1], Ehsan Pishva[1], E.P.I.-A.D. Consortium[2], Gunter Kenis[1], Katie Lunnon[3], Daniel Van Den Hove[1]
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Aims: Increasing evidence suggests that the dorsal raphe nucleus is among the first brain regions affected in the etiopathogenesis of Alzheimer's disease (AD). Furthermore, recent epigenome-wide association studies (EWAS) have implicated a central role for epigenetic alterations in the disease's course and development. Yet the extent of disease-specific deviant epigenetic signatures in the DRN has not been investigated before. Therefore, in the present study, we have conducted the first large-scale epigenetic analysis of the DRN in AD.
Methods: Within the EPI-AD project (http://www.epi-ad.eu/), we performed an EWAS, assessing both DNA methylation and hydroxymethylation profiles, using bulk tissues from the DRN. Subsequently, our discovery EWAS findings were then methodologically validated in a subset of patients from the same cohort using another technique, namely bisulfite pyrosequencing. We followed up these analyses by exploring methylomic signatures in microdissected serotonergic- and non-serotonergic DRN cells using adapted limiting dilution bisulfite pyrosequencing.
Results: Within the DRN bulk tissues, we revealed Braak stage-associated epigenetic abnormalities in *TNXB*, in addition to other dysregulated loci. Interestingly, when comparing methylation levels of *TNXB* in individually isolated serotonergic neurons with those of non-serotonergic cells in the DRN, we found a significant interaction between cell-type and condition. The AD-associated methylation profiles were opposite in the serotonergic neurons and non-serotonergic cells, the latter of which resembled the EWAS data.
Conclusions: Overall, our DRN work highlighted previously identified and novel epigenetic signatures that we hypothesize to play a pivotal role in early AD development. Furthermore, we show that dysregulation in *TNXB* methylation in the DRN is both dependent on the disease phenotype and the cell type analyzed, which warrants the need for cell-type specific neuroepigenetic studies in AD.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

HARNESSING THE CRISPR-CAS9 SYSTEM TO MODIFY METHYLATION MARKS ASSOCIATED WITH ALZHEIMER'S DISEASE

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Aims: Epigenome-wide association studies of DNA methylomic variation in Alzheimer's disease (AD) have identified differentially methylated positions in genes such as ANK1, BIN1 and TREM2 that are hypermethylated and robustly associated with the disease. However, it remains unclear whether these associations are causal in disease development or represent a secondary effect of pathogenesis or medication. Consequently, this project intends to determine if disease-associated methylation has an effect on gene regulation.
Methods: Cell lines of neuronal phenotype (SH-SY5Y) and microglial phenotype (IHM-SV40) were used to explore the functional consequences of loci methylation and demethylation, where addition/removal of the methyl groups was achieved by the modified CRISPR-dCas9 system. The guide RNA (gRNA) constructs were designed to locate the CpG sites associated with differential methylation of target loci in AD. Bisulphite pyrosequencing was applied to analyse the target regions in the modified cells. Furthermore, RT-qPCR was performed to measure transcript variant levels in these cell lines.
Results: Demethylation of the target regions in ANK1 and BIN1 was observed in their respective cell lines when compared to the unmodified control cells. Targeted methylation of the non-CpG island promoter in TREM2 was successful in the IHM-SV40 cells. Analysis of the modified cell lines RNA revealed differences in ANK1 transcript levels, where hypermethylation of the target locus demonstrated an increase in the abundance of isoform 5, 7 and 10 transcripts. Methylation of the TREM2 locus resulted in an increase in whole-gene expression.
Conclusions: We have shown the delivery and activity of CRISPR-dCas9 fusion constructs in cell line models of AD. In the future, we intend to explore long-range interactions between genetic loci via chromatin conformation analysis through which we hope to gain further insight into methylomic variation associated with neurodegeneration.

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POSTERS: A06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

TARGETED BISULFITE SEQUENCING ANALYSIS OF CANDIDATE GENES ASSOCIATED WITH ALZHEIMER'S DISEASE

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Aims: Recent epigenome-wide association studies (EWAS) identified a number of loci in specific genes showing robust and reproducible alterations in DNA methylation in Alzheimer's disease (AD) brain samples. The standard method to assess methylation in EWAS is via microarrays, however, these target a limited number of methylation sites in each gene. Here we have performed targeted bisulfite sequencing for candidate genes associated with AD, with the aim to determine the exact extent and pattern of methylation changes in disease within these loci.
Methods: Prefrontal cortex brain samples from 58 individuals were selected and grouped by Braak stage (Control 0-II; mild cognitive impairment III-IV; AD V-VI). The DNA was extracted, before 30 genomic regions of interest, identified from previous AD EWAS, were captured using Agilent Sure Select target baits. The DNA was next-generation bisulfite sequenced, before the sequence reads were aligned and the methylation status of cytosine residues were called using the Bismark program. Differentially methylated positions (DMPs) were analysed across the three groups.
Results: Methylation levels were quantified for each group. Linear regression controlled for co-variation before differences across the groups were examined using a one-way ANOVA, with Tukey's post-hoc test. Sites in several genes showed step-wise increases in DNA methylation across the groups. Interestingly, amongst the most robust sites, differences in methylation in the MCI group when compared to the control and AD groups were also observed.
Conclusions: This work provides further evidence that dysregulation of methylation is associated with pathological changes in AD prefrontal cortex. The observation of differential methylation with MCI, at sites showing no difference between control and AD groups, potentially indicates early pathological changes. Given the reversible nature of DNA methylation, this could present potential targets for pharmacological intervention.

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P0553 / #2603

POSTERS: A06.I. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

ESTABLISHMENT OF DURAL FIBROBLASTS AND INDUCED PLURIPOTENT STEM CELLS DERIVED FROM KOREAN POSTMORTEM HUMAN BRAIN DONORS

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Aims: Animal cell culture has been the basis for a lot of research in the field of biology. However, experiments using animal cells or animal models have limitations in properly reproducing the pathological environment and physiological characteristics of humans. In this regard, human-derived fibroblasts which can be a source of reprogramming to a pluripotent stem cells or other cell types, could be the important supply of human resource in a less restrictive manner. Therefore, we established the protocol of postmortem human dura mater-derived fibroblast culture and induced pluripotent stem cell (iPSC) generation via autopsy at Seoul National University Hospital Brain Bank (SNUH-BB), and confirmed that it differentiates into brain cell type.
Methods: Fibroblasts culture, iPSC generation by Reprogramming factors(OCT4,SOX2,KLF4,cMYC) in fibroblasts after episomal infection with Sendai virus, and characterization of iPSC and brain cell type differentiation with microscope, immunocytochemistry, and qRT-PCR were performed.
Results: The SNUH-BB established a protocols for dural-derived fibroblast culture and for iPSC generation from the dura of the autopsy brains. Fibroblast cell lines and iPSC derived from dura matter of normal and neurodegenerative disease patients were established, and the cell types were characterized with an antibodies against the fibroblast-specific marker(S100A4), pluripotent stem marker(Oct4,Nanog,TRA-1-60,SSEA4). And it was confirmed that these iPSCs were well differentiated into Brain cells.
Conclusions: All results showed that we successfully established a protocol for culturing fibroblasts generating iPSCs from postmortem dura mater, and confirmed that these iPSCs were well differentiated into brain cell types. These cells are stored in our brain bank for use in the research on brain diseases related to Alzheimer's disease or Parkinson's disease. It also laid a good foundation for establishing an important human resource that can support research on overcoming neurodegenerative diseases.

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POSTERS: A06.I. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

ISOLATION AND CHARACTERIZATION OF NEURAL STEM CELL-LIKE CELLS FROM POSTMORTEM HUMAN BRAIN TISSUE, KNOWN AS ADULT NEUROGENIC NICHES

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Aims: Because biopsy is rarely performed on living patients with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, it is impossible to culture primary patient-derived human cells. Therefore, the culture of primary human neural stem-like cells (primary hNSCs) that maintain the disease state of patients can be a powerful resource for research.
Methods: This study established methods of epilepsy patients' brain and postmortem human brain cell culture, and analyzed the constructed neural stem-like cells with immunohistochemistry, immunocytochemistry, flow cytometry, bulk RNA sequencing, principal component gene set enrichment analysis.
Results: Human neural stem-like cells were isolated from adult postmortem brains from the Seoul National University Brain Bank. As expected, these cultured neural stem cells expressed neural stem cell markers such as SOX2, nestin and CD133, whereas did not express specific cell linage markers, such as neuronal, astrocyte and microglia type markers (NeuN, GFAP and Iba-1). The two RNA sequencing data sets obtained from brain biopsy and autopsy have nearly identical gene expression profiles. These results support the idea that postmortem brain tissue is of similar experimental value and quality to biopsy tissue.
Conclusions: Comparison of bulk RNA-sequencing data showed that primary neural stem-like cells isolated from biopsies and autopsy have similar properties with iPSC-derived NPCs. These cells have nearly identical gene expression profiles and may similar differentiation capacities. Our findings also suggest that the primary hNPCs obtained from human postmortem disease-brain also have the comparable genetic profiles and experimental advantage to cells obtained from biopsy tissue. We will further characterize the dataset to determine detailed subpopulations of neural stem cells.

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POSTERS: A06.I. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

PROFILING OF PERIPHERAL IMMUNE CHARACTERISTICS IN A NOVEL APPNL-G-F KNOCK-IN HUMANIZED MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Studies in transgenic Alzheimer's disease (AD) animal models propose a role of dysregulated peripheral immune system in memory impairment. Contribution of peripheral immune response in driving different pathological stages in AD is less understood. Therefore, the objective of the study is to explore the relation of amyloid beta (Aβ) pathology development in the brain with alterations in the peripheral immune compartment in a novel App knock-in (*App^{NL-G-F}*) AD mouse model.
Methods: Using flowcytometry, we characterized the *App^{NL-G-F}* mice at different stages of Aβ pathology (early-plaque: 2-month-old; plaque + early memory impairment: 7-month-old; late stages: 12-month-old) and investigated the distribution and activation status of various splenic immune cells.
Results: Among various immune cells from innate immunity, significant increases in macrophage number in *App^{NL-G-F}* mice were observed. While the percent distribution of B cells from adaptive immunity was reduced in 12 month, no significant changes in total T cell distribution in any age group compared to wild-type controls were observed. B cells showed reduced activation molecule CD69 and PD-L1 expression in 7 and 12-months old *App^{NL-G-F}* mice. Among T cell subsets, CD4, CD8 and regulatory T (Treg) cell distribution in *App^{NL-G-F}* mice was comparable to control mice in all age groups. However, rise in follicular T helper (Tfh) cells was observed only at 2-month of age, with altered ICOS expression in *App^{NL-G-F}* mice.
Conclusions: These findings in AD mice model show a reduction in B cell and their activation status during aggressive Aβ plaque deposition in brain, reflecting their possible contribution in Aβ pathology reinforcing further investigation. Our data indicate a possible role of Tfh cells in the early stage of Aβ pathology.

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P0556 / #2512

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

GENERATION AND CHARACTERISATION OF FE65/FE65L1/FE65L2 TRIPLE KNOCKOUT MICE

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Aims: The adaptor protein Fe65 and its two mammalian homologues Fe65L1 and Fe65L2 are major interaction partners of the amyloid precursor protein (APP), involved in neuronal development, migration, synaptic plasticity and formation of the neuromuscular junction (NMJ). However, so far the function of Fe65L2 remained unclear, as no Fe65L2 knockout was available, yet.
Methods: Fe65L2 KO mice were established and crossbred to Fe65 and Fe65L1 KO mice to generate Fe65/Fe65L1/Fe65L2 triple KO mice. After validation of the KO mice, different immunohistochemical stainings of the triangularis sterni muscle were performed, using different antibodies (anti-tubulin, synaptophysin and postsynaptic markers, such as bungarotoxin). Moreover, quantitative analysis of pre- and postsynaptic areas as well as apposition of the pre- and postsynapse at different time points of development were performed.
Results: Mice deficient for the ubiquitously N-terminaly truncated Fe65 L2 family member showed similarly, as Fe65 and Fe65L1 single knockout mice no obvious abnormalities. In contrast to this, Fe65(-/-), Fe65L1(-/-), Fe65L2(-/-) triple knockout mice proved lethal early postnatally, whereas Fe65 (-/-) / Fe65 L2 (-/-) or Fe65L1 (-/-) / Fe65 L2 mice were viable and apparently normal. These data indicate high redundancy between Fe65L2 and the two other family members and corroborate a key physiological role for Fe65L2. The lethal triple mutants displayed strong motor deficits and showed strong impairments at the NMJ, such as reduced pre- and postsynaptic areas and diminished apposition.
Conclusions: In summary, our data show that the Fe65 family is crucial for the formation and maintenance of neuromuscular synapses at early and late development stages, mirroring the phenotype of APP/APLPs KO mice, that also die early postnatally. This strongly suggests that Fe65 family members mediate APP signaling function at the NMJ.

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P0557 / #857

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

COMPARATIVE CHARACTERIZATION OF 5XFAD AND HABETASAA MOUSE MODELS OF FAMILIAL AD MUTATIONS

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Aims: The failure of most clinical Alzheimer's disease (AD) trials has been partially attributed to the lack of translatability of current AD animal models. A recently developed knock-in mouse model of familial AD (fAD), expressing Swedish, Arctic and Austrian mutations in App (hAbeta^{SAA}), has been shown to be a useful amyloidogenic model which recapitulates many aspects of AD, including plaque distribution and microglial transcriptional changes. Our aim is to further characterize the hAbeta^{SAA} model and compare it to the widely used 5xFAD transgenic model.
Methods: A fluorescent amyloid probe (Methoxy-X04) was administered to aged hAbeta^{SAA} or 5xFAD mice prior to harvest. An additional fluorophore-conjugated antibody (lectin Dylight®594) was used to visualize vascular morphology and cerebral amyloid angiopathy (CAA). Whole brains were sectioned/imaged using Serial Two-Photon Tomography on the TissueCyte (TissueVision), creating a high-resolution 3D model of each brain and a library of sections. Sections were used for standard immunohistochemistry as well as spatial proteomic profiling, performed by Ambergen's MALDI-IHC technique, which allows for detection of up to 100 targeted proteins. Independent brain hemispheres were used for bulk RNA-Seq.
Results: Transcriptomics show an age-dependent phenotype in hAbeta^{SAA} that more closely aligns with human AD than 5xFAD. Neuropathology shows an age-dependent, less aggressive amyloid burden in the hAbeta^{SAA} brain than the 5xFAD model. Analysis of vasculature, CAA and spatial proteomics are underway
Conclusions: We showcase hAbeta^{SAA} as an amyloidogenic mouse model of fAD that aligns more closely with human disease than 5xFAD. This model is available with no licensing restrictions and is devoid of artifacts related to transgenic overexpression, positioning it as an improved mouse model for preclinical testing of amyloid- and neuroinflammatory-based therapies.

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P0558 / #2226

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

DEVELOPING AN ANIMAL MODEL OF MIXED DEMENTIA; ALZHEIMER'S DISEASE WITH LEWY BODIES.

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Aims: Alzheimer's disease (AD) is characterized by the presence of two misfolded proteins, amyloid-β peptide and hyperphosphorylated tau. Pathological studies demonstrated that AD brains often contain misfolded proteins associated with other neurodegenerative disorders. α-Synuclein is often found in the form of Lewy Bodies or Lewy neurites in the autopsied brains of AD patients. These patients have unique pathology and disease outcomes compared to those with pure AD pathology. This study aims to develop a rat model that can faithfully recapitulates the pathology found in patients with Alzheimer's disease with Lewy Bodies using a previously established model for AD (F344TgAD rat).
Methods: F344TgAD and non-transgenic littermate rats received a unilateral injection of AAV 2/5 serotype virus containing full length or C-terminally truncated α-synuclein (SYN119) into the amygdala at nine months of age. The contralateral hemisphere was used as an internal control. C-terminally truncated α-synuclein has been shown to have a higher propensity to aggregate compared to the full-length protein. Three months post-injection, brain tissue was collected for analyses.
Results: Over-expression of both full length α-synuclein and SYN119 produced aggregates within the amygdala proximal to the injection site with no evidence of propagation to surrounding brain regions. Rats injected with the full-length form displayed greater area coverage compared to those injected with the SYN119. When comparing F344TgAD and non-transgenic littermate rats, no difference was observed in α-synuclein pathology. There was no observable difference in astrocyte activation between hemispheres or between those injected with either form of α-synuclein.
Conclusions: While both forms of α-synuclein produce Lewy neurite pathology proximal to the injection site, pathological spread wasn't observed after a 3-month incubation period. As prion-like spread has been observed at longer time points, we will increase the incubation period.

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P0559 / #2454

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

A CLU/APOJ GWAS AD RISK VARIANT SUPPRESSES THE ASTROCYTIC RESPONSE TO PLAQUES AND REDUCES AXONAL AND NEURITIC DAMAGE IN 5XFAD MICE

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Aims: Genome-Wide Association Studies (GWAS) implicate clusterin (*CLU,* also known as apolipoprotein J) as a risk factor for late-onset Alzheimer's disease (LOAD), with elevated expression of *CLU* being associated with increased risk of LOAD. The region surrounding the SNP risk allele *rs2279590* is poorly conserved within the mouse genome. Consequently, to model the effect of the *rs2279590* risk allele on development of AD-related pathology in mice we developed mice with a partially humanized allele of *Clu*.
Methods: CRISPR was used to substitute a 2kb region of human *CLU* (intron 7 to exon 9) containing the enhancer region and the *rs2279590* SNP variant for the orthologous region of *Clu* within the C57BL/6J mouse genome. *Clu*-rs2279590_h2kb mice were crossed with 5xFAD mice and aged to 4 and 12. Coronal brain sections were immunolabeled to visualize dense-core plaques, microglia, astrocytes, axonal (Neurofilament Light Chain (NfL)) and neuritic damage, confocal images of subiculum and cortical regions were taken and analyzed. Aβ and NfL levels were quantified in the brain tissue and plasma.
Results: *Clu-rs2279590_h2kb* variant in 5xFAD background significantly increased the density of S100β astrocytes in subiculum at 4 months and decreased the total S100β volume at 12 months. Reduced GFAP (reactive astrocytes) levels were found in cortex at 4 and 12 months. Despite comparable plaque load and insoluble Aβ42 levels, neuritic and axonal damage was decreased in the brain of 5xFAD;*Clu-rs2279590_h2kb* mice at 12 months. Plasma NfL was also significantly decreased.
Conclusions: Despite the lack of impact on Aβ plaque deposition, humanization of 2kb of *Clu* allele and introduction of *rs2279590* risk SNP supresses astrocytic response to plaques and is protective against axonal and neuritic damage which is mirrored by the reduced levels of plasma NfL.

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P0560 / #1084

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

COMBINING AGING, GENETIC RISK AND ENVIRONMENTAL FACTORS TO IMPROVE TRANSLATIONAL VALIDITY OF ANIMAL MODELS FOR PRECLINICAL TESTING FOR ALZHEIMER'S DISEASE

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Aims: Existing animal models have been shown to have poor translational relevance for Alzheimer's disease (AD). In the MODEL-AD Consortium, our approach is to combine mouse models expressing knocked-in genetic risk variants associated with late-onset AD with environmental risk factors and aging to enable improved translational validity. Here we present a phenotypic characterization of a novel mouse model based on the combination of genetic and environmental risk factors at an extended age.
Methods: A mouse model expressing humanized Aβ and two genetic risk factors (APOE4 and Trem2*R47H) was fed a high-fat, high-sugar diet and analyzed from 4 to 24 months of age for neuropathology, biomarkers, transcriptomics and metabolomics, and *in vivo* imaging.
Results: By 12 months of age, we detected increases in insoluble Aβ42 in brain, Aβ42:Aβ40 ratio in plasma, inflammatory cytokines in brain/plasma, and NfL in CSF. Glucose uptake and cerebral perfusion changes were also detected by *in vivo* imaging with FDG and PTSM. By 18 months, we showed a decrease in hippocampal neuron number, and serum metabolomic signatures that mimic AD patients. Brain proteomics matched postmortem AD cases in myelination and post-synaptic density protein modules, and disease-relevant changes were amplified on the high-fat diet. Brain transcriptomic data exhibited enrichment for multiple AD-related pathways and also matched with synaptic, myelination and cellular stress response-associated human AMP-AD modules at advanced ages. Dense core neuritic plaques were not detected even at 24 months of age.
Conclusions: We demonstrate that combining genetic and environmental risk factors with aging may recapitulate the early stages of AD prior to significant amyloid deposition in an animal model. Therefore, this approach may have utility in the evaluation of potential prophylactic treatments for AD.

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POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

LATE-ONSET AD RISK MUTATION PICALM*H458R INITIALLY PREVENTS PLAQUE GENERATION IN 5XFAD MICE

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Aims: To understand the processes that drive late-onset Alzheimer's Disease (AD), genome-wide association studies (GWAS) have uncovered many risk loci. One of these is within the *phosphatidylinositol-binding clathrin assembly protein (PICALM)* gene, and a coding mutation has been identified (H458R) which conveys increased risk. The role of PICALM in AD has not fully defined, however, several reports have indicated that PICALM affects AD risk primarily by modulating the production, transportation, and clearance of Aβ.
Methods: We generated and crossed *Picalm*^{H465R} mice with the 5xFAD mouse model of AD, generating 4 groups: wild-type, *PICALM*^{H458R}, 5xFAD, and 5xFAD/*PICALM*^{H458R}, naming the mice based on the human variant. They were aged to 4 and 12 months, when plaque loads are being established and plateaued, respectively. Coronal brain sections were immunolabeled to visualize dense-core plaques in the subiculum and cortex. Plasma neurofilament light chain (NfL), a surrogate measure of brain damage, and soluble and insoluble Aβ levels were measured via meso scale discovery technology.
Results: 5xFAD/*PICALM*^{H458R} mice exhibit significant reduction in plaque density in both brain regions compared to 5xFAD mice at 4-month. However, at 12-month, 5xFAD/*PICALM*^{H458R} mice develop a similar level of plaques compared 5xFAD mice. Aβ40 and Aβ42 levels in the insoluble and soluble fractions of both brain regions reflect the observed plaque load at 4 and 12 months with initial reductions in 5xFAD/*PICALM*^{H458R} compared to 5xFAD mice and no difference at 12 months. Plasma NfL levels mirror the reduced brain damage at 4-month in 5xFAD/*PICALM*^{H458R} and the rise to similar level as 5xFAD at 12-month, consistent with plaque load.
Conclusions: The results indicate *PICALM*^{H458R} variant induces age-dependent effects on Aβ accumulation in 5xFAD mice, with an initial suppression of plaque genesis but ultimately leading to higher plaque burden with age.

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P0562 / #1834

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

A MODIFIED BARNES MAZE FOR AN ACCURATE ASSESSMENT OF SPATIAL LEARNING IN MICE

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Aims: The Morris water maze (MWM) and the Barnes maze (BM) are among the most widely-used paradigms for assessing spatial learning in rodents, with specific advantages and disadvantages for each apparatus. Compared with the intense water-related stress exerted during the MWM, the BM exhibits a milder light-induced stress, while suffering from biasing animals towards non-spatial strategies such as serial search, a heuristic non-spatial search strategy. To overcome this problem, we have developed a modified Barnes maze (MBM) apparatus that recapitulates natural environments more accurately without inducing undesirable exploration strategy bias.
Methods: Apparatus. A circular 122 cm-wide table with 40 randomly placed holes. One target hole is leading to an escape chamber. Task. Three target locations were examined, varying in their distance from the center. C57BL6/j male mice were given three trials per day to find the target. Following acquisition, a probe test was performed by removing the escape chamber.
Results: Spatial-encoding-depended reduction in latency to reach the target was observed, along with improvement in path efficiency with test progress. Mice tested with peripheral and distal targets outperformed mice tested with a central target. A robust exploration pattern was identified in the probe test.
Conclusions: Spatial learning in the MBM is a target-location sensitive process, providing flexibility in task difficulty. Along with overcoming biases towards non-spatial strategies, the MBM represents an improvement over the well-validated BM.

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POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

COGNITIVE AND EMOTIONAL PHENOTYPING OF TGF344-AD RATS; A RAT MODEL OF ALZHEIMER'S DISEASE

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Aims: To gain further insight into the pathology and progression of Alzheimer's disease, animal research is particularly important. Several transgenic mouse models of AD were developed, although none of them have proven successful as translational models. Rat models, on the other hand, might prove more successful, as these have higher translational potential to a clinical setting. We have used the valid TgF344-AD rat model to address cognitive and emotional symptoms in AD.
Methods: The Barnes maze was used to assess spatial learning/memory functions. Learning acquisition, short-term and long-term memory were addressed. General and focused exploration, grooming activity and immobility was assessed on the hole-board. Multivariate Temporal-pattern analysis was applied to highlight strategic behavior.
Results: We present data on learning/memory functions, using the Barnes maze; on probe day 3 primary latency was increased in AD rats, however, total latency was increased in WT rats. On probe day 10 primary latency was increased in AD rats, as well as primary errors, while time spent in target block was increased for WT on day 10. Multiple parameters were obtained on the hole-board. Decreased focused exploration represent the most significant one rating emotional anxiety-related behavior in AD rats and, furthermore, AD rats are less explorative undertaking less complex and articulated strategies.
Conclusions: Learning acquisition and long-term memory is impaired in AD rats and they accomplish more anxiety-related behavior. WT rats are more explorative and better at framing strategic thinking; e.g. performing series of choices impacted by real and perceived constraints as well as existing patterns of behavior.

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P0564 / #2339

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

A NOVEL HUMANIZED MOUSE MODEL FOR ALZHEIMER'S DISEASE

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Aims: First generation transgenic mice that overexpress human familial Alzheimer's disease (AD) mutations are a common research model. However, overexpression paradigms result in altered phenotypes that limit the model's clinical relevance. Although, second generation knock-in models have eliminated such artifacts, their murine background precludes studies of human immunity in AD.
Methods: To solve the notable dilemma of biological relevance when using a rodent immune system to study human AD immunopathology, we created a novel humanized AD mouse. These mice contained human $APP^{KM670,671NL}$, $PS1^{M146V}$, or $MAPT^{P301S}$ mutations knocked-in (KI) under an immunodeficent NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Sug}/JicTac (NOG) background. This was accomplished using CRISPR-Cas9 gene editing of endogenous replicate murine wild-type genes. Humanization was confirmed by Sanger sequencing and mice were evaluated for development of AD pathology.
Results: In $APP^{KM670,671NL\ (+/+)}$ KI NOG mice expression of chimeric APP assessed by 6E10 antibody was significantly increased compared to wild-type controls. Additionally, expression of APP-CTF-β was increased while APP-CTF-α decreased significantly with ageing in $APP^{KM670,671NL\ (+/+)}$ KI mice compared to wild-type controls. The elevated APP-CTF-β levels corelated with soluble and insoluble human $Aβ_{42}$ ELISA levels in brains of $APP^{KM670,671NL\ (+/+)}$ KI mice, and confirmed amyloid pathology development. At 10 months of age, $APP^{KM670,671NL\ (+/+)}$ KI mice showed Aβ fibril deposition in brain subregions surrounded by reactive microglia.
Conclusions: Herein, we developed a humanized KI AD mouse model that exhibits a gradual deposition of human misfolded proteins to reflect AD pathology. Crossbreeding these mice with our recently developed human interleukine-34(hIL-34-NOG) transgenic mice, will allow development of "human-like" microglia in the brain. Transplantation of haemopoietic stem cells will allow the study of human immune cell interactions with human pathological proteins, which is not possible with any existing models.

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P0565 / #2068

POSTERS: A07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

THE RHESUS MACAQUE AS AN EXPERIMENTAL MODEL FOR HUMAN AGING AND ALZHEIMER'S DISEASE PATHOLOGY

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Aims: Amyloid beta (Aβ) plaques and phosphorylated tau (P-tau) protein are well-established hallmarks of Alzheimer's disease (AD) pathology in the brain. However, progress in identifying the underlying cause of these pathological changes has been hampered by the lack of appropriate animal models for experimentation. Therefore, in the present study we used old rhesus macaque monkeys to test whether estradiol hormone replacement therapy (HRT) could delay development of Aβ and P-tau in the amygdala, a brain area that is rich in estrogen receptors.
Methods: Like women, adult female rhesus macaques show ~28-day menstrual cycles and eventually undergo menopause with similar neuroendocrine changes; and therefore represent an ideal translational animal model. In our study immunohistochemistry was performed on amygdala sections from animals aged 20-29 years of age, using specific antibodies against Aβ (4G8) and P-tau (AT8). Approximately half of the animals were subjected to 2-4 years of HRT, while the remained served as untreated controls.
Results: Aβ plaque density was especially pronounced in the untreated ovariectomized controls but not in the age-matched HRT animals. In contrast to Aβ, only one animal showed P-tau expression in the amygdala, which agrees with previous reports of P-tau expression being observed much later in life than Aβ. Interestingly, this animal was the same one that showed the highest density of Aβ plaques, suggesting a possible causal relationship between these two pathological markers.
Conclusions: Taken together, the results establish the rhesus macaque as an incomplete model for AD but with significant translation potential. Specifically, the results suggest that estradiol supplementation may significantly delay or block Aβ plaque deposition in postmenopausal women, which in turn could delay the progression of AD.

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P0566 / #696

POSTERS: A07.C. ANIMAL MODELS: NON-MAMALIAN MODELS

ZEBRAFISH AS A NEW FUNCTIONAL GENOMICS TOOL FOR ALZHEIMER'S DISEASE

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Aims: Recent studies increased the number of genes that are related to Alzheimer's disease (AD); however, their biological functions in AD pathology are largely unknown. Therefore, animal models that allow functional screens in a biologically relevant manner are required. We generated two adult zebrafish models of acute and chronic amyloid toxicity to functionally analyze the role of AD-related genes.
Methods: Acute model is generated by cerebroventricular injection of human amyloid-beta42 monomers into the cerebrospinal fluid of the adult zebrafish brain. Chronic model includes expression of amyloid beta42 open-reading frame under several promoters that delineate various cell types. By performing immunohistological analyses, electron microscopy, biophysical aggregation studies, single cell transcriptomics, gene editing, functional knockdown of candidate genes, comparison to human AD brain transcriptomics datasets, we determined the similarities of zebrafish amyloid pathology to humans.
Results: We identified that amyloid pathology in zebrafish brain is histologically and molecularly similar to that in human brains. Amyloid in zebrafish activate microglia, degenerate synapses, promote neuronal death and learning/memory deficits. Integration of single cell transcriptomics showed remarkable similarities in neurons to amyloid in humans and zebrafish. Interestingly, zebrafish brain responds to amyloidosis by enhancing neurogenesis. We identified several molecular mechanisms that underlie this pathology-induced neuroregenerative response and translated to mammalian models including rodent brains. By performing genome-wide association in AD patients, we identified that the gene FMNL2 links cerebrovascular disease and AD, by regulating the astroglial and blood vessel interactions and controlling the efficient clearance of toxic proteins from the brain.
Conclusions: Zebrafish is a new model for functional investigation of AD-related genes identified in clinical studies by providing in vivo biological knowledge on disease mechanisms, on which drug development strategies can be based.

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POSTERS: A07.C. ANIMAL MODELS: NON-MAMALIAN MODELS

A NEW FLY MODEL OF ALZHEIMER'S DISEASE UNVEILED TARGETS THAT MEDIATE COEXISTENT AB42 AND TAU TOXICITY

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Aims: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by dementia and cognitive decline due to progressive cerebral cortical atrophy. Brains of AD patients are characterized by the accumulation of microscopic extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau. The deposition of Aβ42, which is one of the fragments of amyloid precursor protein (APP), has been known to play a role in initiating the events leading to the formation of amyloid and subsequently hyperphosphorylation of tau. However, animal models expressing either Aβ42 or tau individually do not mimic the complexity of the human condition. Indeed, recent evidence suggests that Aβ42 and pathological tau interact synergistically to modulate neurotoxicity in AD.
Methods: To shed light on their concerted roles in AD pathogenesis and to discover pathways mediating Aβ42 and tau interactions, we generated transgenic flies co-expressing human Aβ42 fused to a signal peptide along with the longest wild-type tau isoform.
Results: Overexpression of Aβ42 or tau in *Drosophila* using the UAS-Gal4 system causes mild to the moderate rough eye. In comparison, co-expression of Aβ42 with tau causes severe roughening and reduction of the eye size. The level of neuronal cell death in eye tissues was also significantly enhanced in flies co-expressing Aβ42 and tau. To identify pathways mediating Aβ42+tau interactions, we are currently using the Aβ42+tau eye phenotype as platform to screen 1,500 UAS lines expressing a variety of human genes.
Conclusions: We have identified few enhancers and suppressors not previously known to be involved in AD pathogenesis, which will be helpful to uncover new molecular pathways and potential therapeutic targets. This work is supported by NIH grant R21AG069050 to DERL.

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POSTERS: A07.E. ANIMAL MODELS: OTHER

CEREBROSPINAL FLUID CIRCULATION IS IMPAIRED BY AMYLOID BETA

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Aims: Our aim was to test whether amyloid beta$_{1-42}$ peptide impairs glymphatic function acutely.
Methods: We used landrace pigs which have highly gyrified brains, similar to the human brain. We co-injected amyloid beta$_{1-42}$ peptide with a protein-based fluorescent tracer into the CSF of the cisterna magna of adult landrace pigs. We performed epifluorescence and confocal microscopy of amyloid and the CSF tracer in brain slices and light sheet microscopy of optically cleared brain tissue.
Results: We found that the tracer circulation through peri-arterial spaces was impaired by co-injection with amyloid beta$_{1-42}$. The results also showed that amyloid was retained in the peri-arterial space of pial arteries and proximally in the penetrating arterioles, despite the fluorescent tracer being several fold larger than the amyloid peptide.
Conclusions: These findings show that excess amyloid beta$_{1-42}$ peptide in the CSF can inhibit glymphatic function acutely. This suggests that soluble amyloid beta in the CSF can cause a spiral of impaired glymphatic clearance and build-up of amyloid beta in the CSF.

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P0568 / #823

POSTERS: A07.E. ANIMAL MODELS: OTHER

NEUROFILAMENT LIGHT LEVELS IN CEREBROSPINAL FLUID OF THE BEAGLE DOG INCREASE WITH AGE

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Aims: In humans, neurofilament light (NfL) chain levels and amyloid beta (Aβ) in cerebrospinal fluid (CSF) are used as biomarkers to evaluate disease progression in Alzheimer's disease. Similarly, the aged Beagle dog has previously been shown to have biomarker changes, such as changes in Aβ. The current study sought to further characterize biomarker changes in the aged dog by investigating whether NfL concentrations in canine CSF vary with age.
Methods: CSF samples from 3 age groups (young, middle-aged, and senior) were quantified for NfL, Aβ42 and Aβ40, using commercially available canine Mesoscale Discovery biomarker kits and analyzed by the MESO QuickPlex SQ. Data were analysed using the GraphPad Prism 9 statistical software.
Results: NfL chain levels increased significantly with age in Beagle dogs. The senior and middle-aged groups had significantly higher NfL chain levels in CSF compared to young. Aβ also increased with age with Aβ42 concentrations significantly higher in the senior group compared to young and Aβ40 levels significantly higher in the senior and middle-aged groups compared to young animals. However, %Aβ42 was significantly lower in the senior and middle-aged groups compared to young.
Conclusions: The age-related increases in NfL chain levels in CSF of Beagle dogs further supports the use of the aged dog as a model of Alzheimer's Disease progression. The decreases in %Aβ42 with age confirms previous findings in the aged dog, which showed %Aβ42 was inversely correlated with amyloid brain load. Additional studies will need to be conducted to determine how changes in NfL relates to other clinically relevant biomarker changes and if there is a correlation with changes in cognitive function that has been previously reported in aged dogs.

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POSTERS: A07.E. ANIMAL MODELS: OTHER

EARLY CHANGES OF BRAIN INSULIN SYSTEM IN RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE

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Aims: Recent studies of sporadic Alzheimer's disease (sAD) suggest the import role of central metabolic changes, particularly glucose hypometabolism and insulin resistant brain state (IRBS), in sAD pathogenesis. Streptozotocin (STZ) given intracerebroventricularly (icv) induces most of sAD-like pathology in rats, including IRBS whose onset is yet unclear. We explored alterations in brain insulin system in STZ-icv rat model of sAD, developed within 24h post injection.
Methods: Adult male Wistar rats were injected icv with STZ (1.5 mg/kg) or vehicle (control) and sacrificed 15 minutes, and 1, 6 and 24 hours afterwards. Protein expression of insulin receptor (IR), phosphorylated glycogen synthase kinase 3β (pGSK3β), total GSK3β (tGSK3β), phosphorylated tau proteins (pSer396, PHF13; pSer202/Thr205, AT8) and total tau (tTau) in hippocampus (HPC) and parietal cortex (PC) was measured by SDS-PAGE electrophoresis, followed by Western blot analysis. Data were analysed by Mann-Whitney U test ($p<0.05$).
Results: Fifteen minutes after STZ-icv injection only the expression of PHF13 was significantly increased in HPC (+29%) and PC (+26%). In both regions increase was more pronounced after 24h (+121% HPC, +49% PC), when also other parameters were altered in HPC; increased AT8 (+124%) and decreased IR (-34%) expression and p/tGSK3β ratio (-64%).
Conclusions: In brain IR signalling cascade, tau hyperphosphorylation is one of the earliest changes in a STZ-icv rat model, manifested in PC and HPC, persistent and later on followed additionally by upward dysfunction in IR expression and GSK3β activity only in HPC, up to 24h. These findings confirm the importance of STZ-icv model in research of early IRBS in sAD.

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P0570 / #1336

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

STRATEGIES TO DETECT TAU PROTEIN IN WASTEOSOMES (CORPORA AMYLACEA) FROM HUMAN BRAIN.

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Aims: *Corpora amylacea*, recently renamed as wasteosomes, are polyglucosan bodies that appear in the human brain during aging and some neurodegenerative conditions. They collect waste substances and are part of a brain cleaning or protecting mechanism. In this work, we aim to reveal strategies to detect tau protein in wasteosomes.
Methods: Post-mortem human hippocampal sections collected from four cases of neuropathologically confirmed Alzheimer's disease, and two cases of vascular encephalopathy were used. We applied an antigen retrieval procedure consisting of boiling the samples for 0, 10, 20, 30 or 40 min, and then performed immunohistochemistry techniques and periodic acid-Schiff staining.
Results: In the present work we show that some wasteosomes from Alzheimer's disease patients contained tau protein, while those from non-Alzheimer's disease patients did not. Moreover, we also point out a methodological problem in the immunolabeling of these structures. Although tau immunostaining requires antigen retrieval, an excessive antigen retrieval with boiling dissolves the polyglucosan structure of the wasteosomes, releasing the entrapped proteins in them and, thus, preventing their detection in wasteosomes.
Conclusions: For decades, studies on the composition of wasteosomes have produced inconsistent results, and the effect of the antigen retrieval on wasteosomes can be the origin of some of these inconsistences. To end with, it must be pointed that the different composition of wasteosomes in different patients, and the fact that wasteosomes can be collected from cerebrospinal fluid, reinforce the possible use of the wasteosomes as a possible tool for diagnosing brain disorders.

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POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

CRYO-EM STRUCTURE OF THE AMYLOIDOGENIC CORE OF IN VITRO TAU FIBRILS

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Aims: Tau is notoriously soluble and the study of *in vitro* fibril formation often uses negatively charged polymers like, heparin, polyphosphate, RNA or fatty acids, to name a few, to trigger aggregation. Recent cryo-EM structures of recombinant *in vitro* formed tau fibrils, show that they differ in polymorphism and fibril fold, from that of the structures solved using *ex vivo* filaments from patients with Alzheimer's disease (AD). This poses the question of how physiologically relevant these systems are in regard to disease. The aim of the study is to investigate if the tau AD core can be created *in vitro* using cryo-EM for validation.
Methods: We have found a fragment of tau, spanning the amyloidogenic core in AD, 304-380C322S that forms fibrils under mild *in vitro* conditions without the need of inducers. Sample optimization, blotting time/power and grid type are all parameters that greatly influence the corresponding micrographs. Well isolated and nonoverlapping fibrils are a prerequisite for downstream data processing after collecting high-resolution cryo-EM data for single particle analysis.
Results: High-resolution cryo-EM data has been collected on the fibrils formed by the fragment and data processing is currently ongoing.

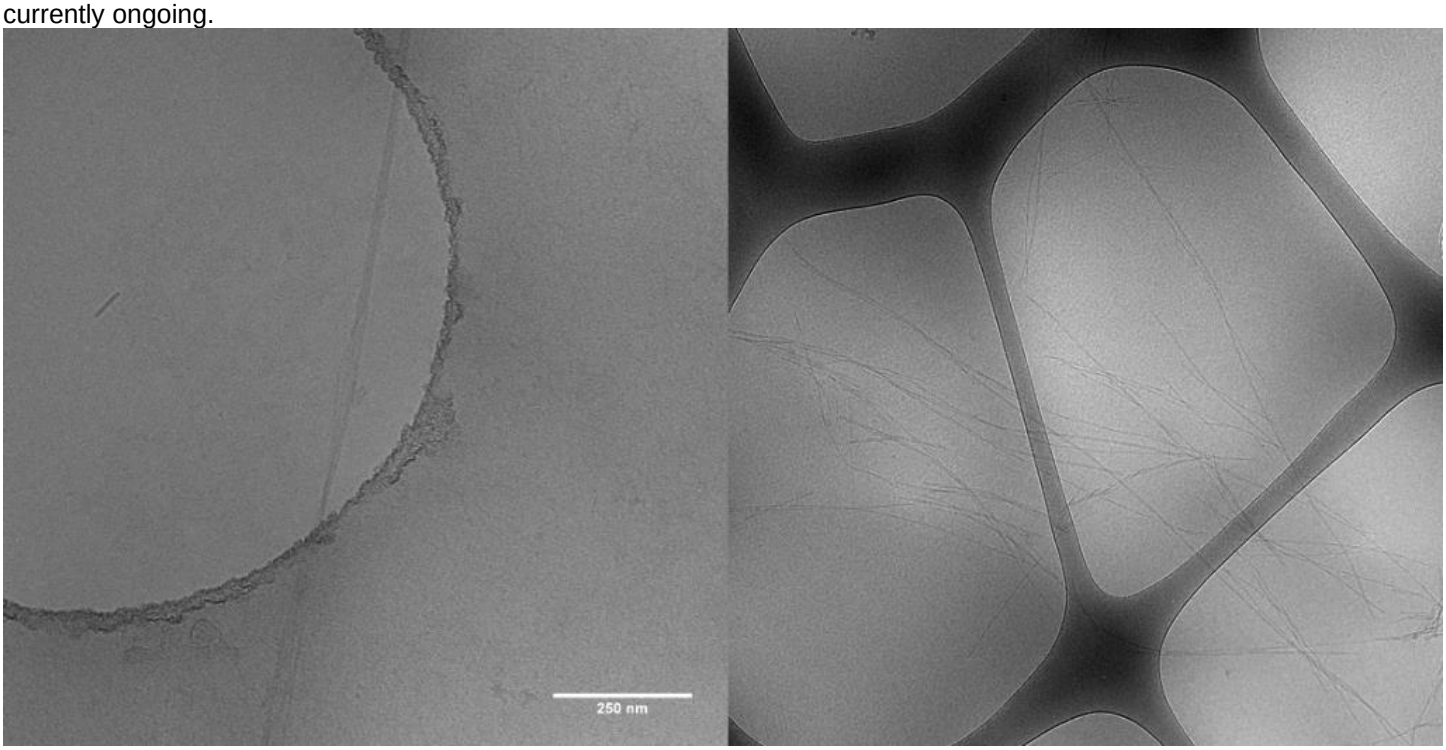

Figure 1a Figure1b Figure 1 Shows micrographs of 20 mM 304-380C322S tau in 20 mM sodium phosphate formed at 37 °C under quiescent conditions (a) on a quantifoil 1.2/1.3 grid and (b) on lacey carbon.
Conclusions: The creation of the AD tau fibril morphology *in vitro* under mild conditions has the potential to become a powerful platform on which fundamental molecular mechanisms underlying the disease can be investigated. Such a platform could also be utilized for high throughput screening for disease-modifying compounds.

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P0572 / #912

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

PARTICULATE MATTER EXPOSURE ACCELERATES TAU PATHOPHYSIOLOGY, INFLAMMATION AND COGNITIVE DEFICITS IN TAU-BIFC MICE

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Aims: Objectives Particulate matter (PM) exposure has been recognized as a critical issue and potential risk factor for health. Conventionally, the larger sized particles (PM10) have been shown to negatively influence pulmonary and cardiovascular health, leading to an inflammatory effect. The smaller sized particles, such as PM2.5, can freely pass through to blood vessels and the circulatory system, leading to direct penetration of particulate matter to the brain. Clinical investigations indicate a relationship between particulate matter exposure and brain disease, such as Alzheimer's disease (AD), in terms of neurodegeneration, inflammation and decline in cognitive abilities.
Methods: Methods To evaluate the effects of particulate matter on the brain, we utilized a direct inhalant-based exposure mechanism of particulate matter to our 6 and 12-month old Tau-BiFC mice for a three-week, 8-hour daily exposure period. The Tau-BiFC system is a fluorescence Turn-ON sensor that indicates neuronal degeneration associated with tauopathies that induce AD.
Results: Results Using a consistent, long-term daily exposure of PM2.5 led the 6-month old Tau-BiFC mice to develop early-onset tau pathology in diverse brain regions, indicating an effect of PM2.5 on the whole brain. An increased intensity in BiFC, AT8 and GFAP in hippocampal and cortical regions upon PM exposure speculates an increase in tau hyperphosphorylation and astrocytic inflammation. Further mRNA sequencing results indicate epithelial cells and astrocytes as the most affected cell types, suggesting PM penetrates the brain via blood vessels and subsequently activates astrocytes, which in turn may lead to tau pathology and disease exacerbation.
Conclusions: Conclusion PM exposure causes a rapid progression of AD-related tau-pathophysiology and inflammation indicated by increase of Tau-BiFC intensity and inflammatory markers, as well as anxiety and impaired recognition function.

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POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

THE ROLE OF PHOSPHORYLATION IN LLPS OF TAU PROTEIN IN VITRO

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Aims: Hyperphosphorylation is a key feature of tau isolated from the brains of patients with Alzheimer's disease and other tauopathies. Recent reports demonstrated that tau can undergo liquid-liquid phase separation (LLPS). Here we aim to determine the relationship between tau phosphorylation and LLPS and the effect of phosphorylation on tau aggregation within liquid droplets.
Methods: The role of phosphomimetic substitutions within different regions of tau on protein's capacity to undergo LLPS and aggregate *in vitro* was evaluated by using a combination of several methods including turbidity measurements, optical microscopy, fluorescence recovery after photobleaching, Thioflavin T fluorescence assay, and atomic force microscopy
Results: We assessed the capacity of different phosphomimetic tau441 variants to undergo LLPS by comparing their saturation concentrations. Our data show that phosphomimetic substitutions within the proline-rich domain of tau441 inhibit LLPS, whereas substitutions within the C-terminal domain promote LLPS. Furthermore, we found that phosphomimetic substitutions influence the material properties of tau441 within the condensed phase, with those in the proline-rich region and the repeat domain increasing dynamic properties of the droplets and slowing down their maturation into more rigid structures. This correlates with the aggregation kinetics of phosphomonetic tau variants within the droplets.
Conclusions: This data indicates that the phosphorylation patterns that increase the polarity of charge distribution in tau441 promote protein LLPS, whereas those that decrease charge polarity has an opposite effect. Overall, this study further supports the notion that tau LLPS is driven by attractive electrostatic interactions between oppositely charged domains.

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POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

A DROSOPHILA MODEL OF TAU ACCUMULATION IN NORADRENALINE/OCTOPAMINE NEURONS

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Aims: Locus coeruleus (LC), a major noradrenergic (NA) nucleus located in the brainstem, is one of the earliest regions affected by Alzheimer's disease (AD). LC-NA neurons have a variety of functions including cognition, sleep, emotion, and stress responses, which are severely affected in AD. Neurofibrillary tangles composed of abnormally hyperphosphorylated tau proteins are a neuropathological hallmark of AD. LC is an initial site accumulates hyperphosphorylated tau proteins and undergoes neuronal loss in AD, suggesting that abnormality in LC initiates AD pathogenesis. However, mechanisms underlying tau accumulation and toxicity in LC-NA neurons remain unclear. To elucidate these questions, we utilized *Drosophila* as a genetic model system.
Methods: In *Drosophila*, the functional counterpart of noradrenaline is octopamine. We generated a transgenic fly expressing human tau in fly octopamine neuron, and analyzed lifespan, sleep, tau accumulation with aging and pathology-related phosphorylation of tau.
Results: The flies expressing human tau in octopaminergic neurons showed shortened lifespan and reduced amount of sleep time. Tau proteins expressing octopaminergic neurons accumulated with age and the phosphorylation levels of tau at AD-related sites were increased. We also found that activation of octopamine neurons reduced sleep and increased tau accumulation.
Conclusions: This study demonstrate that the reduction of sleep may be involved in tau accumulation in noradrenergic neurons. This fly model is a useful tool to elucidate mechanisms underlying tau accumulation/toxicity and sleep disturbance.

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POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

HIGH-THROUGHPUT CELL-BASED ASSAY IDENTIFIES TAU AGGREGATION INHIBITORS

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Aims: Tauopathies are characterized by the ordered assembly of soluble, intrinsically disordered Tau into insoluble, β-rich amyloid fibrils. Tau aggregation can be modeled by biosensor cell lines. In cellula, Tau aggregates can be induced by adding exogenous Tau seeds like heparin-free Tau fibrils. This study aimed to optimize cell-based high-throughput assays for Tau biosensor cells to identify small molecules which inhibit Tau aggregation.
Methods: HEK 293T Tau biosensor cell lines were generated that stably express a mutated repeat domain of Tau, carboxy-terminally tagged with GFP. To screen for small molecules with an inhibitory effect on Tau aggregation, a 384-well format high-throughput assay was optimized for automated confocal microscopy and image analysis. Cells were exposed to Tau seeds of different origins and the aggregation of expressed Tau was monitored. Selected compounds were further tested for broad anti-amyloid effects.
Results: One compound was identified that potently reduced the number of cells with aggregates induced by recombinant Tau fibrils. An inhibitory effect was also observed when Tau misfolding was induced with Tau aggregates from different sources, including extracellular vesicles containing misfolded Tau. Inhibition of protein aggregation was not restricted to Tau, as the compound had similar effects on the fibril-induced aggregation of the Sup35 prion domain expressed in mammalian cells. Experiments are ongoing to test derivatives with an increased blood-brain barrier penetrance.
Conclusions: In summary, by using different cellular models of protein aggregation, we identified novel small molecules with anti-amyloid activity. Our assay is a strong tool to pre-select compounds that inhibit seed-induced cytosolic amyloid formation and can be further tested in animal models.

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POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

CELLULAR POLYAMINES CONDENSE HYPERPHOSPHORYLATED TAU TRIGGERING ALZHEIMER'S DISEASE

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Aims: We examine the intermolecular interactions between the tau protein in its native and hyperphosphorylated forms and the cellular polyamine spermine to probe the possibility of the two undergoing liquid-liquid phase separation.
Methods: We performed microsecond-long all atom molecular dynamics simulations on four model tau systems: two phosphorylated and two unmodified, two with spermine and two without spermine. From our simulations, we calculated the radial distribution function of spermine around tau, the propensity of tau to form bridging interactions between different protein chains, the diffusion coefficient of spermine around tau, and the enthalpy of spermine – tau interactions (using the MM-GBSA method).
Results: We find that spermine positions itself away from native tau into bulk solvent. Conversely, with hyperphosphorylated tau, spermine exhibits the opposite behavior, making extensive interactions with the proteins' posttranslationaly modified residues. Spermine also enhances the bridging interactions between different tau chains. We find that the polyamine becomes nearly 100-fold less mobile around phosphorylated tau than unmodified tau, and characterize the energetics underpinning the drastically different behaviors of the phosphorylated and unmodified systems.
Conclusions: We describe extensive molecular dynamics simulations and analysis on physiologically relevant model systems, which suggest that it is not positively charged, unmodified tau that is condensed by cytosolic polyanions but negatively charged, hyperphosphorylated tau that is condensed by cytosolic polycations. Our work has broad implications for anti-Alzheimer's research and drug development and the broader field of tauopathies in general, potentially paving the way to future etiologic therapies.

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P0577 / #1919

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

THE ROLE OF THE CUL3 ADAPTOR PROTEIN SPOP IN TAU PROTEOSTASIS

Randall Eck, Rebecca Kow, Nicole Liachko, Brian Kraemer
University of Washington, Medicine, Seattle, United States of America

Aims: The pathological accumulation of the microtubule binding protein tau drives age-related neurodegeneration in a variety of disorders, collectively called tauopathies. Here we aim to explore the role of nuclear speckles in tauopathy disorders.
Methods: We employed classical forward genetic approaches and identified multiple loss of function alleles in the *C. elegans spop-1 g*ene that ameliorate tauopathy, suggesting SPOP is required for tau mediated neurodegeneration. CRISPR based genome editing methodology enabled the generation of customized *SPOP-1* loss of function and null alleles. Molecular genetics, behavioral, neuronal reporter assays, and biochemical analyses were also employed to characterize the consequences of *spop-1* loss of function on tauopathy related phenotypes in model systems.
Results: Knockout of SPOP-1 rescues tau mediated behavioral deficits caused by neuronal dysfunction in tau transgenic *C. elegans.* Biochemical analysis revealed that SPOP-1 loss of function promotes clearance of phosphorylated and total tau species from *C. elegans* neurons, but no change in tau transgene mRNA levels. Tau transgenic animals exhibit obvious neurodegeneration of GABAergic neurons, but loss of *spop-1* rescues neurodegeneration. While SPOP functions as an CUL3 E3 ligase adaptor protein, CUL3 function is not required for SPOP loss of function rescue of tauopathy. Genetic epistasis analysis suggests the nuclear speckle resident poly(A) RNA binding protein *sut-2* and *spop-1* function in a parallel molecular pathway.
Conclusions: SPOP is a novel modifier of tauopathy phenotypes. Combined with previous findings investigating ALYREF, PARN/TOE1, SUT-1 and SUT-2/MSUT2, this work suggests phase-separated nuclear speckles are an important cellular site controlling susceptibility to pathological tau. Recent work showing SPOP modification of PR dipeptides derived from C9orf72 expansion suggests common pathways may be at work in the neurodegenerative molecular mechanisms of tauopathy and repeat dipeptides.

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P0578 / #2268

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

MATHEMATICAL MODELLING REVEALS RATE-DETERMINING PROCESSES IN PROTEIN AGGREGATION IN VIVO.

Georg Meisl[1], Jiapeng Wei[1], Shih-Huan Huang[1], Eric Hidari[1], Catherine Xu[2], Sarah Devos[3], Justin Sanchez[4], Timothy Rittman[5], Adriano Aguzzi[6], Christina Sigurdson[7], Keith Johnson[8], James Rowe[9], Sara Linse[10], Bradley Hyman[11], David Klenerman[12], Tuomas Knowles[1]
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Aims: The molecular mechanisms that underlie the process of protein aggregate formation have been studied in detail under controlled in vitro conditions. However, connecting the fundamental physical properties of protein self-assembly to the formation and proliferation of protein aggregates in the brains of affected individuals remains a key challenge in the field. The aim is to use first-principle-based mathematical models to both analyse in vivo data and use simulations bridge the gap between the test tube and living systems.
Methods: Starting from a knowledge of the underlying physics, we build coarse-grained mathematical models that are able to describe the temporal and spatial distribution of aggregates in the brains of lab animals and human patients, linking back to the underlying molecular processes (Meisl et al. arXiv 2008.09699).
Results: Our minimal models not only provide a qualitative understanding of the ranges of possible behaviors but also allow quantification of the relative importance of different classes of processes in protein self-assembly (Meisl et al. Sci. Adv. 7:eabh1448, Meisl et al. Nature Struc Mol Biol 28:365). In particular, the ability of protein aggregates to self-replicate emerges as a central property across systems, with a strong link between the rate of self-replication in test tube experiments and involvement in disease (Meisl et al. Sci Adv 8:eabn6831).
Conclusions: The application of our models can identify the rate-limiting process in the appearance of tau aggregates in Alzheimer's disease, establish the mechanism of prion self-replication in mice and allow quantitative comparison of the rates of these processes between different systems.

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P0579 / #2082

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

STRUCTURAL MAPPING TECHNIQUES DISTINGUISH THE SURFACES OF FIBRILLAR 1N3R AND 1N4R HUMAN TAU

Virginie Redeker, Emilie Caroux, Karine Madiona, Ronald Melki
Laboratory of Neurodegenerative Diseases, CNRS UMR9199, Mircen, Cea, Fontenay-aux-Roses, France

Aims: The rigid core of intracellular tau filaments from Alzheimer's disease (AD), Pick's disease (PiD) and Cortico-basal disease (CBD) brains have been shown to differ by cryo-EM. To complete structural information of tau fibrillar assemblies and provide insights into the surfaces that define their interactions with numerous cellular components, we mapped the surfaces of two distinct *in vitro* assembled tau fibrils, previously shown to produce traffic between neurons and impair the distribution of synaptic membrane receptors.
Methods: Using proteomic approaches such as proteolysis and molecular covalent painting, we mapped the amino acid stretches exposed at the surface of *in vitro*-assembled fibrils from htau containing one N-terminal domain and three (1N3R) or four (1N4R) C-terminal microtubule-binding repeat domains. We also mapped those constituting the fibrillar core of the fibrils.
Results: Limited proteolysis provided proteolytic fragments composing the molecular "bar-code" for each type of 1N3R and 1N4R htau fibrils. Covalent molecular painting identified amino acid stretches exposed at the surface of these fibrils. Our results demonstrate that the structure of full-length 1N3R and 1N4R htau fibrils differs from that reported for 2N3R and 2N4R htau fibrils assembled in the presence of heparin, and are in agreement with structural data reported for tau filaments from AD, PiD, and CBD cases predigested with the pronase. Finally, we report two amino acid stretches belonging to the fuzzy coat of tau fibrils (118-133; 381-402) that distinguish the surfaces of these two kinds of fibrils.
Conclusions: The differences in surface accessibility we report (doi: 10.1016/j.jbc.2021.101252) suggest for the first time a contribution of the so-called fuzzy coat to distinct fibrillar polymorphs intrinsic organization, and open new perspectives for the design of highly specific ligands with diagnostic and therapeutic potential.

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P0580 / #2257

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

LOCUS COERULEUS PATHOLOGY DIFFERS IN ALZHEIMER'S DISEASE, DOWN SYNDROME AND COVID-19 CONTROL CASES

Hannah Saternos[1], Elisabet Englund[2], Eric Hamlett[3], Steven Carroll[3], Elizabeth Head[4], Elliott Mufson[5], Ann-Charlotte Granholm[1], Aurelie Ledreux[1]
[1]University of Colorado Denver Anschutz Medical Campus, Neurosurgery, Aurora, United States of America, [2]Division of Pathology,, Dept Of Clinical Sciences Lund, Lund, Sweden, [3]MUSC, Department Of Pathology & Laboratory Medicine, Charleston, United States of America, [4]University of California Irvine, Department Of Pathology And Laboratory Medicine, Irvine, United States of America, [5]Barrow Neurological Institute, Neurology, Phoenix, United States of America

Aims: Aging and neurodegenerative disorders are associated with a loss of noradrenergic (NA) neurons of the pontine nucleus locus coeruleus (LC). The LC is the first brain region to show tau pathology in Alzheimer's (AD). While AD is the most common form of dementia, adults with Down syndrome (DS) experience "accelerated aging" as more than half develop dementia symptoms by age 50. Tau aggregation and amyloid deposits are hallmarks disease progression; however the relationship between tau tangle stages and amyloid beta plaques or glial reactivity has not been directly investigated. Here we present findings on the relationship of tau markers, oligomeric tau (TOC1), pretangle (pS422), early tangle (T231), and late-stage tangle (AT8) to each other, amyloid beta plaques (6e10) and glial reactivity in the LC as well as preliminary evidence from confirmed COVID-19 *postmortem* cases.
Methods: We utilized immunofluorescent techniques to investigate neuropathological changes in adult human brain tissue. These findings were derived using *postmortem* brain tissue from adults with AD, DSAD, and controls with and without severe COVID-19.
Results: We found statistically significant moderate correlations between tau antibodies that label different isoforms or epitopes of p-tau but low correlations to amyloid beta. Significant group and sex differences were observed in both amyloid beta and tau immunostaining. Further, glial morphology notably differed between all groups.
Conclusions: This evidence suggests that tau and amyloid beta immunostaining were minimally correlated within the LC. Our results show that tau correlates with altered glial localization, differences in morphology, and distinct patterns of neurodegeneration between groups. COVID-19 exacerbated AD-like pathology in DSAD and AD cases, while tau aggregation might appear earlier in healthy individuals with COVID-19 compared to age-matched controls. Funded by BrightFocus Foundation CA2018010 and NIH R01AG070153.

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P0581 / #323

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

A NOVEL ROLE OF TAU PROTEIN IN CHRONIC PAIN-DRIVEN HIPPOCAMPAL PATHOLOGY AND MEMORY DEFICITS

Anastasia Vamvaka-Iakovou[1,2], Sara R. Guerreiro[3], Marco R. Guimaraes[3], Joana Silva[3], Chrysoula Dioli[1,3], Patricia Gomes[3], Anastasia Megalokonomou[1], Carlos Campos-Marquez[3], Ana Cunha[3], Armando Almeida[3], Nuno Sousa[3,4], Hugo Leite-Almeida[3], Ioannis Sotiropoulos[1,3]
[1]NCSR, Demokritos, Institute Of Biosciences & Applications, Agia Paraskevi, Greece, [2]University of Ioannina, Department Of Biological Applications & Technology, Ioannina, Greece, [3]Life and Health Sciences Research Institute, University of Minho, School Of Medicine, Campus De Gualtar, Braga, Portugal, [4]Clinical Academic Center (2CA), Clinical Academic Center (2ca), Braga, Portugal

Aims: Persistent pain has been recently suggested as a risk factor for dementia. Indeed, chronic pain is frequently accompanied by maladaptive brain plasticity and cognitive deficits whose molecular underpinnings are poorly understood. Despite the emerging role of Tau as a key regulator of neuronal plasticity and pathology in diverse brain disorders such as Alzheimer´s disease, the role of Tau has never been studied in the context of chronic pain.
Methods: For modelling chronic pain, we used spared nerve injury (SNI) model of peripheral (sciatic) neuropathy in 5 months-old wild-type (WT) and P301L-Tau transgenic mice. Furthermore, in order to unravel the mediating role of Tau in the pain-evoked hippocampal deficits, we performed SNI in Tau knockout and their WT littermates. Molecular understanding experiments also included the analgesic drug, gabapentin or virus-driven overexpression of Rab35, a regulator of Tau degradation.
Results: Our findings showed that SNI triggers AD-related neuropathology characterized by Tau hyperphosphorylation, accumulation, and aggregation in hippocampus followed by neuronal atrophy and memory deficits. Molecular analysis suggests that SNI inhibits autophagy and reduces levels of the Rab35, a regulator of Tau degradation while overexpression of Rab35 or treatment with an analgesic drug reverted the above molecular changes leading to neurostructural and memory recovery. Interestingly, the absence of Tau blocks the SNI-induced hippocampal deficits related to neuronal atrophy and related memory impairment supporting the mediating role of Tau in SNI-evoked hippocampal pathology and memory impairment.
Conclusions: Our findings reveal that exposure to chronic pain triggers Tau-related neuronal pathology in hippocampus and may be relevant for understanding how chronic pain precipitates memory loss leading to dementia.

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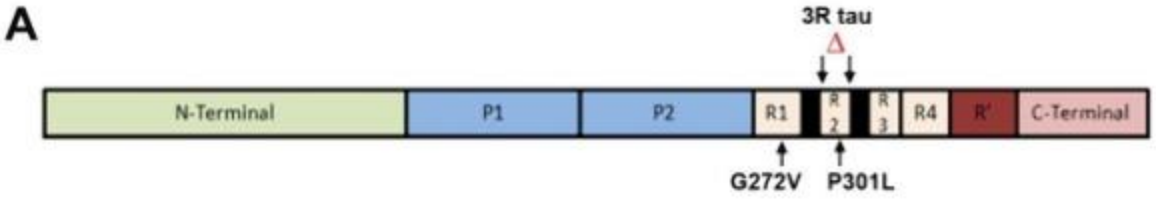
P0582 / #2266

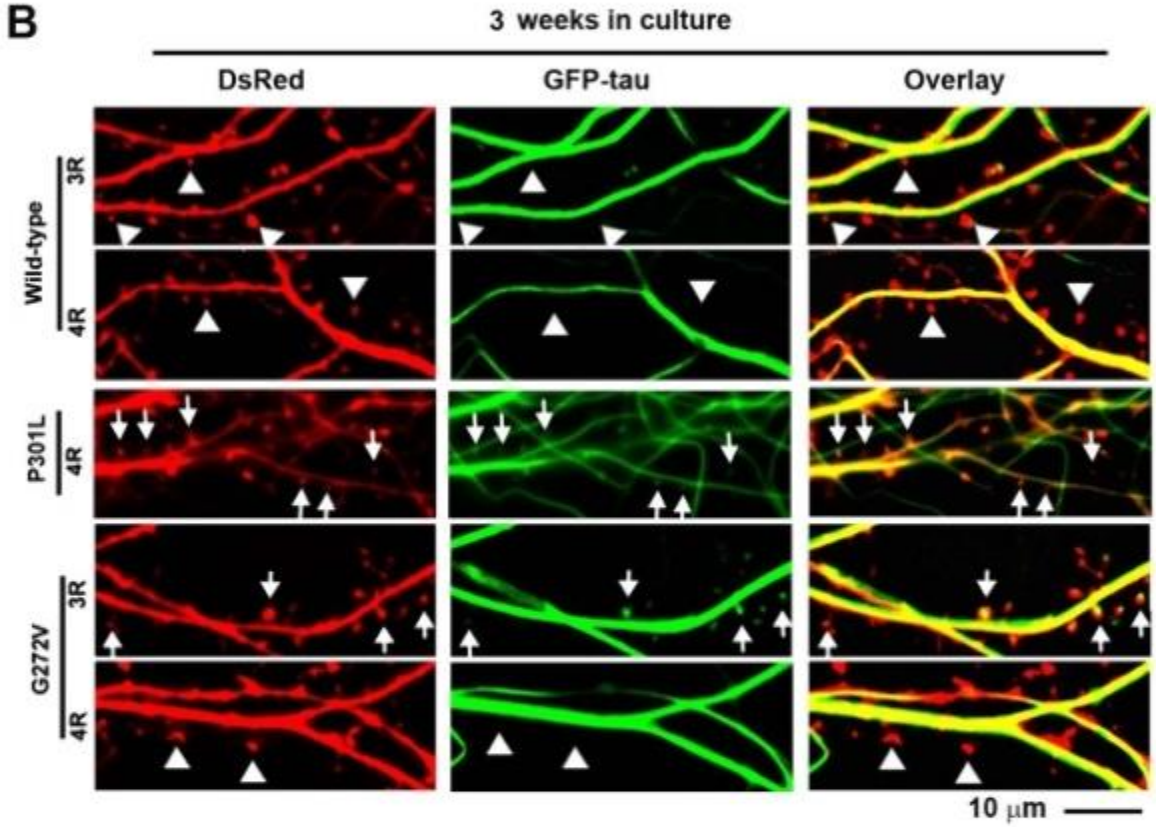
POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

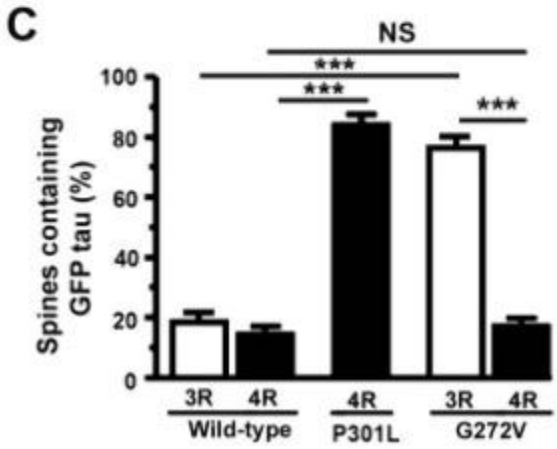
P301L AND G272V MUTATIONS INDUCE ISOFORM SPECIFIC TAU MISLOCALIZATION TO DENDRITIC SPINES AND SYNAPTIC DYSFUNCTIONS IN CELLULAR MODELS OF 4RTAU FTDP-17 AND FAMILIAL PICK'S DISEASE

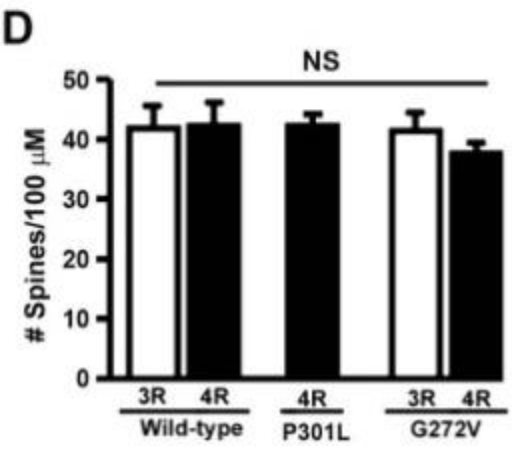
Katherine Yao[1], Ke Yu[2], Jessica Choquette[1], Dezhi Liao[1]
[1]University of Minnesota, Department Of Neuroscience, Minneapolis, United States of America, [2]The General Hospital of Western Theater Command, Department Of General Practice, Chengdu, China

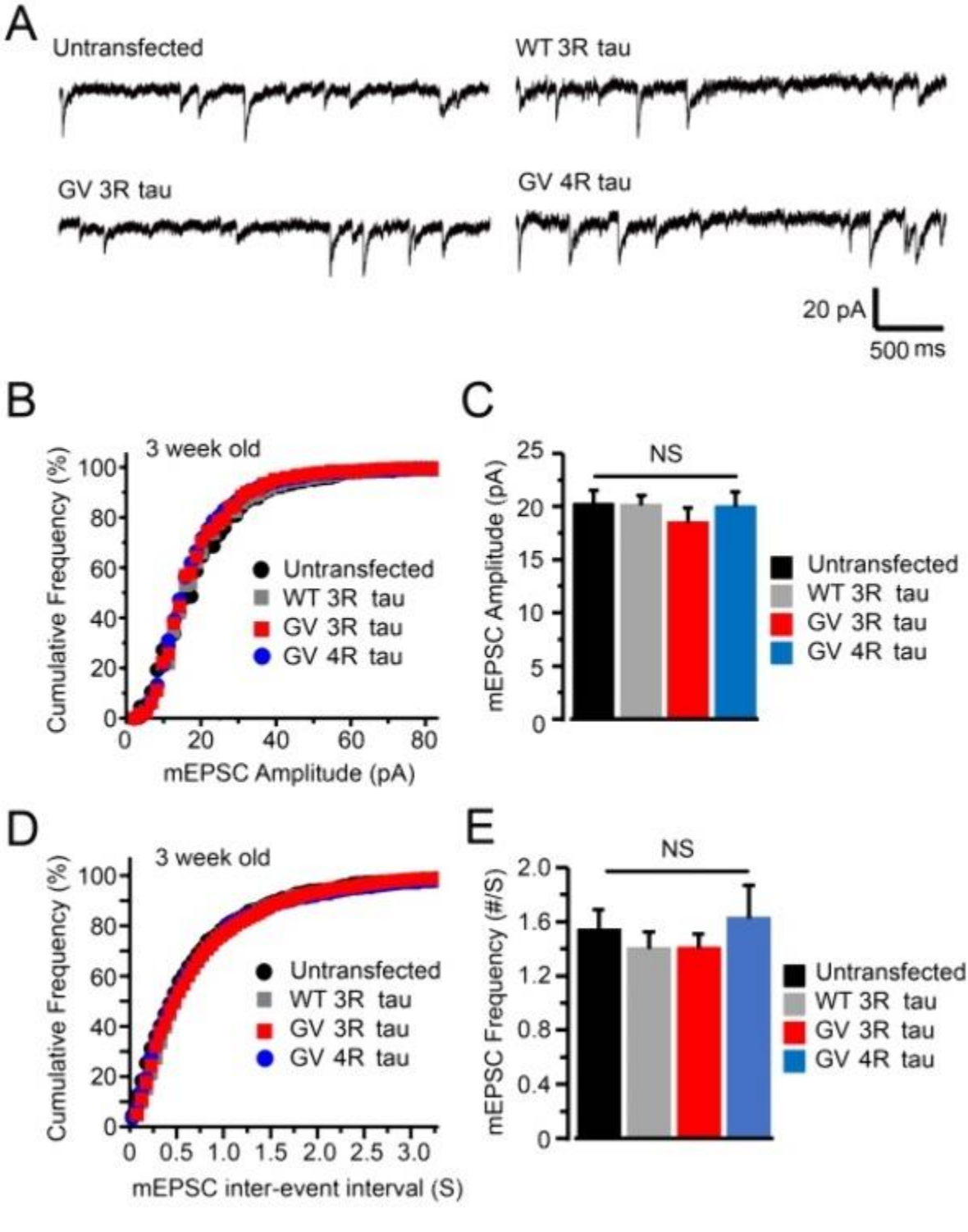
Aims: There has been no systematic comparison between the roles of the 6 tau isoforms in pathophysiology of dendritic spines. Here, we distinguish the role of 3R and 4R tau isoforms in postsynaptic deficits caused by disease linked mutations in tau.
Methods: Miniature excitatory postsynaptic currents (mEPSCs) were recorded from cultured dissociated rat hippocampal neurons at 19-24 DIV or 33-36 DIV. Additionally, images of both GFP and DAPI were taken in the same neuron expressing GFP-tagged tau proteins. Asymmetric aggregation of tau was quantified.
Results: The P301L mutation, linked to familial 4R tau FTD, induces mislocalization of 4R tau to dendritic spines. Contrastingly, the G272V mutation, linked to familial Pick's disease, induces phosphorylation dependent mislocalization of 3R tau but not 4R tau proteins to dendritic spines in primary rat hippocampal cultures. The mislocalization of 3R tau requires the activation of two tau kinases, GSK3β and CDK5. The overexpression of G272V mutant 3R tau, but not 4R tau proteins, leads to the reduction of dendritic spine density and suppression of mEPSCs in 5-week-old primary rat hippocampal cultures. It also leads to the formation of Pick's body-like structures adjacent to the nucleus.
Conclusions: The reported isoform specificity of tau mislocalization, synaptic dysfunction and asymmetric tau aggregation next to the nucleus provides a plausible cellular mechanism underlying the distinct pathohistological differences between 4R tau FTD and familial Pick's disease. The temporal difference between 3R and 4R tau-mediated synaptic deficits here provides a new neurobiological basis for the difference between disease progression of human 3R and 4R tauopathies. The phosphorylation dependent 3R mislocalization will help us better understand the pathobiology of AD and CTE as both diseases exhibit concurrent aggregates of highly phosphorylated 3R and 4R tau proteins.

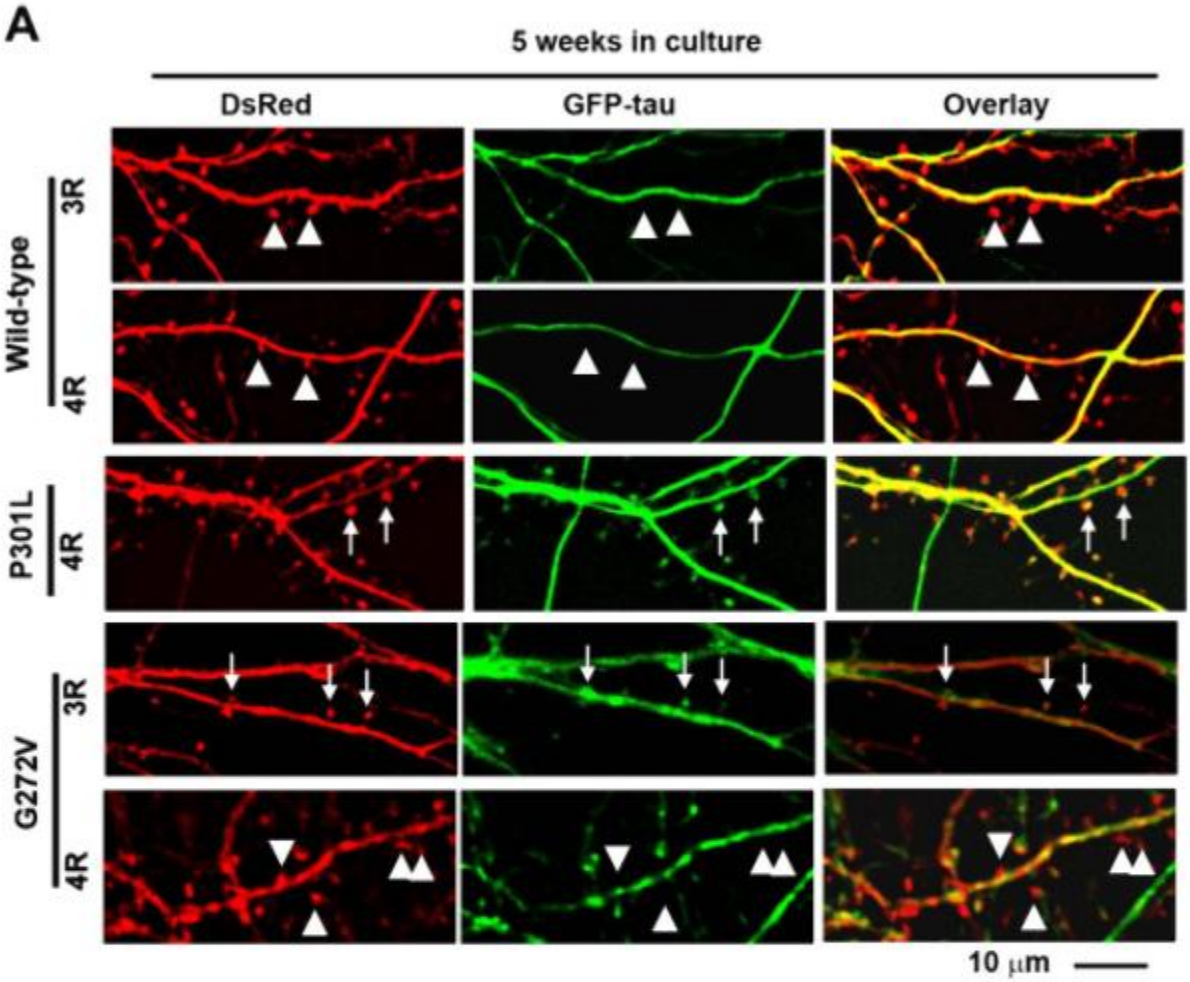

A
3R tau
Δ
N-Terminal
P1
P2
R1
R 2
R 3
R4
R'
C-Terminal
G272V
P301L

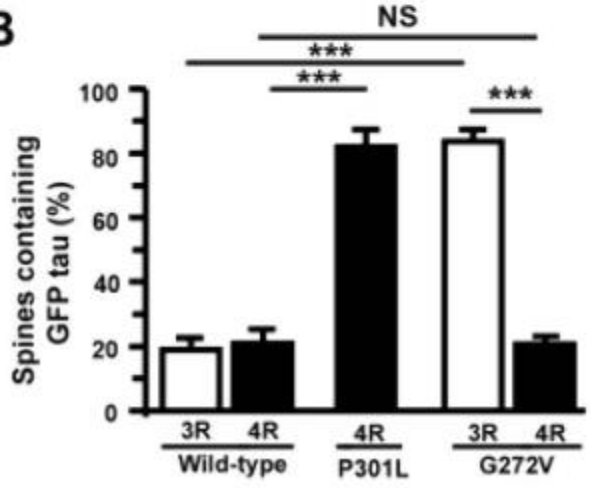

B
3 weeks in culture
DsRed
GFP-tau
Overlay
Wild-type
3R
4R
P301L
4R
G272V
3R
4R
10 μm

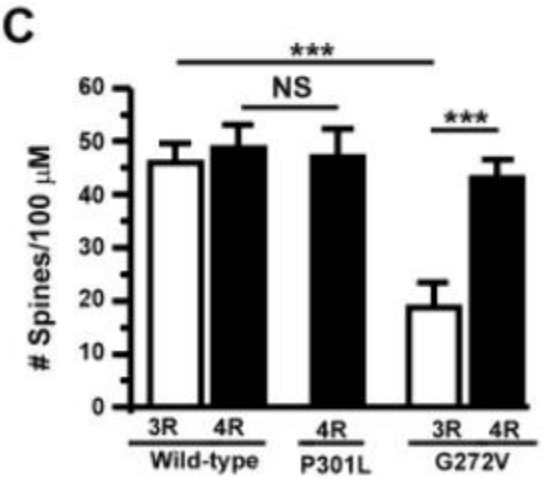

C
NS
***
***
***
Spines containing GFP tau (%)
100
80
60
40
20
0
3R
4R
Wild-type
4R
P301L
3R
4R
G272V

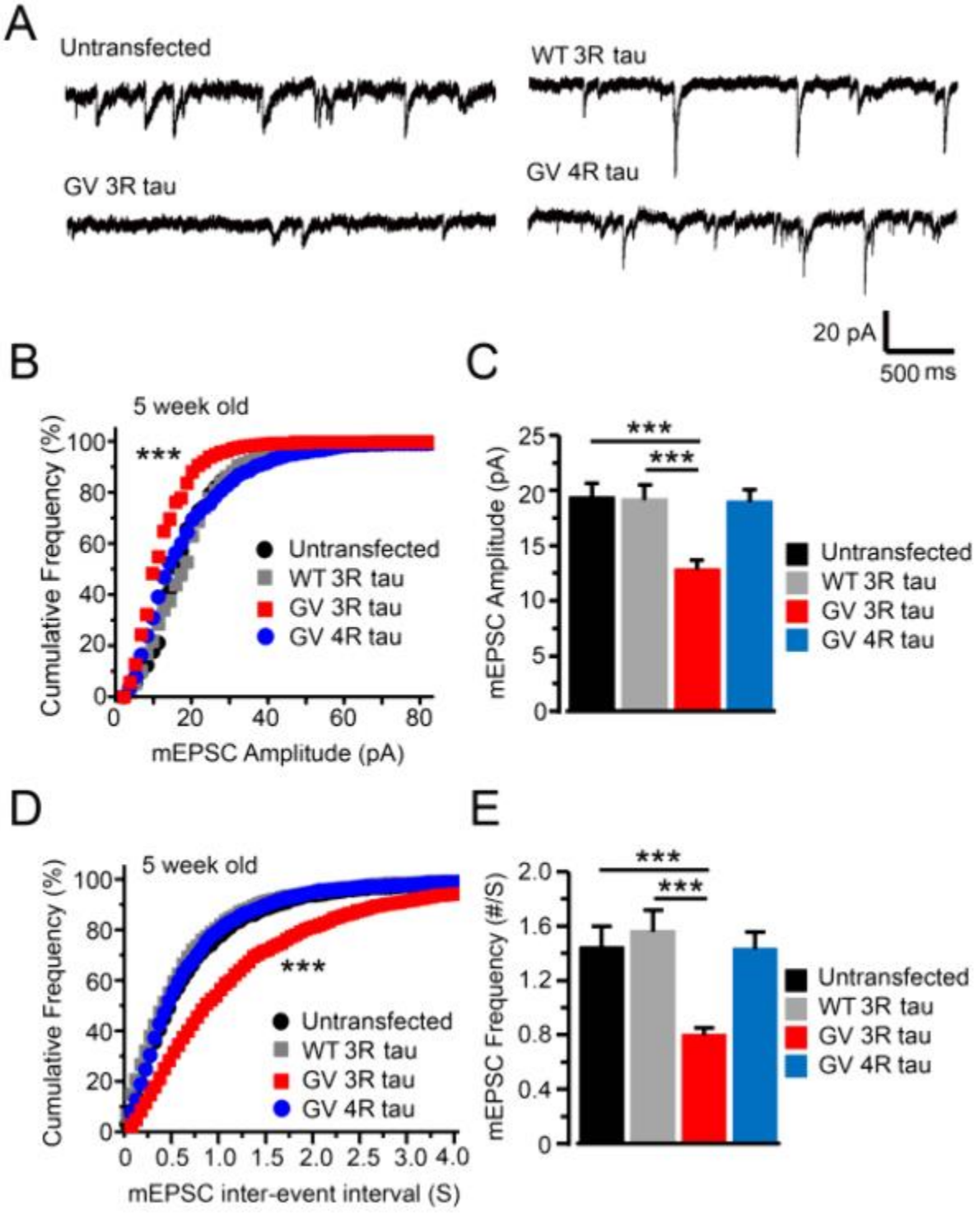

D
NS
Spines/100 μM
50
40
30
20
10
0
3R
4R
Wild-type
4R
P301L
3R
4R
G272V

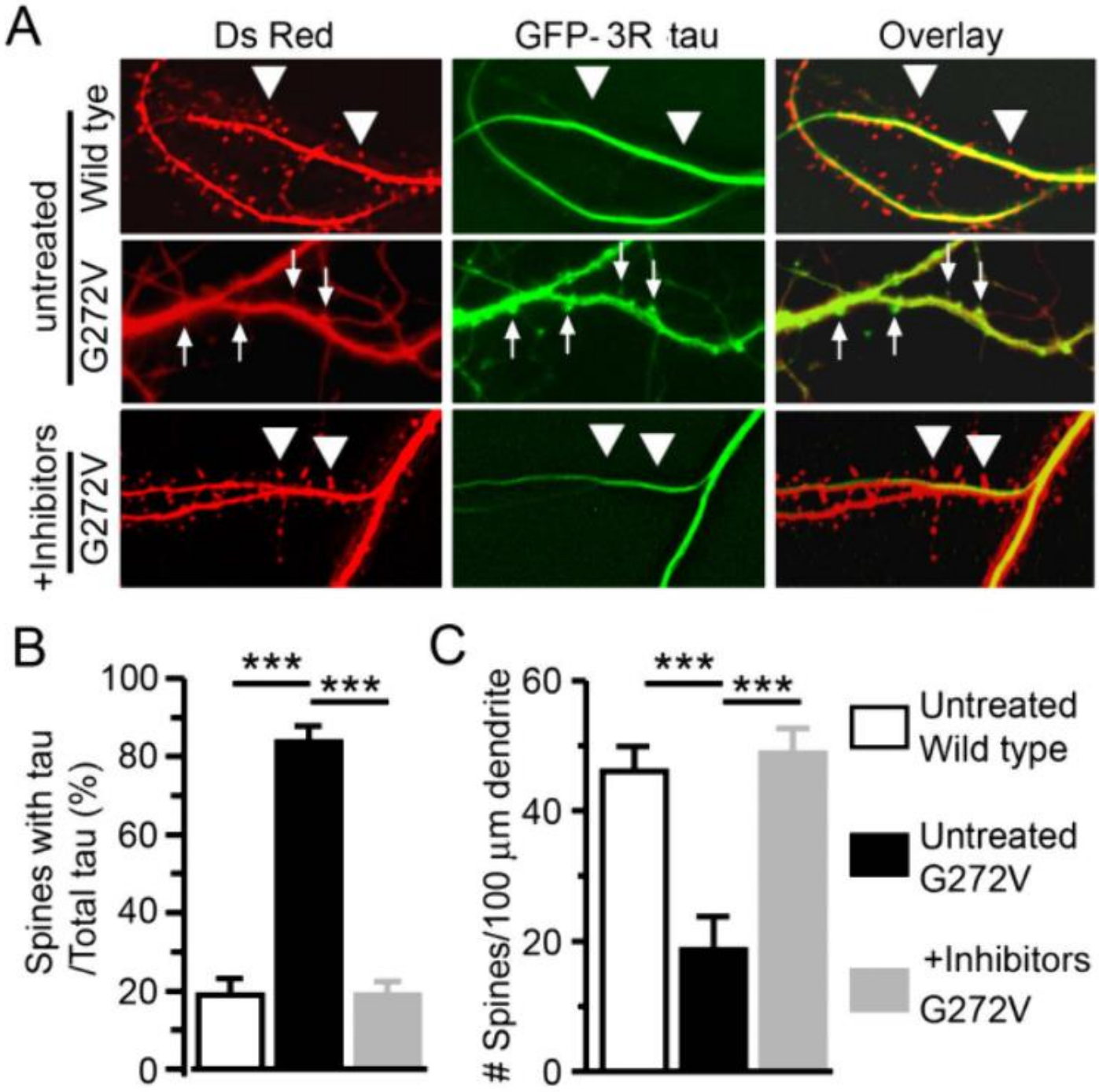

A
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
20 pA
500 ms
B
3 week old
Cumulative Frequency (%)
mEPSC Amplitude (pA)
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
C
NS
mEPSC Amplitude (pA)
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
D
3 week old
Cumulative Frequency (%)
mEPSC inter-event interval (S)
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
E
NS
mEPSC Frequency (#/S)
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau

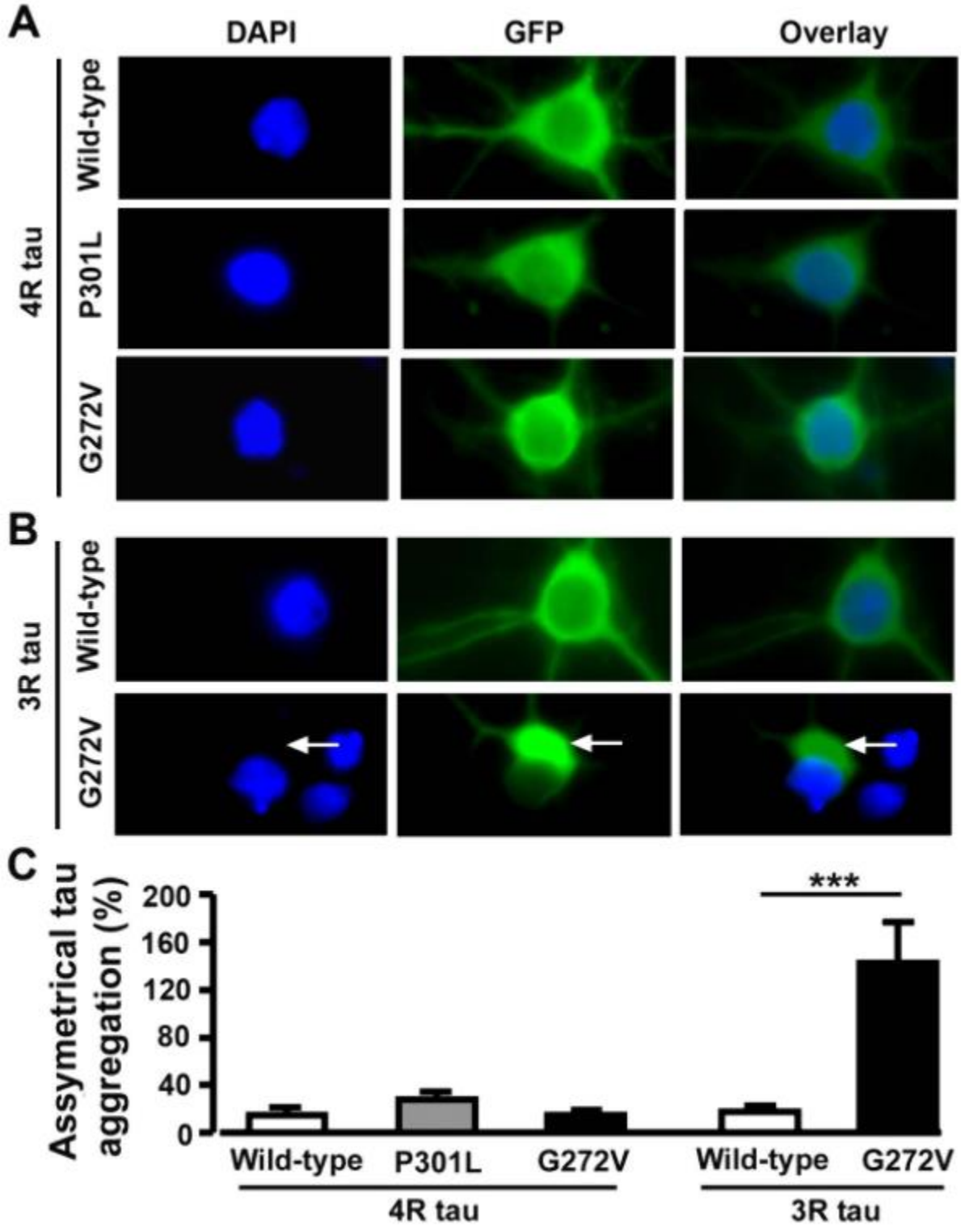

A
5 weeks in culture
DsRed
GFP-tau
Overlay
Wild-type
3R
4R
P301L
4R
G272V
3R
4R
10 μm

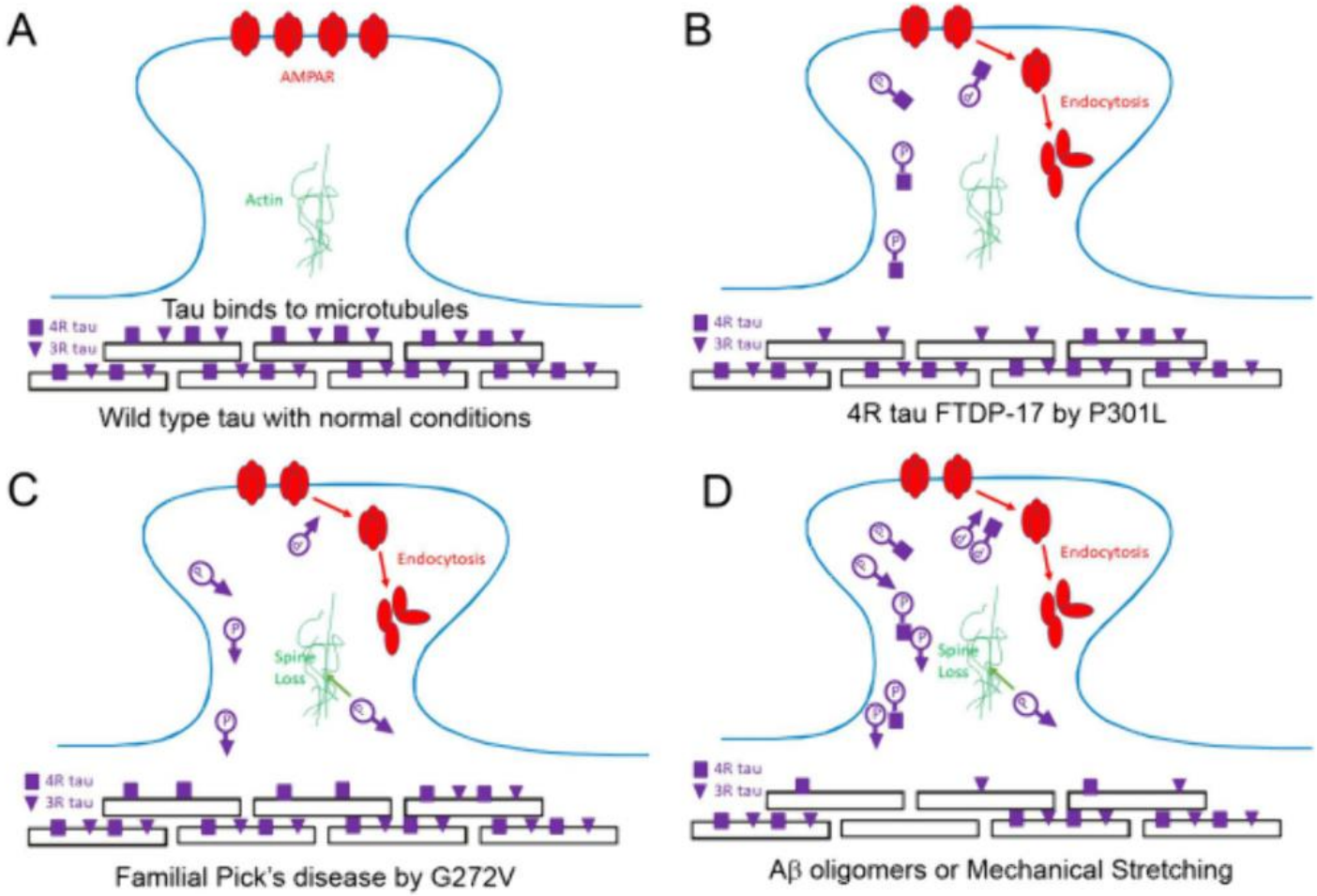

B
NS
***
***
***
Spines containing GFP tau (%)
100
80
60
40
20
0
3R 4R
Wild-type
4R
P301L
3R 4R
G272V


C
***
NS
***
Spines/100 μM
60
50
40
30
20
10
0
3R 4R
Wild-type
4R
P301L
3R 4R
G272V


A
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
20 pA
500 ms
B
5 week old
Cumulative Frequency (%)
***
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
mEPSC Amplitude (pA)
C
mEPSC Amplitude (pA)
***
***
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
D
5 week old
Cumulative Frequency (%)
***
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau
mEPSC inter-event interval (S)
E
mEPSC Frequency (#/S)
***
***
Untransfected
WT 3R tau
GV 3R tau
GV 4R tau


A
Ds Red
GFP- 3R tau
Overlay
untreated
Wild tye
G272V
+Inhibitors
G272V
B
Spines with tau
/Total tau (%)
100
80
60
40
20
0
***
***
C
Spines/100 µm dendrite
60
40
20
0
***
***
Untreated
Wild type
Untreated
G272V
+Inhibitors
G272V


A
DAPI
GFP
Overlay
4R tau
Wild-type
P301L
G272V
B
3R tau
Wild-type
G272V
C
Assymetrical tau aggregation (%)
200
160
120
80
40
0
***
Wild-type
P301L
G272V
Wild-type
G272V
4R tau
3R tau


A
AMPAR
Actin
Tau binds to microtubules
4R tau
3R tau
Wild type tau with normal conditions
B
Endocytosis
4R tau
3R tau
4R tau FTDP-17 by P301L
C
Endocytosis
Spine
Loss
4R tau
3R tau
Familial Pick's disease by G272V
D
Endocytosis
Spine
Loss
4R tau
3R tau
Aβ oligomers or Mechanical Stretching

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P0583 / #2645

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

MODELING CYTOSOLIC ENTRY AND SEEDED AGGREGATION OF TAU IN 2D AND 3D STEM-CELL DERIVED MODELS.

Kimberly Cheam[1], William Mcewan[2]
[1]University of Cambridge, Department Of Clinical Neurosciences, University Of Cambridge, Cambridge, United Kingdom, [2]UK Dementia Research Institute, Department Of Clinical Neurosciences, University Of Cambridge, Cambridge, United Kingdom

Aims: Tau aggregation can be initiated when tau assemblies impart their misfolded structure onto endogenous tau in a process referred to as “tau seeding”. Extracellular assemblies of tau must gain entry to the cytosol to initiate seeded aggregation. Primary neurons and immortalised cell lines have provided valuable insights into our understanding of tau spreading in tauopathies. However, these cellular models cannot fully recapitulate most aspects of human disease due to genetic heterogeneity. We aim to develop iPSC-based models to understand tau spreading and aggregation.
Methods: Human iPSC-derived cortical neurons and brain organoids were derived through NGN2 overexpression and directed-differentiation using small molecules respectively. Cells were exposed to seed-competent tau derived from various recombinant and brain-origin sources. Mature organoids were thinly sliced and grown on membrane inserts. Entry assays were performed using tau-HiBiT which complemented cytosolic LgBiT. Immunocytochemistry was used to detect seeded aggregation.
Results: Tau aggregation differs between the cellular models.AT8-positive structures were detected in organoid slice cultures in a manner that was dose-dependent on supplied tau assemblies. Within the 2D cortical neurons, there was likewise a dose-dependent induction of seeded aggregation. However, in these cells, seeded aggregation was accompanied by neuronal death.
Conclusions: Cytosolic entry of tau and its seeded aggregation can be modeled using iPSC-based systems. Neurons in 2D iPSC-derived cultures and sliced 3D organoids accumulate hyperphosphorylated inclusions following exposure to Alzheimer’s brain-derived tau assemblies. These models will substantially advance our capacity to study the biology of tau spreading and aggregation in human systems.

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P0584 / #1969

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

NEXOPATHY IN SILICO (NEXIS): A PLATFORM FOR COMPUTATIONAL DISCOVERY IN NEURODEGENERATIVE TAUOPATHIES

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Aims: 1. Efficiently model the spread of tau using publicly available data from mouse models of tauopathy, mouse connectome, and baseline gene expression. 2. Provide an effective platform (Nexopathy *in silico,* 'Nex*is*') to model and quantify neurodegeneration, specifically pathology accumulation and clearance, along the brain's connectome while considering the effect of microglial and non-microglial genes.
Methods: Nex*is* is an extension of our previous Network Diffusion Model which models transneuronal transmission as a passive diffusion process between connected regions. However, Nex*is* augments it with a protein accumulation/clearance term and flexible inclusion of extra-connectomic modulators of pathology spread, such as microglia. Nex*is* is applied to the 426-region mouse connectome, using publicly available datasets on spatiotemporal tau pathology in mice and baseline gene expression. Model parameters are optimized and model fits are compared.
Results: With the additional accumulation parameter, Nex*is:*global recapitulated original pathology significantly better than NDM (R^2 = 0.44 and 0.25 respectively). Nex*is*:microglia models (homeostatic or *Trem2*) outperformed NDM and Nex*is*:global for all datasets. Specifically, *Trem2* produced significantly better model fits for all datasets with R^2 reaching 0.59. Nex*is*:*Trem2* fits incurred an increase in the microglia-dependent spread parameter b; indicating that *Trem2* appears to allow more pathology to efflux from the hippocampal seed regions at early time points. We observed that model parameters also depended on the source of injected tau. Additional genes were tested where *Sorl1* showed significant model performance as well, but *Apoe* and *App* had negligible effects.
Conclusions: Inclusion of microglia quantitatively improved the model's predictive power. *Trem2* appeared to reduce tau accumulation rate while increasing its transmissibility from the hippocampal seed area causing a higher tau burden in connected regions. Nex*is* is a flexible platform for diverse hypotheses generation, testing, and validation.

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POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

THE ILLUSIVE ACT OF NEUROINFLAMMATION IN TAU SPREADING

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Aims: Tau pathology and neuroinflammation are two intimately connected, mechanistically linked processes. However, while epidemiological data suggests an early and substantial involvement of neuroinflammation in the etiopathogenesis of Alzheimer's Disease (AD), lack of clinical efficacy observed for nonsteroidal anti-inflammatory drugs (NSAIDs), warrants further research. Consequently, with this study we aspired to apprehend the neuroinflammatory link to tau spreading and associated pathological changes by modulating neuroinflammation in AD-tau seeded sporadic tauopathy model.
Methods: To address the prevailing challenges of reproducibility, the sarkosyl insoluble AD-tau fraction was subjected to robust proteomic analysis in western blots and ELISA. The fraction was validated *in vitro*, for its proteopathic seeding activity, uptake propensity, and spreading propensity upon lipopolysaccharides (LPS) treatment in neuronal and microglial co-cultures. Furthermore, taking advantage of *in vivo* AD-tau seeding in R3m/4 mice expressing truncated 3R tau (aa151-391), we explored the role of chronic neuroinflammation via LPS. At final timepoint, immunological, immunohistochemical, and biochemical analyses of AD-associated neuropathological changes were performed.
Results: We found that pro-inflammatory stimuli of LPS-treatment induces a strong tau phosphorylation and glial activation. A partial exacerbation of tau burden was implied by a non-significant positive trend. No significant change in cortical atrophy was detected in either LPS-treated groups. Intriguingly, sham-treated AD-tau seeded group also demonstrated elevated microglial activation.
Conclusions: The pertinence of tau phosphorylation as a readout for tau pathology is greatly misleading. Therefore, with the present study, using *in vivo* tangle load we comprehensively deciphered a partial inflammatory involvement in tau spreading and propagation. Moreover, the elevated microglial activation observed in response to tau seeding suggests the existence of a negative spiral of tau pathology coupled to immunological dysfunction. This work is supported by APVV-20-0331, APVV-19-0585, APVV-20-0585, and VEGA 2/0127/22 grant.

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P0586 / #1110

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

MODELING ALZHEIMER'S DISEASE IN MATURE PRIMARY NEURONS: DIVERGENT PROPAGATION AND SYNAPTIC EFFECTS OF POPULATIONS OF PRION-LIKE TAU CONFORMERS

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Aims: Phenotypic variations and different progression rates of Alzheimer's disease (AD) are linked to the diversity of misfolded prion-like tau conformers present in individual AD cases (Kim et al., Sci Transl Med 2022) and our aim is to investigate their effects on mature neurons and mechanism of their formation and propagation.
Methods: We exposed mice primary neurons to Sarkosyl-insoluble tau isolated from frontal cortex of six AD cases at seven days in vitro and monitored the impact for 14 days. The misfolding rate, 2N4R / 2N3R tau ratio, and conformational characteristics of de novo induced mice tau aggregates were correlated with the effects on key synaptic markers at three different time-points after inoculation by conformation-dependent immunoassay (CDI), western blots, and high-resolution confocal immunocytochemistry.
Results: AD tau samples induce highly reproducible progressive misfolding and aggregation of predominantly 2N4R mice tau with variable rates and distinctly different conformational characteristics leading to different degree of synapses alteration at different postinoculation times. The major tau strain-dependent and divergent effects were observed first with both pre-/post-synaptic markers (Bassoon, Synaptophysin, Homer, PSD95) with more prevalent effect on post-synaptic proteins as 40% decreased amount compared to controls after 14 days of some AD inoculum treatment.
Conclusions: The data provide direct evidence for an ensemble of misfolded tau conformers that are present in individual AD cases, and for their selection and evolution in divergent neuronal induction of misfolding that result in a major variation of synaptic impacts. These divergent mechanisms of formation and propagation of prion-like tau conformers in neurons are implicated in clinical manifestations and progression rates of AD and the better understanding of these effects is crucial in seeking new therapeutic targets and approaches.

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P0587 / #1959

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

USP11 ENHANCES THE SEEDING AND PROPAGATION OF PATHOLOGICAL TAU

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Aims: The abnormal accumulation of tau is associated with neuronal loss, synaptic dysfunction, and cognitive impairments. It is well established that women are more affected by AD than men by a factor of ~2:1. We recently showed that X-linked ubiquitin specific peptidase 11 (USP11), which escapes complete X-inactivation, exhibits higher expression in females compared to males. This aggravates pathological tau aggregation through direct deubiquitination and subsequent acetylation of tau, with greater effect in females compared to males. However, whether such USP11-mediated tauopathy enhancement occurs through increasing the seeding and propagation of pathological tau is unknown. This is a significant issue, as tau spreading also occurs faster in women than in men. In this study, we evaluated the role of USP11 in the seeding and propagation of pathological tau.
Methods: To determine the effects of USP11 on tau insolubility and aggregation, we utilized transiently transfected iHEK-tau^{P301L} cells. To assess USP11 in tau seeding, we utilized transiently transfected tau-RD biosensor cells and tau^{P301S} brain lysates. To evaluate cell to cell propagation of tau, we utilized tau^{P301S} and tau^{P301S};*usp11*$^{-/-}$ primary neurons grown in microfluidic chambers and tau^{P301S}brain lysates.
Results: We found USP11^{wt} increases tau aggregation in iHEK-tau^{P301L} cells. However, USP11^{CS} failed to increase tau aggregation. Furthermore, we found that USP11^{wt} significantly increases tau seeding in tau-RD biosensor cells, whereas USP11^{CS} overexpression does not. Conversely, USP11 siRNA significantly reduced tau seeding in tau-RD biosensor cells. TauP301S neurons exhibited strong tau seeding and propagation from cell to cell, whereas tau^{P301S};*usp11*$^{-/-}$ neurons showed inhibition of these measures.
Conclusions: We conclude that USP11 not only increases tau aggregation through it catalytic DUB activity but also enhances the seeding and propagation of pathological tau.

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P0588 / #1627

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

MTBR/C TAU IS ABUNDANT IN TAUOPATHY BRAIN AND EFFICIENTLY ENDOCYTOSED BY HUMAN NEURONS AND ASTROCYTES

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Aims: In Alzheimer's disease and other tauopathies, tau pathology progresses through the brain in a stereotypical spatial pattern, mediated by the inter-neuronal transfer of disease-specific tau forms. We characterised disease-specific tau forms, and identified tau domains necessary for uptake by neurons.
Methods: Tau forms in AD and control cerebral cortex were characterised by western blot using a panel of proprietary and commercial antibodies. pHrodo-labelled tau uptake by human iPSC-derived neurons and astrocytes was quantified using an OPERA-Phenix (Evans *et al*., 2018, Cell Reports). Uptake of tagged tau fragments was quantified by immunofluorescent detection and confocal imaging.
Results: A range of high and low molecular weight tau species that contain the tau MTBR and C-terminus were specifically found in tauopathy cerebral cortex, but not control brain samples. In contrast, N-terminal and mid-region forms of tau were equally abundant in both tauopathy and control brain. MTBR/C-terminal tau entered human excitatory neurons efficiently, whereas N-terminal/mid-region and C-terminal tau did not. Antibodies binding to MTBR and adjacent 12 amino acids (MTRB/C tau), the core region of the tau aggregate, block neuronal entry of tau, whereas antibodies targeting the N- and C-terminus had no significant effect.
Conclusions: MTBR/C-terminal tau fragments, lacking the N-terminus/mid-region, are enriched in tauopathy brain. These forms also efficiently enter human neurons and astrocytes. Antibodies that target the MTBR/C region prevent uptake of tau into human neurons and astrocytes by blocking receptor-mediated uptake. Data support therapeutic targeting of MTBR/C tau to slow tauopathy pathogenesis and highlight the importance of antibody epitope in the determining functional outcome of anti-tau antibodies.

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P0589 / #985

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

RAGE TRANSMITS TAU PATHOLOGY AND MEMORY DEFICITS IN AD

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Aims: In tauopathies, brain regions with tau accumulation strongly correlates with clinical symptoms and spreading of misfolded tau along neural network leads to disease progression. However, the underlying mechanisms by which tau proteins enter neurons during pathologic propagation remain unclear.
Methods: To identify membrane receptors responsible for neuronal propagation of tau oligomers, we established a cell-based tau uptake assay and screened cDNA expression library. Tau uptake and propagation were analyzed *in vitro* and *in vivo*, particularly using microfluidic device and stereotaxic injection. The cognitive function of mice was analyzed by behavioral tests.
Results: From a genome-wide cell-based functional screening, RAGE (receptor for advanced glycation end products) was isolated to stimulate the cellular uptake of tau oligomers. *Rage* deficiency reduced neuronal uptake of pathological tau prepared from rTg4510 mouse brains or cerebrospinal fluids from Alzheimer's disease patients, and slowed tau propagation between neurons cultured in a three-chamber microfluidic device. RAGE levels were increased in the brains of rTg4510 mice and tau oligomer-treated neurons. *Rage* knockout decreased tau transmission in the brains of nontransgenic mice after injection with Alzheimer's disease patient-derived tau and ameliorated memory loss after injection with GFP-P301L tau AAV. Treatment of RAGE antagonist FPS-ZM1 blocked transsynaptic tau propagation and inflammatory responses, and alleviated cognitive impairment in rTg4510 mice.
Conclusions: These results suggest that RAGE on neurons and microglia binds to pathological tau, and facilitates tau pathology progression and behavioral deficits in tauopathies.

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POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

BIOSENSOR CELL LINES FOR THE SPECIFIC QUANTIFICATION OF TAU SEEDING COMPETENCY IN HUMAN SAMPLES

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Aims: The prion-like propagation of tau implies that some misfolded pathological tau can recruit the normal protein and template its aggregation. Several groups have demonstrated that the amount of seeding-competent tau species correlates with rate of disease progression in Alzheimer's disease. Here, we aimed at developing sensitive biosensor cell lines for the detection of tau seeding activity in human biofluids.
Methods: We performed the rational design of novel tau probes based on the current structural knowledge of pathological tau aggregates in AD. We generated Förster resonance energy transfer (FRET)-based biosensor stable cell lines and characterized their sensitivity, specificity, and overall ability to detect bioactive tau in human samples. We characterized the solubility and structure of the generated intracellular tau probe aggregates.
Results: As compared to the reference biosensor line, the optimized probe design resulted in an increased efficiency in the detection of tau seeding. The newly formed aggregates accumulated in the insoluble fraction and recapitulated some features of AD aggregates. The increased sensitivity allowed for the detection of tau seeding competency in human brain samples, while preserving specificity for tau.
Conclusions: This next generation of FRET-based biosensor cells can be used to quantify minute amount of tau seeds in human samples and opens to way to the detection of seeding capacity in biofluids such as lumbar cerebrospinal fluid.

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P0591 / #737

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

DEVELOPMENT OF AN AAV-BASED MODEL OF TAUOPATHY TARGETING THE DENTATE GYRUS TO STUDY THE SPREADING OF TOXIC TAU SPECIES

Pauline Leal, Charlotte Duwat, Gwennaëlle Auregan, Charlène Josephine, Marie-Claude Gaillard, Caroline Jan, Anne-Sophie Herard, Philippe Hantraye, Gilles Bonvento, Karine Cambon, Alexis-Pierre Bemelmans
CEA/MIRCen, Neurodegenerative Diseases Laboratory, Fontenay-aux-roses, France

Aims: Alzheimer's disease is characterized by a spatiotemporal spread of tauopathy from cell to cell, which is strongly correlated with the progression of cognitive symptoms. Consequently, targeting this propagation might be a valuable therapeutic option; however, the underlying mechanisms of tau spreading are still poorly understood. We aim to develop focal tauopathy models by AAV gene transfer to tackle this issue.
Methods: To easily distinguish transduced from secondarily affected neurons, we developed a new model targeting mossy cells of the dentate gyrus (DG) in the mouse hippocampus. The DG of the two hemispheres are indeed connected by the contralateral mossy cell projection pathway. We therefore injected AAVs to overexpress tau and the GFP reporter gene in one DG, and assessed the spreading of tau in the contralateral one. In this experimental paradigm, transduced neurons express GFP and tau, while secondarily affected ones express tau only.
Results: One month following AAV injection, we detected transgenic tau presence in cell somas of the contralateral DG while reporter gene expression was absent and viral genome remained undetected by in situ hybridization. Hence, our data show that in our model, tau is able to spread from transduced neurons to contralateral non-transduced ones. To study the influence of microglia and Aβ, we applied this model respectively to TREM2-deficient mice and to APPswe/PSEN1dE9 mice. Our results suggest that TREM2-deficiency does not affect the spreading of tau in a non-amyloid context, and that this spreading is increased with amyloid plaques.
Conclusions: We established a novel AAV-based model to study the propagation of tauopathy, and are currently assessing, using different tau transgenes - more or less prone to aggregation - whether promoting aggregation reduces or enhances tau spreading.

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P0592 / #1101

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

THE IMPACT OF AGING ON THE TAU SEEDING IN THE MICE CARRYING ALZHEIMER`S DISEASE RISK GENE

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Aims: The seeding of tau pathology is increasingly suggested as a critical pathologic mechanism resulting in the clinical onset of Alzheimer`s disease (AD). Recently, it was reported that tau seeding is affected by the apolipoprotein E4(ApoE4) isoform. Considering that, aging is the most influential in AD development. The interaction between ApoE4 and aging could be implicated in tau propagation. In this study, we focus on revealing if the behavior and brain pathology is affected by aging in the *in vivo* model of tau seeding.
Methods: Human ApoE4 knock-in(KI) mice were used for the study. Brain extracts of P301S mice were stereotaxically injected into the hippocampus and overlying cortex of ApoE4 KI mice when mice were 3-, 9-, and 20- months of age. Before and three months after inoculations, their behaviors were assessed, and the brain pathology was examined using immunohistochemistry according to age.
Results: The oldest mice group showed an equivalent interest in the novel and familiar objects in the novel object recognition test after injection, which differs from their behavior before the injection. It suggests an impaired recognition memory in old ApoE4 mice after tau application. The tau inoculation-related lower performance was also noted in the limb clasping test in these mice (*$p<0.05$). Other age groups were persistent regardless of tau injections. The correlation analysis did not reveal evidence to support the contribution of limb weakness to cognitive performance. Immunohistochemistry is working on determining whether differential behavior response is affected by tau spreading and related neuropathology according to aging.
Conclusions: This result demonstrates that mid-term recognition memory deteriorated in the old ApoE4 mice after the pathologic tau inoculations. It suggests that ApoE4 carriership and aging have an interactive relationship to enhancing tau pathology.

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P0593 / #258

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

BRAIN INJECTION OF PATIENT-DERIVED TAU EXTRACTS INDUCES PROGRESSIVE SUPRANUCLEAR PALSY PATHOLOGY AND SYMPTOMS IN PRIMATES

Morgane Darricau[1], Taxiarchis Katsinelos[2], Flavio Raschella[3], Tomislav Milekovic[3], Louis Crochemore[1], Qin Li[4], Grégoire Courtine[3], William Mcewan[2], Benjamin Dehay[1], Erwan Bezard[1], Vincent Planche[1]
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Aims: Recently, it has been suggested that progressive supranuclear palsy (PSP) tauopathy may spread in the brain from cell to cell in a "prion-like" manner. However, direct experimental evidence of this phenomenon, and its consequences on brain functions, is still lacking in primates.
Methods: We derived sarkosyl-insoluble tau fractions from post-mortem brains of PSP patients and isolated the same fraction from age-matched control brains. After *in vitro* characterization of PSP-tau fractions, we bilaterally injected two male rhesus macaques in the supranigral area with PSP-tau extracts, and two other macaques with control extracts. Motor and cognitive behavior were assessed every 6 months. Macaques were euthanized 18 months after injection.
Results: The *in vitro* characterization of PSP-tau fractions demonstrated a high seeding activity in P301S-tau expressing cells, displaying after incubation abnormally phosphorylated, misfolded, filamentous and sarkosyl-insoluble tau. *In vivo*, PSP-tau injected macaques exhibited symptoms suggestive of parkinsonism as early as six months after injection and the progressive appearance of a significant dysexecutive syndrome. We found AT8-positive tau inclusions only in PSP-tau injected macaques, with globose and neurofibrillary tangles, tufted astrocytes, and coiled bodies. Lesions were found close to the injection sites but also in connected brain regions that are known to be affected in PSP (striatum, pallidum, thalamus). The number of nigral dopamine neurons was also reduced in PSP-tau macaques.
Conclusions: Our results demonstrate that PSP patient-derived tau aggregates can induce motor and behavioral impairments in non-human primates related to the prion-like seeding and spreading of typical pathological PSP lesions. The present data pave the way for supporting PSP-tau injected macaque as a relevant animal model to accelerate drug development targeting this rare and fatal neurodegenerative disease.

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P0595 / #1198

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

ARC MEDIATES THE INTERCELLULAR SPREAD OF TAU

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Aims: Aggregation of hyperphosphorylated tau is one of the hallmarks of Alzheimer's disease (AD) and correlates with cognitive decline in AD patients. As the disease progresses, tau pathology spreads across the brain in a stereotypical pattern. Pathological tau can be transferred between neurons but the mechanisms underlying the intercellular spread of tau remain unclear. Tau may be released from neurons in extracellular vesicles (EVs) or as naked oligomers. However, recent studies show EV-tau is more potent at seeding tau pathology. We recently discovered that the neuronal gene *Arc,* a critical regulator of synaptic plasticity and memory, mediates a novel form of intercellular communication. Arc protein self-assembles into viral-like capsids that are released from neurons in EVs that carry RNA/proteins to neighboring neurons. **We hypothesized that Arc EVs may facilitate the release of pathological tau and intercellular spread.**
Methods: To test this, we virally expressed GFP-2A-human Tau (P301L) in wild-type and Arc knockout primary hippocampal neurons and in 6-month-old mouse medial entorhinal cortex.
Results: We found intercellular tau transfer decreases significantly in the absence of Arc, both *in vitro* and *in vivo*.
Conclusions: This indicates that Arc facilitates intercellular tau transfer. We are now investigating the molecular mechanisms of Arc-dependent tau transfer. Our findings reveal a new molecular mechanism for tau spread and seeding, potentially opening new therapeutic interventions for AD.

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P0596 / #1481

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

RATE OF TAU PROPAGATION IS A HERITABLE DISEASE TRAIT IN GENETICALLY DIVERSE MOUSE STRAINS

Lindsay Welikovitch[1], Simon Dujardin[1], Amy Dunn[2], Analiese Fernandes[3], Anita Khasnavis[3], Lori Chibnik[4], Catherine Kaczorowski[2], Bradley Hyman[1]
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Aims: One of the most important risk indicators for developing Alzheimer's disease (AD) is a family history of dementia. Despite growing interest in understanding how AD-associated genetic polymorphisms lead to pathological outcomes, it remains unclear how polygenic factors contribute to the formation and expansion of tau neurofibrillary lesions, which are the closest correlate of neural degeneration and clinical symptoms during AD. While clinical data indicate that severity of tau pathology is likely influenced by heritable factors, studying this phenomenon in an experimental setting is especially difficult. We tested whether the rate of tau propagation is a heritable disease trait using a large, well-characterized cohort of 19 genetically diverse mouse strains, based on the BXD genetic reference panel.
Methods: P301L-mutated human tau (hTau) was introduced into the entorhinal cortex using an AAV-based model system of tau propagation, distinguishing hTau-producing cells from recipient neurons of tau protein transfer.
Results: Interestingly, some mouse strains were relatively resistant to tau spread despite strong AAV expression, while others were particularly vulnerable. Importantly, the heritability (h^2_{RIX}) of tau propagation was calculated to be 0.435; that is, ~43.5% of the observed variance in tau propagation could be explained by heritable factors. Total fluorescence and percent area of microglia- and astrocyte-specific markers, Iba1 and GFAP respectively, varied significantly across BXD groups. However, there was no correlation between glial abundance and tau propagation.
Conclusions: Given that the risk of developing AD has a strong heritable component, identifying genetic variants that influence tau propagation may help uncover novel molecular targets to prevent or slow the pace of tau spread and cognitive decline.

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P0597 / #2467

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

ANTI-TAU ANTIBODY INHIBITS TAU SEEDING AND PROPAGATION IN NOVEL PHYSIOLOGICAL NEURONAL MODELS

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Aims: Tau protein misfolds into aggregates that spread from neuron-to-neuron in Alzheimer's disease. Propagation of these aggregates along synaptically connected brain regions defines pathology progression. Targeting extracellular tau seeds using antibodies to stop propagation is a promising therapeutic intervention but proven to be difficult due to a lack of pathophysiological propagation models. Here we developed microfluidic neuronal tau propagation models using primary murine hippocampal neurons and demonstrate targeting a specific epitope, but not others effectively stops tau propagation.
Methods: Primary murine hippocampal neurons Microfluidic chambers Tau propagation
Results: Here we developed microfluidic neuronal tau propagation models using primary murine hippocampal neurons and demonstrate targeting a specific epitope, but not others effectively stops tau propagation.
Conclusions: Antibody targeting a specific epitope, but not others effectively stops tau propagation.

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P0598 / #1708

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

MICROGLIA REGULATE LEVELS OF EXTRACELLULAR, NEURON-DERIVED TAU IN A HUMAN NEURON-MICROGLIA COCULTURE SYSTEM IN AN ACTIVATION-DEPENDENT MANNER

Thomas Campbell, Rosanna La Rocca, Martin Crossley, Hannah Maxwell, Pedro Garção, James Smith, Sergey Sitnikov, Wei-Li Kuan, Clare Jones, Frederick Livesey
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Aims: Genetic associations between multiple immune genes and risk of developing Alzheimer's disease highlight the role of neuroinflammation in dementia pathogenesis. We aimed to develop a fully human iPSC-derived cortical neuron-microglia coculture system, enabling mechanistic studies of neuroinflammation, suitable for neuroinflammation target identification and validation. Given the importance of neuronal release and uptake of pathogenic forms of tau protein in dementia pathogenesis, this system was used to investigate whether microglial activation status affects levels of extracellular, neuron-derived tau.
Methods: iPSC-derived cortical neurons and microglia were generated from non-demented control iPSCs, and combined to form cocultures. Cells were QCed and characterised using transcriptomic analysis, immunofluorescence and ELISA. Compound profiling was performed by stimulating pro-inflammatory cytokine release from microglia (LPS-driven and inflammasome-driven) in the presence of a half-log compound dilution series, and quantifying relevant cytokine release by ELISA/MSD. Levels of extracellular, neuron-derived tau were measured by MSD.
Results: In coculture with neurons, microglia were functionally active and released cytokines (TNFα, IL-6) in response to pro-inflammatory stimuli (LPS or LPS/IFNγ). Inflammasome activation was robustly induced with LPS and nigericin or ATP, accompanied by IL-1β and IL-18 release. Release of TNFα/IL-6 was blocked by p38α inhibition (CP-863187), and release of IL-1β/IL-18 by NLRP3 inhibition (MCC950), in each case in a dose-dependent manner. Microglia reduced steady-state extracellular levels of neuron-derived tau under resting conditions, whereas microglial activation resulted in increased extracellular tau.
Conclusions: This fully human *in vitro* iPSC-derived neuron-microglia system is scalable, robust and captures relevant neurodegenerative and neuroinflammatory outcomes. Microglia regulate extracellular levels of neuron-generated tau in an activation-dependent manner.

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P0599 / #2158

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

MAXILLARY BONE LOSS AND NEUROINFLAMMATION ARE INCREASED IN A MURINE ALZHEIMER'S DISEASE MODEL OF PERIODONTITIS.

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Aims: To determine the extent to which AD predisposition established in 3xTG AD mice, exacerbates ligature-induced periodontitis. Conversely, the extent to which periodontitis exacerbates AD-like neuropathology, cognitive decline, and inflammation.
Methods: We induced periodontitis in female transgenic AD (3xTg-AD) mice or WT controls by tying a silk ligature unilaterally around the right second maxillary molar. We assessed bone loss with repeated *in vivo* micro-computed tomography (microCT) at days 0, 3, 7, and 14. Brain tissue from one hemisphere, gingiva and peripheral tissues were harvested and analyzed for inflammatory markers using RT-PCR. The other brain hemisphere was collected, fixed, and sliced for immunohistochemical analysis of amyloid-beta and tau.
Results: WT and AD mice showed no differences in bone volume at baseline. Furthermore, the control non-ligature side showed minimal bone loss after 14 days. However, there was a significant increase in bone loss in AD mice 2-weeks post ligature placement when compared to WT mice. qPCR data indicated an increase in inflammatory cytokine gene expression in the hippocampus of AD mice at 7 days post ligature placement. Additionally, there was a significant decrease in gene expression of glutamate receptors, and synaptic elements (PSD95 and Synaptophysin) in the AD hippocampus 7 and 14 days after ligature placement.
Conclusions: Our data support a synergistic relationship between AD and PD. Induced periodontitis led to exaggerated hippocampal neuroinflammation and synaptic dysregulation in AD mice, while WT mice were spared. Additionally, we found accelerated PD-evoked bone loss in AD mice compared to WT controls. These observations are the first steps in uncovering the mechanisms that drive this interaction. Moving forward, we plan to investigate behavioral dysfunction and AD neuropathology in the presence of these two disease processes.

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P0600 / #428

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

SINGLE-CELL RNA SEQUENCE ANALYSIS OF POST-MORTEM MIDBRAIN TISSUE REVEALS ALTERED GLIAL CELL FUNCTION IN PARKINSON'S DISEASE

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Aims: Several neurodegenerative diseases (NDDs) including Parkinson's disease (PD) and Alzheimer's disease are characterized both as proteinopathies, with aberrant post-transcriptional modifications and protein aggregation, and neuroinflammatory disorders, with reactive glial cells. The inflammatory hypothesis suggests that dysregulated pathways in glial cells contribute to neurodegeneration. Using a public dataset (Broad Institute) containing sc-RNA seq data from post-mortem midbrain tissue, we attempted to characterize functional alterations in several glial cell populations in PD. We specifically focused on functions associated with inflammation and damage response.
Methods: Astrocytes, microglia, and oligodendrocyte progenitor cells (OPCs) were annotated into subtypes based on clustering parameters in the published study. We performed differential gene expression (DGE) analysis on each cell subtype and annotated the data using the Gene Ontology (GO) resource. The DGE lists were analyzed to identify altered molecular functions in microglia in PD versus control. The results were filtered by their relevance to aspects of neuroinflammation as presented in the current literature.
Results: Preliminary analysis showed that molecular functions associated with proinflammatory functions were downregulated in microglia and OPCs. Resting state microglial functions such as neurogenesis and repair were down or upregulated in different microglial populations. Functions mediating responses to oxidative stress and DNA damage were upregulated in some microglia subtypes and most astrocytes.
Conclusions: The results suggest a degree of glial crosstalk between microglia and astrocytes during propagation of inflammatory cascades. A general dysregulation of microglial functioning implies exhausted microglia populations follows prolonged inflammation, rather than a maladaptive switch in rest/repair versus inflammation functions occurs in PD.

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P0601 / #541

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

THE ROLE OF FYNT TYROSINE KINASE IN MODULATING MICROGLIAL ACTIVATION AND INFLAMMASOME SIGNALING IN TAUOPATHY MOUSE MODEL

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Aims: Our laboratory demonstrated that FynT tyrosine kinase was significantly upregulatesd in post-mortem brains derived from patients with Alzheimer's disease (AD) and Lewy body dementia, as well as in aged P301S tauopathy mouse model (PS19) and positively correlated with tau pathology and neuroinflammatory markers. In view of FynT was highly expressed in microglia and Fyn kinase being reported to mediate priming and activation of microglial NLRP3 inflammasome and amplifying neuroinflammation in Parkinson's diseases, we hypothesize that FynT induction in AD and tauopathies may be involved in microglial activation and inflammasome signaling, leading to aggravation of inflammatory symptoms and neurodegeneration. In this study, we use PS19 line as the disease model and crossed with FynT knockout mice to test our hypothesis.
Methods: Brain tissues derived from PS19 and WT littermates (at young and old age), as well as aged males PS19 (with and without FynT depletion) were compared with gene expression in association with microglial and inflammasome activation using real-time RT-PCR. Inflammasome activation was confirmed by Western blot analysis.
Results: We confirmed that aged PS19 mice manifested tau pathology and have distinctive profiles in association with microglia/ macrophages activation when compared with WT littermates. Furthermore, molecules associated with inflammasome (e.g. NLRP3, AIM2, ASC, cleaved IL1b) and pyroptosis (e.g. GSDMD, CASP1)) were significantly upregulated in aged PS19 mice during the disease progression. Interestingly, FynT depletion in PS19 mice significantly downregulated the expression of disease-associated microglia markers and attenuated inflammasome and pyroptosis activation.
Conclusions: Pyroptosis has been recognized as an inflammatory cell death that occurs downstream of inflammasome activation. Our findings suggested that FynT kinase may directly or indirectly modulate microglial and inflammasome activation, contributing to neuroinflammation and neurodegeneration.

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P0602 / #2040

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

BLOOD VASCULATURE FACILITATES MACROPHAGE MIGRATION FROM PERIPHERY INTO THE BRAIN AFTER SYSTEMIC LPS CHALLENGE IN AN A152T MODEL OF ZEBRAFISH TAUPATHY VIA MECHANISMS INVOLVING INTERLEUKIN-34

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Aims: This study aims to investigate the role of interleukin-34 in modulating macrophage recruitment to the brain parenchyma after peripheral challenge in a model of neurodegenerative taupathy.
Methods: To investigate the mechanisms mediating peripheral-neuroimmune crosstalk, wildtype and A152T taupathy zebrafish, Tg(UAS::dendratau)A152T, were subjected to intraperitoneal LPS injections. Changes in neuroinflammation were confirmed through qPCR, and immunohistochemical staining of microglia (lcp1) and astrocytes (GFAP). Live imaging of Tg(mpeg1:egfp), followed by BrdU labelling was used to examine directional trafficking and proliferation of macrophage from the site of peripheral LPS challenge to the brain parenchyma in zebrafish adults. 3D-reconstruction of double transgenic zebrafish larvae labelling blood vasculature and macrophage (mpeg1+/kdrl+) was used to determine the role of blood vessel-associated macrophages (BVMac) in modulating neuroinflammation after peripheral LPS challenge. BVMac were investigated in the presence and absence of tau.
Results: demonstrate increased migration of macrophage from the site of peripheral LPS challenge to the brain in both zebrafish larvae and adults. Of interest, macrophage migration is directional towards the brain and associated with increased proliferative macrophages. Indeed, co-localizations between 3D-reconstructed mpeg1+/kdrl+ confocal micrographs demonstrate increased BVMac after peripheral LPS injury. However, the presence of tau A152T point mutation decreased recruitment of BVMac toward the head region in zebrafish larvae after LPS challenge compared to wildtype. This is associated with decreased il34 mRNA levels in the A152T compared to wildtype.
Conclusions: Our data highlights the vital role of macrophage in promoting peripheral-neuroimmune crosstalk via blood vasculature, and that these mechanisms are found to be compromised in A152T zebrafish, likely through modulation of IL34. The study was supported by HKU Seed Funding for Basic Research (202111159215).

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P0603 / #769

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

DYSFUNCTION OF THE GLUTAMATERGIC PHOTORECEPTOR SYNAPSE IN A MOUSE MODEL OF TAUOPATHY

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Aims: Tauopathies, including Alzheimer's disease, are characterized by retinal ganglion cell loss associated with amyloid and phosphorylated tau deposits.
Methods: We investigated the functional impact of these histopathological alterations in the murine P301S model of tauopathy.
Results: Visual impairments were demonstrated by a decrease in visual acuity already detectable at six months, the onset of disease. Visual signals to the cortex and retina were delayed at six and nine months, respectively. Surprisingly, the retinal output signal was delayed at the light onset and advanced at the light offset. This antagonistic effect, due to a dysfunction of the cone photoreceptor synapse, was associated with changes in the expression of the vesicular glutamate transporter and a microglial reaction.
Conclusions: This dysfunction of retinal glutamatergic synapses suggests a novel interpretation for visual deficits in tauopathies and it highlights the potential value of the retina for the diagnostic assessment and the evaluation of therapies.

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P0604 / #784

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

COMBINING ARRAY TOMOGRAPHY WITH DSTORM: A CLOSER INSIGHT INTO SYNAPTIC TAU PATHOLOGY IN ALZHEIMER'S DISEASE

Érika Sánchez-Aced[1], Jordi Pegueroles[1], Soraya Torres[1], Martí Colom-Cadena[2], Alba Cervantes González[1], Natalia Valle-Tamayo[1], Laia Lidon[1], Oriol Dols-Icardo[1], Olivia Belbin[1], Juan Fortea[1], Tara Spires-Jones[2], Sílvia Pujals[3], Sònia Sirisi[1], Alberto Lleó[1]
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Aims: Studying the brain at the nanoscale allows for a closer insight into synaptic pathology. Our main goal is to compare the resolution obtained by different advanced microscopy methods when applied to human brain tissue from Alzheimer's Disease (AD) subjects and controls. We applied direct two-colour Stochastic Optical Reconstruction Microscopy (dSTORM) to paraffin-embedded and resin-embedded human tissue (Array Tomography samples, AT) from both control subjects and sporadic Alzheimer's Disease (SAD) patients.
Methods: We immunostained human tissue from controls and SAD patients (n=3), with antibodies against presynaptic (Synaptophysin) and postsynaptic (PSD-95) terminals or against oligomeric (T22) and phosphorylated (AT8) forms of tau protein in paraffin-embedded and AT samples and compared the resolution obtained with conventional and dSTORM microscopy.
Results: Combining AT samples with dSTORM provides a significant improvement in resolution when compared to paraffin-embedded samples as well as to AT samples observed with conventional microscopy, allowing us to resolve the nanoscale architecture of individual synapses (Figure 1), including the synaptic cleft. We also could observe the presence of pathological tau at the synapse (phosphorylated and oligomeric forms) in both presynaptic and postsynaptic terminals of SAD tissue samples.

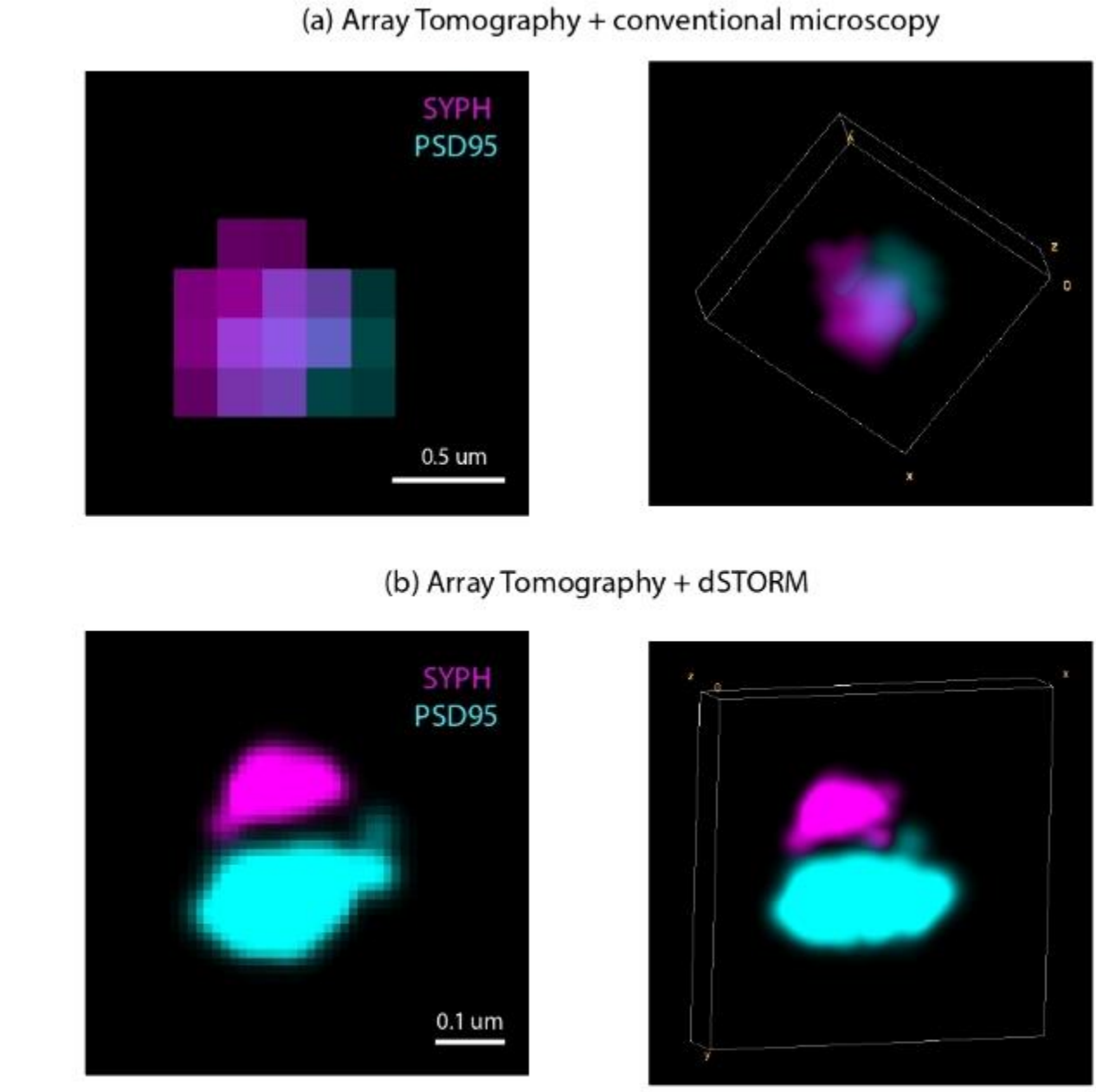

Figure 1. Pre and post synaptic markers imaged by (a) AT + fluorescence microscopy and by (b) AT + dSTORM, both in frontal cortex from a HC. This result indicates that the combination of both techniques allows to differentiate the pre- and post-synaptic terminals.

Conclusions: Our results demonstrate that the combination of AT with dSTORM achieves improved resolution for studying synaptic pathology in the human AD brain. Using these microscopy techniques we confirmed the presence of pathological forms of tau at the synapse, supporting the value of these techniques for the study of integrity and pathology of synapses.

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P0605 / #2192

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

INTERFERENCE OF RIVASTIGMINE WITH TAU AGGREGATION INHIBITOR ACTIVITY AT THE SYNAPSE IN TAU-TRANSGENIC MICE.

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Aims: In recent Phase 3 trials testing the tau aggregation inhibitor hydromethylthionine, significant differences in treatment response were observed according to whether patients were taking hydromethylthionine as monotherapy or as an add-on to symptomatic treatments. We have investigated the effect of hydromethylthionine alone and in combination with the cholinesterase inhibitor rivastigmine on the level of synaptic proteins in L1 tau transgenic mice.
Methods: Female, homozygous L1 and wild-type NMRI litters (8-10 per group) aged 6 months were used. During phase 1, mice were pre-treated for 5 weeks with rivastigmine (0 or 0.5 mg/kg/day) and, during phase 2, the dosing was continued for 6 weeks with additional hydromethylthionine (0 or 15 mg/kg/day). The relative abundance of several synaptic proteins was measured as integrated density in paraffin sections stained with antibodies against synapsin-1, synaptophysin, alpha-synuclein, syntaxin-1, SNAP-25, and VAMP-2 in six different brain regions of interest (medial septum, vertical limb of the diagonal band of Broca, nucleus accumbens, motor cortex, visual cortex, and hippocampal CA1).
Results: In NMRI mice, there is a high degree of correlation in levels of multiple synaptic proteins. These correlations were largely lost in L1 mice. Monotherapy with hydromethylthionine partially recovered these protein correlations in L1 mice, but there was strong interference with the efficacy of hydromethylthionine by chronic pretreatment with rivastigmine.
Conclusions: The chronic neuronal activation of the brain with rivastigmine produces compensatory homeostatic changes in the synapse that weakens/abolishes their sensitivity to hydromethylthionine.

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P0606 / #210

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

SEX DIFFERENCES IN ALZHEIMER'S DISEASE: MOLECULAR PATHWAY FOR SYNAPTIC LOSS

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Aims: Multiple studies have suggested that females are affected by Alzheimer's Disease (AD) more severely than males. Our previous studies have shown that females with AD are more likely to progress to severe cognitive dysfunction and have a greater proportional loss of brain weight. For this study, we wanted to further investigate possible molecular pathways involved in AD synaptic loss.
Methods: Subjects were volunteers as part of the Brain and Body Donation Program (BBDP) at the Banner Sun Health Research Institute in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Subjects for the current study (N=93) were chosen by searching the BBDP database for cases with a clinicopathological diagnosis of AD (N=49) or control (N=44) from both genders. Gray matter from frozen frontal cortex was dissected for protein and RNA isolation. M
Results:

There were significant sex differences in multiple genes involved in to synaptic vesicle release, synaptic pruning and neurotransmit gene C5 and astrocyte-associated Megf10.

Conclusions: Our data suggest that males can better mitigate synaptic loss than females. In addition, we observed a higher immune response to AD in females. We proposed that the combination of increased inflammatory genes in females and an inability to compensate as well by increasing expression of synapses and neurotransmitters may explain why females have a greater loss of synaptic density.

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POSTERS: B01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

EARLY DEREGULATION OF WNT SIGNALING IN THE HIPPOCAMPUS OF 3XTG-AD MODEL

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Aims: Introduction: Alzheimer disease (AD) is the most common age-related dementia characterized by progressive loss of cognitive abilities, synaptic damage, and accumulation of extracellular deposits of amyloid beta-protein and intracellular accumulation of neurofibrillary tangles composed by tau. Emerging studies suggest a deregulation of Wnt signaling in the brain of AD patients, suggesting that this pathway may also contribute to the disease progression. However, whether alterations in the Wnt pathway are cause or consequence of disease and the precise contribution of deficient Wnt signaling remains to be determined. **Objective:** the present study aims to describe the status of different components of the canonical Wnt pathway along with the expression of markers of AD.
Methods: Methods: We analyzed by Western-blot the contents of canonical Wnt ligands (agonist Wnt7a and antagonist Dkk-1) in the hippocampus of the female 3xTg-AD at different ages: young (2–3-month-old), middle-age (9-11-month-old) and aged (18-24-month-old) and the activation of the master enzyme GSK3b.
Results: Results: We found a progressive increase in the levels of Dkk1 from juvenile stage compared to control mice. Similarly, Wnt7a levels were markedly reduced accompanied by the presence of the active form of GSK3b. All these alterations were evident at 3 months of age, when the hallmarks of AD are not yet clearly expressed, since pS^{202}-tau, increases until 9-12 months of age.
Conclusions: Conclusions: Our results suggest an early deregulation of Wnt signaling that may participate in the expression of some pathological markers of AD and open the possibility that the activation of this pathway could be a therapeutic tool to delay the disease This work was supported by PAPIIT, DGAPA UNAM IN204621 and CONACYT A1-S9559

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P0608 / #2088

POSTERS: B01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

TOLL-LIKE RECEPTOR EXERTS NEUROPROTECTION THROUGH P38 MAPK/SAPK IN DROSOPHILA MODEL OF TAUOPATHY

Yasufumi Sakakibara[1], Risa Yamashiro[2], Sachie Chikamatsu[1], Yu Hirota[1,3], Yoko Tsubokawa[1], Risa Nishijima[1], Kimi Takei[1], Michiko Sekiya[1,2], Koichi Iijima[1,2]
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Aims: Innate immune responses and anti-stress signaling are altered during aging and in neurodegenerative diseases. Toll-like receptors (TLRs) are evolutionarily conserved across animal species and play a central role in host defense mechanisms by activating the nuclear factor-kappa B (NF-kB), c-Jun N-terminal kinase (JNK), and p38 stress-activated protein kinase (SAPK) pathways. Among nine Toll receptors in *Drosophila*, Toll-9 is most closely related to mammalian TLRs; however, the physiological functions of Toll-9 in adult flies remain elusive. In this study, we examined roles of Toll-9 in fly brains under normal aging and neurodegenerative conditions.
Methods: We investigated roles of Toll-9 in the maintenance of the brain integrity under normal aging and neurodegeneration using *Drosophila* models of acute axon injury and human tau-mediated neurodegeneration.
Results: *Toll-9* mRNA levels were increased upon aging in fly heads accompanied by induction of genes downstream of NF-kB and JNK/SAPK pathways. Many of these changes were attenuated by *Toll-9* knockout or knockdown in glial cells, suggesting that glial Toll-9 modulates both NF-kB and JNK/SAPK signaling during aging. The loss of *Toll-9* did not affect brain integrity during normal aging, whereas it slightly exacerbated hydrogen peroxide-induced lethality. Interestingly, specifically *Toll-9* expression was induced by acute nerve injury together with upregulation of genes downstream of NF-kB and JNK/SAPK signaling. In a fly tauopathy model, *Toll-9* deficiency significantly enhanced disease-related tau phosphorylation and neurodegeneration. SAPK activity was reduced in these flies, and blocking SAPK functions was sufficient to enhance tau phosphorylation and neurodegeneration. Using human cultured cells, the effects of pharmacologic inhibition of SAPK kinases on tau phosphorylation are currently under investigation.
Conclusions: These results suggest that activation of TLRs and SAPKs may be protective against acute and chronic neurodegeneration such as tauopathy.

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P0609 / #1556

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

NEURON-SPECIFIC RESILIENCE TO TAU-INDUCED PROTEOSTATIC STRESS

Wiep Scheper[1], Jasper Franciscus Maria Smits[2], Marta Jorge-Oliva[3], Kevin Batenburg[1], Kim Wolzak[1]
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Aims: Neurons are highly specialized cells that heavily depend on the maintenance of protein homeostasis or "proteostasis" as they are post-mitotic and therefore cannot self-renew. Neurodegenerative tauopathies are characterized by a collapse of neuronal proteostasis, demonstrated by the massive accumulation and aggregation of tau proteins. Neurons are more resilient to proteostatic stress than other cell types, indicating the presence of neuron-specific stress pathways. We aim to understand the mechanisms underlying the neuron-specific resilience to proteostatic stress by studying the integrated stress response (ISR) that controls protein synthesis and the lysosomal system that controls protein degradation.
Methods: To investigate the proteostatic responses to tau aggregation, our lab has developed primary mouse and human iPSC neuronal models that reflect a broad spectrum of tau pathology load. We employ molecular interventions (cKO, shRNA, lentiviral transduction) and cell biological techniques (immunofluorescence, confocal and automated high content microscopy) for intervention and analysis of tau pathology and proteostatic stress responses.
Results: We identified 3 neuron-specific proteostatic stress responses: - GranuloVacuolar degeneration Bodies (GVBs) are neuron-specific proteolytically active lysosomal structures that accumulate specific cargo that are induced by intracellular tau and alpha-synuclein pathology. - In contrast to other cell types, neurons deficient for the ISR kinase PERK retain translational control by activating Angiogenin and HRI. - Intraneuronal tau pathology results in cell non-autonomous activation of the ISR activate the in astrocytes in human co-culture.
Conclusions: We have identified cell type specific responses to proteostatic disturbances that may explain the neuronal resilience to protein aggregation. Employing these neuron-intrinsic pathways may provide an opening for therapeutic intervention.

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P0610 / #1022

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

CK1DELTA ACTIVITY IS REQUIRED FOR THE ACCUMULATION OF TAU-INDUCED GRANULOVACUOLAR DEGENERATION BODIES

Jasper Franciscus Maria Smits[1], Marta Jorge-Oliva[1], Wiep Scheper[1,2]
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Aims: Granulovacuolar degeneration bodies (GVBs) are lysosomal organelles that often accompany intraneuronal tau aggregates in multiple tauopathies. GVBs contain a dense core consisting of diverse cargo, including the tau-kinase casein-kinase 1 delta (CK1δ) and pPerk. CK1δ is the best marker for detecting GVBs in the brain. Recently our lab developed the first *in vitro* model for GVBs and demonstrated that CK1δ is selectively targeted to GVBs. Therefore, we aim to elucidate the function of CK1δ in the accumulation of GVBs.
Methods: We employed a spontaneously aggregating tau model in primary mouse neurons to study the effect of our interventions on GVB and cargo accumulation. Quantitative high-content automated microscopy was used to measure the effect of CK1δ inhibition on endogenous pPerk punctae (from here on out referred to as GVBs). Furthermore, we overexpressed GFP-tagged wild-type CK1δ (GFP-CK1δ), a kinase-dead CK1δ (GFP-K38M-CK1δ) and a nuclear-exit-signal tagged CK1δ (GFP-NES-CK1δ) in our model and used confocal and quantitative automated microscopy to study the effects on GVB and cargo accumulation.
Results: Inhibition of CK1δ decreases GVB accumulation and increases nuclear localization of CK1δ. Yet, GFP-NES-CK1δ was unable to rescue GVB accumulation in the presence of the CK1δ inhibitor. Furthermore, GFP-K38M-CK1δ also localizes to GVBs in the presence of endogenous CK1δ. Moreover, CK1δ inhibition did not affect the intraneuronal tau pathology.
Conclusions: Our data show that CK1δ activity is required for the accumulation of GVBs. In addition, CK1δ activity *in cis* is not required for its localization to GVBs. The effects are not mediated by an indirect effect on tau aggregation. We conclude that CK1δ is an essential upstream regulator for the accumulation of GVBs in response to tau pathology.

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P0611 / #2016

POSTERS: B01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

IDENTIFICATION OF NOVEL REGULATORS OF TREM2 PATHWAY IN IPS DERIVED HUMAN MICROGLIA-LIKE CELLS USING ARRAYED CRISPR SCREENING

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Aims: Designing reverse genetic experiments to ascertain the function of microglial Alzheimer's Disease (AD)-associated genes are hindered by both the inability to obtain and manipulate postmortem tissue from AD patients and the absence of functionally relevant human microglia cell lines. Human-induced pluripotent stem cell (hiPSC)-derived microglia cells represent a novel strategy to examine the relationship between genetic risk factors and late-onset AD. Functional analysis of induced microglial-like cells (iMGLs) reveals that they secrete cytokines in response to inflammatory stimuli and CNS disease-associated substrates, including amyloid beta fibrils. The ability to precisely introduce disease-associated genetic mutations in iMGLs using CRISPR/Cas9 technology will help define the contribution and function of genes associated with late-onset AD.
Methods: We have established an arrayed CRISPR screening platform that can be used to evaluate the functional consequences of genetic perturbations in iMGLs. A CRISPR screen was performed using a library of 150 genes representing the TREM2/DAP12 interactome identified by proteomics in myeloid cells after stimulation with an anti-TREM2 agonistic antibody.
Results: Putative hits from the arrayed CRISPR screen include genes that are involved in: (I) regulation of microglial functions including morphological change, migration, and phagocytosis; (II) a component of a dysfunctional TREM2-dependent signaling node; (III) direct targets of a microRNA circuit that regulates chronic peripheral neuropathic pain. Those hits were evaluated by a secondary screen to determine impact on positive and negative cytokine regulation.
Conclusions: This functional genomics screen demonstrates the utility of iMGLs as a platform for identifying novel targets and regulators of microglial activation states.

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P0612 / #1901

POSTERS: B01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

INVESTIGATING BIN1 INVOLVEMENT IN TAU HANDLING AND EXTRACELLULAR VESICLE SECRETION IN IPSC-MICROGLIA

Anne Hedegaard, Sally Cowley, William James, Maria Kreger
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Aims: BIN1 has emerged as a very attractive genetic target for sporadic Alzheimer's Disease (AD), being the next-highest risk factor after APOE. Importantly, BIN1 associates both with risk of disease onset, tau burden and disease progression. Certain BIN1 isoforms have been shown in mouse microglia to contribute to increased incorporation of tau into extracellular vesicles (EVs), and conversely, knocking out BIN1 reduced tau spread via EVs (Crotti et al., 2019). This project utilises human microglia derived from induced Pluripotent Stem Cells (iPSC), to investigate the function of BIN1 in the context of tau processing by microglia, secretion via EVs, and potential implications for neuronal tau pathology.
Methods: We use human iPSC-derived microglia and manipulate their level of BIN1 expression either through knock-down strategies or overexpression of relevant isoforms. Exposing these isogenic microglia with low/endogenous/high BIN1 levels to tau protein then allows assessment of microglial processing of misfolded tau, along with EV production and incorporation of tau into secreted EVs.
Results: We have verified that human iPSC-microglia express various isoforms of BIN1, and that EVs displaying canonical characteristics can be isolated from supernatants. Further, we have explored the cellular localisation of BIN1 and tested assays to quantify rates of tau uptake and degradation.
Conclusions: By carefully characterising BIN1 expression and EV production in human iPSC-microglia, we have laid the groundwork for the next phase of investigations into microglial handling of tau in the context of BIN1.

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P0613 / #801

POSTERS: B01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

SILENCING OF PHAGOCYTIC RECEPTOR MERTK IN ASTROCYTES ALLEVIATES TAU PATHOLOGY IN RODENT MODELS OF PRIMARY TAUOPATHIES

Nathan Louvel[1], Anastasie Maté De Gérando[1], Isabel Paiva[2], Gwennaëlle Auregan[1], Charlène Josephine[1], Mylène Gaudin- Guerif[1], Martine Guillermier[1], Anne-Sophie Herard[1], Caroline Jan[1], Fanny Petit[1], Emilie Faivre[3], David Blum[3], Laurette Boutillier[2], Philippe Hantraye[1], Marie-Claude Gaillard[1], Gilles Bonvento[1], Alexis-Pierre Bemelmans[1], Karine Cambon[1]
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Aims: Abnormal forms of Tau are present in both astrocytes and neurons in most primary Tauopathies. Astrocytes can engulf neuronal Tau species and accumulate them, likely via phagocytosis of pathological synapses/debris. Here we tested the hypothesis that 1) MERTK mediates phagocytosis and engulfment of Tau in astrocytes and 2) silencing MERTK- mediated phagocytosis alleviates pathology.
Methods: We modelled Tau pathology using AAV gene transfer to overexpress hyperphosphorylated Tau (soluble with human WT Tau, or aggregated with pro-aggregating vector TauProAggr) in the hippocampus of adult C57Bl/6J mice. We designed an AAV encoding artificial miRNA to silence MERTK specifically in astrocytes. Mice were co-injected in the hippocampus with AAVs-CBA-TauWT or ProAggr, and either AAV-GFA-mirShMERTK or mirShControl. Three months later Tau pathology and astrocytic reactivity were assessed in the hippocampus using immunohistology, confocal microscopy and image analysis software. The hippocampal volume was determined by stereology.
Results: Overall Tau pathology in the hippocampus was significantly reduced by MERTK silencing in hTauProAggr-injected mice, accompanied by a decrease in astrocyte reactivity. In contrast, the treatment did not alter the severity of pathology nor astrocyte reactivity in hTauWT model. Hippocampal volume tended to be restored with mirShMERTK treatment in both Tau groups. On-going studies are quantifying the accumulation of Tau within astrocytes.
Conclusions: Silencing MERTK-mediated phagocytosis alleviates both global Tauopathy and astrocyte reactivity in the model presenting Tau aggregates, not in the one with soluble forms of Tau only, suggesting a differential astrocytic implication in both models. The mechanisms at play remain to be determined.

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P0614 / #1584

POSTERS: B01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

FILAMENTOUS TAU CAN INDUCE PRO-INFLAMMATION ASTROCYTIC TRANSCRIPTOME AND SECRETOME THROUGH A CELL ADHESION MOLECULAR COMPLEX.

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Aims: We previously reported that filamentous Tau-mediated activation of integrin signaling could induce astrocytic conversion towards a neurotoxic state, but whether these changes contribute to neuronal dysfunction through secretion and the mechanisms how astrocytes distinguish physiological and pathological integrin signaling, is still unknown.
Methods: Here we addressed these questions by generating reactive astrocyte transcriptome and secretome from Tau-treated primary astrocytes. We also compare Osteopontin (OPN) induced phisilogical integrin signaling pathway with Tau induced pathological integrin signaling pathway. Biochemistry methods and neuro toxicity assays were further employed to provide an in-depth understanding how astrocyte-secreted proteins and the underlying pathways contribute to neuronal death.
Results: Our comprehensive RNA-seq data suggests a pro-inflammation astrocytic transcriptome following Tau treatment, including upregulation of cytokines and chemokines, inflammasome component, interferons and complement cascade. This phenotype is under stringent regulation of a cell adhesion molecular complex composed of integrins, co-receptor Ncam1, adaptor Talin, focal adhesion kinase (FAK) and downstreat Akt kinase. In a line with this, we further found that some neurotoxic factors including complement components and matrix metalloproteinases, which are important sensors of innate immunity and intensively explored in health and disease, were secreted from astrocyte induced by Tau. The major effector of complement cascade- C3 was cleaved into C3a and C3b, further into iC3b in the media of astrocyte exposed to Tau, finally leading to neuronal death. More importantly, this secretion was blunted either by knocking down integrin complex and its co-receptor and adaptor, inhibiting downstream FAK, Akt, or blocking transcription factor NFkb.
Conclusions: The identification of astrocytic proteome and secretome profiles made by this research has provided new insights into the maintenance of neuronal health and survival, hence present as an interesting therapeutic approach to target crucial pathogenetic processes in Alzheimer's disease.

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P0615 / #1204

POSTERS: B01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

PERSISTENCE OF MENINGEAL BLOOD-BRAIN BARRIER DISRUPTION FOLLOWING A TRAUMATIC BRAIN INJURY

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Aims: We examined whether traumatic meningeal enhancement (TME) is present months after a TBI and whether TME is associated with increased serum concentrations of neurofilament light (NfL), total tau (tau), ubiquitin c-terminal hydrolase-L1 (UCH-L1), and glial fibrillar acidic protein (GFAP) biomarkers.
Methods: Participants with TBI were prospectively enrolled at the National Institutes of Health between 2011 and 2020. All participants were offered pre- and post-contrast-enhanced MRIs, blood, and functional assessments at 30, 90, and 180 days, and 1, 2, 3, 4, and 5 years after TBI. Presence of TME was assessed using pre-and post-gadolinium contrast T1 and FLAIR.
Results: A total of 144 participants with TBI underwent pre-and post-contrast-enhanced MRIs, serum biomarkers, and functional assessments; 76 of the cohort underwent multiple assessments. Overall, of 144 initial assessment (median 189 days) from injury, 25 (17%) were positive for TME. Among those who were positive for TME, 15 had TME resolve by the follow-up assessments (median 83 days), and 10 exhibited persistent TME for months to years. All the 119 participants who were negative on TME at initial assessment continued to have no enhancement on the multiple follow-up contrast-enhanced MRI scans up to five years. Patients with TME had significantly increased concentrations of serum NfL and GFAP as compared to those who had no enhancement. There were no significant associations between the presence of TME and functional outcome.
Conclusions: In a subset of patients with a history of single TBI, we found MRI evidence of meningeal blood-brain barrier (BBB) disruption, which persisted for months to years after initial injury. Furthermore, meningeal BBB disruption was associated with increased concentrations of serum NfL and GFAP indicating the release of these proteins could be partially mediated by long-term BBB disruption.

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P0616 / #515

POSTERS: B01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

THE EFFECT OF HIGH-FAT DIET ON TAU PATHOLOGY

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Aims: Obesity is a modifiable risk factor in Alzheimer's disease and related tauopathy. The aim of the study is to elucidate the contribution of obesity to tauopathy with special consideration of brain functions in animal models.
Methods: PS19 mice with the mutation of P301S 1N4R human tau gene and wild-type (B6C3) mice were used. The high-fat diet(60%, HFD) or normal diet(ND) was fed for 6 months, from 3m to 9m of age. The differences in the behavior, brain pathology and functional neuroimaging were examined according to the type of diet in each mouse group.
Results: HFD-induced obesity and hyperglycemia were evident in PS19 mice contrary to the wild-type in which the individual variability impair the significance of the changes. However, the performance in behavior tests was comparable between ND and HFD in PS19 mice, while tended impaired cognitive function was noted in wild-type with HFD. In concordance with it, NeuN expression in brain homogenates was diminished in cortex ($p < 0.01$) and tending decreased in hippocampus ($p < 0.1$) along with lower insulin receptor β expression ($p < 0.01$) when examined by western blot. The levels of tau proteins, both total and phosphorylated forms, were markedly higher in PS19 mice than in the wild-type when examined using serially extracted brain tissues. However, HFD-related alterations were not distinct. On the contrary, the phosphorylated tau that was reactive with AT8 antibody was markedly increased in the RIPA-soluble fraction of hippocampus of the wild-type mice taking HFD.
Conclusions: Our study could be implicated that the continually existing and severe tau pathology might render the mice to be less susceptible to HFD-induced neuronal damage and tauopathy whereas wild-type mice were taken harmful effects with HFD.

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P0617 / #1351

POSTERS: B01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

ESTABLISHMENT OF A COMBINED MODEL FOR PARKINSON'S DISEASE AND DIABETES IN ENGRAILED-1 HEMIZYGOUS MICE ON A HIGH FAT DIET

Olivia Trujeque[1], Lautaro Belfiori[1], Kajsa Brolin[1], Filip Bäckström[1], Osama Elabi[1], Gesine Paul-Visse[2], Maria Swanberg[1]
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Aims: To investigate the effects of Type-2 Diabetes Mellitus (T2DM) on Parkinson's Disease (PD) susceptibility and progression we compare the effects of Engrailed-1hemizygozity (En1+/−) in SwissOF1(symptomatic) and C57Bl/6 (subclinical) mice and if introduction of a High Fat Diet (HFD) overrides the genetic resistance to neurodegeneration in the C57Bl/6-En1+/−mouse.
Methods: WT and En1+/- male mice are fed with control diet (CD) or HFD from 4-5 weeks of age (10% or 60% fat respectively). Blood glucose and weight are followed weekly. Glucose tolerance tests (2g/kg glucose i.p.) and insulin measurements are performed monthly. PD-like phenotypes are assessed by behavioural tests and histological analyses of nigral and striatal dopaminergic neurodegeneration.
Results: On CD, SwissOF1-En1+/-mice develop progressive PD-like neurodegeneration with 23% loss of nigral-dopaminergic neurons compared to WT mice at 16 weeks (mean 418±356 vs 5442±433, $p<0.0001$) and progressively more dystrophic neuroites in the striatum between 4 and 16 weeks. In contrast, C57Bl/6J-En1+/-mice on CD show a subclinical-phenotype with moderate/constant load of dystrophic dopaminergic neurites in the striatum at 4 and 16 weeks and no nigral cell loss. C57Bl/6J-mice on HFD have a dramatic increase in body weight compared to CD at 2 weeks after dietary intervention (28.26±0.7384gr and 23.8±0.4915gr respectively). At 6 weeks, C57Bl/6J-mice on HFD showed a significant impaired glucose tolerance compared to CD at 15 min (266.14±7.66mg/dl vs 156±11.72mg/dl), 30 min (259.2±21.24mg/dl vs 142.8±5.51mg/dl) and 60 min (245.05±14.26mg/dl vs 124.8±6.69mg/dl), returning to baseline at 120 min (166.88±9.79mg/dl vs 108.6±5.94mg/dl). Assessment of motor impairment and neurodegeneration of tyrosine hydroxylase-positive (TH+) nigral neurons and striatal TH+ neurites are ongoing.
Conclusions: In conclusion we have established a combined model for idiopathic PD and diabetes that allows for the identification of modifiable nutritional risk factors relevant for new therapeutic strategies for PD.

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P0618 / #2762

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

TRANSCRANIAL MAGNETIC STIMULATION DISTINGUISHES PATIENTS WITH BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA FROM PRIMARY PROGRESSIVE APHASIA PATIENTS

Francesco Di Lorenzo[1], Martina Assogna[2], Caterina Motta[2], Sonia Bonnì[2], Alessandro Martorana[2], Giacomo Koch[2]
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Aims: Introduction: In the recent years the use of neurophysiological techniques, combined with clinical and neuroimaging biomarkers, allowed to further deepen pathophysiological mechanisms of neurodegeneration. Here we aimed to determine whether a transcranial magnetic stimulation (TMS) approach can distinguish the behavioral variant of frontotemporal dementia (bvFTD) from Primary Progressive Aphasia (nf-PPA).
Methods: Methods: 30 patients with bvFTD and 30 PPA patients were enrolled. 30 Alzheimer`s Disease (AD) patients and 20 age-matched Healthy Subjects (HS) was also enrolled. Paired-pulse TMS was used to investigate short-interval intracortical inhibition (SICI) and facilitation (ICF), long-interval intracortical inhibition (LICI) , and short-latency afferent inhibition (SAI) to measure the activity of different intracortical circuits in all the participants. We also tested Long-term Potentiation (LTP) cortical plasticity with iTBS protocol. All the patients underwent an extensive neuropsychological evaluation, MRI and CSF sampling.
Results: Results: bvFTD patients exhibited abnormalities in SICI, LICI and iTBS induced cortical plasticity in comparison to PPA patients and HS. On the contrary PPA patients showed abnormal ICF and preserved SICI and LTP mechanisms. No differences were observed for SAI protocol. As expected AD patients exhibited an impaired iTBS-induced LTP and SAI in comparison to HS, PPA and bvFTD.
Conclusions: Conclusions: Intracortical circuitry investigation and iTBS protocol showed clear differences among bvFTD patients and PPA, probably reflecting distinct pathophysiological mechanisms. These preliminary findings pave to way for a more spread use of neurophysiological techniques in the diagnostic process of neurodegenerative diseases and also to find new biomarkers to use in future clinical trials.

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P0619 / #2698

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

ALZHEIMER'S DISEASE RISK GENE BIN1 MODULATES NEURAL NETWORK ACTIVITY THROUGH THE REGULATION OF L-TYPE CALCIUM CHANNEL EXPRESSION IN HUMAN INDUCED NEURONS

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Institut Pasteur de Lille, Inserm U1167, Lille, France

Aims: Bridging Integrator 1 (BIN1) is the second most important Alzheimer's disease (AD) risk gene after APOE, but its physiological roles and contribution to brain pathology are largely elusive. In this work, we tackled the short- and long-term effects of BIN1 deletion in human induced neurons (hiNs) grown in bi-dimensional cultures and in cerebral organoids.
Methods: We used three different models to generate human induced pluripotent stem cell (hiPSC)-derived neurons (hiNs) - including cerebral organoids, spontaneously differentiate neural progenitor cells and the novel ASCL1-mediated cell-lineage reprogramming to generate functional and highly synchronized networks of human neurons. Functional and molecular alterations in these cells were investigated using multi-electrode array (MEA) electrophysiology, single-nuclei RNA-sequencing (snRNAseq) and immunoassays.
Results: We show that BIN1 loss-of-function leads to specific transcriptional alterations in glutamatergic neurons involving mainly genes associated with calcium homeostasis, ion transport and synapse function. We also show that BIN1 regulates calcium transients and neuronal electrical activity through interaction with the L-type voltage-gated calcium channel Cav1.2 and regulation of activity-dependent internalization of this channel. Treatment with the Cav1.2 antagonist nifedipine partly rescues neuronal electrical alterations in BIN1 knockout hiNs.
Conclusions: To the best of our knowledge, this is the first demonstration of a BIN1-dependent activity in human neuronal physiology. Moreover, the convergence of phenotypes in our BIN1-deficient cellular models and the AD brain may suggest the involvement of this process in AD pathogenesis, leading to the breakdown of calcium homeostasis, dysregulation of neuronal electrical activity and gene expression that could be approachable by treatments with commonly used calcium channel blockers, such as nifedipine.

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P0620 / #2452

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

DIFFERENTIAL IMPACT OF NEURONAL AND ASTROCYTIC TAU EXPRESSION ON THE ACTIVITY OF NEURONAL NETWORKS.

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Aims: Tau pathology is strongly linked to neuronal network dysfunction and clinical symptoms in Alzheimer's disease and other tauopathies. Detailed understanding of how the presence of intracellular tau inclusions in various cell types affects the activity of neurons, however, is still missing. We have evaluated the impact of neuronal and astrocytic tau pathology on spontaneous neuronal activity of pyramidal and parvalbumin-positive (PV) interneurons in awake head-fixed mice.
Methods: We have used adeno-associated viral (AAV) vectors expressing aggregation-prone human truncated tau (amino acids 151-391/4R) and mCherry in equal ratio under synapsin or GFAP promotors to create mouse models with specific neuronal or astrocytic tau pathology and to study the downstream effects on neuronal network activity. We have used two-photon calcium imaging in awake-head fixed mice to assess the neuronal activity of cortical pyramidal cells and PV-interneurons in mouse models of tauopathies.
Results: AAV-induced expression of human truncated tau led to the accumulation of hyperphosphorylated tau in excitatory neurons and all tested classes of interneurons (synapsin promotor) or in astrocytes (GFAP promotor). In the neuronal AAV model we have detected hyperexcitability of PV interneurons in active head-fixed mice at stages with abundant accumulation of hyperphosphorylated tau, but no changes in the activity of pyramidal neurons. In the astrocytic AAV model we have observed no alterations in firing patterns of excitatory cortical neurons.
Conclusions: Our results suggest that alterations in the activity of PV interneurons might be an early event in tau-induced neuronal network dysfunction. Astrocytic tau pathology, however, had no detectable impact on spontaneous neuronal activity. For more detailed understanding of the impact of truncated tau on neuronal activity and function we are evaluating sensory-evoked neuronal responses in mouse models of tauopathies. Supported by APVV-19-0585.

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P0621 / #1648

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

HOW AMYLOID BETA AND TAU PATHOLOGIES IMPACT ENTORHINAL CORTEX-HIPPOCAMPAL CIRCUIT IN ALZHEIMER'S DISEASE?

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Aims: The entorhinal cortex and hippocampus (EC-HPC) are intimately involved in several memory functions, including spatial memory – a cognitive process affected early in Alzheimer's disease. In this presentation we will show how amyloid beta and tau pathologies affect neuronal and network function. We will demostrate how specific neuronal and network changes can be identified in the EC-HPC circuit using in vivo recordings.
Methods: Mouse models of Alzheimer's disease including App NL-G-F and hTau knockins were implanted with electrodes in the hippocampus or the entorhinal cortex and recorded extracellularly to obtain single units and local field potentials. The data was analyzed to identify changes in properties of specific cell types such as grid cells, border cells and head direction in EC and place cells in hippocampus. Network activity was also analyzed to identify dysfunction in specific oscillation frequencies. Data was also analyzed using machine learning tools to identify dysfunction in spatial decoding.
Results: We show that amyloid beta and tau pathologies affect neuronal and affect place cell and grid cell coding in AD mouse models. Analysis of high frequency oscillation revealed that network function was also affected. Further, we show how neuronal activity influences pathology and how ameliorating the firing rate can rescue neurodegeneration. Finally, we show how spatial decoding using machine learning tools could help identify neuronal changes earlier than currently possible.
Conclusions: We show that amyloid beta and tau pathologies can have a detrimental impact on the neuronal and network function which possibly leads to impaired coding of neurons responsible for spatial memory function. We also show that reducing neuronal activity could serve as a potential strategy to ameliorate neuronal dysfunction and reduce pathology.

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P0622 / #1214

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

A STUDY TO CORRELATE ALZHEIMER'S DISEASE CSF BIOMARKER PROFILE WITH ELECTROPHYSIOLOGICAL CHANGES TO NEURONAL FUNCTION AND SYNAPTIC PLASTICITY

Emily Lane-Hill[1], Thomas Karikari[2,3], Juan Lantero-Rodriguez[4], Elena Camporesi[5], Maria Olsson[6], Kaj Blennow[5], Henrik Zetterberg[7,8,9], Mark Wall[1]
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Aims: Although the toxicity of tau is well established, the mechanistic basis of its actions on neuronal function remains poorly understood. A fraction of the synaptotoxic tau pool in human Alzheimer's disease (AD) brains is released into cerebrospinal fluid (CSF). CSF biomarkers (Aβ42, total tau, P-tau181) are reliable and accurate predictors in the early stages of disease, however we do not fully understand what the functional changes are at these early stages.
Methods: CSF samples from patients with AD (collected in Gothenburg) were pooled for analysis and quantified for biomarker levels including tau, p-Tau181, Aβ1-42 and Aβ1-40. A fraction of this pool was then immunodepleted for tau to enable us to look at the tau-specific effects. Acute mouse brain slices were incubated with human AD CSF samples for 1 hour and then a suite of electrophysiological recordings were made to look at neuronal function, synaptic plasticity and hippocampal theta oscillations.
Results: Short (1 hour) incubation in AD CSF resulted in increased neuronal excitability in CA1 hippocampal pyramidal neurons, changes in basal synaptic transmission and synaptic plasticity (long-term potentiation) as well as altering the generation and maintenance hippocampal theta oscillations compared to control recordings. Whereas incubation with the fraction of the CSF pool that had been immunodepleted for tau did not result in significant effects to any of the tested parameters. Thus, confirming that the tau found within the AD CSF samples is playing a key role in the alteration of neuronal function and synaptic plasticity.
Conclusions: This proof of principle study outlines a method which can be used to correlate CSF biomarker profile, stage of disease progression and the acute tau-mediated electrophysiological changes to neuronal function and long-term synaptic plasticity.

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P0623 / #2222

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

DISAGGREGATING SINGLE CELL GENE EXPRESSION BY CELL TYPE IDENTIFIES ENDOGENOUS STRATEGIES OF RESISTANCE TO TAUOPATHY

Christopher Ayoub, Jeff Kuret
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Aims: Neurofibrillary tangles are a key marker of neurodegeneration in AD. Here we disaggregate single cell human gene expression data on the basis of cell type to identify differentially expressed genes associated with resistance to tauopathy.
Methods: We used the preprocessed single soma RNAseq dataset GSE129308, which includes AT8 positive and negative cells from human AD and control prefrontal cortex, clustered into 20 neuron subtypes. Using the AT8 positivity rate for each cell type as a proxy for vulnerability to tauopathy, we identified closely clustered cell types with disparate rates of vulnerability. We then used a Ratio-of-Ratios approach to test differential expression between vulnerable and resistant, AD and control, using a Hurdle model and likelihood ratio test. Differentially expressed genes were then analyzed for biological pathway enrichment.
Results: Excitatory neurons (Ex) distributed across a spectrum of vulnerability from a median AT8+ rate of 3.5% (Ex11) to 67% (Ex01). The nearest clustered cell type to Ex01 is Ex02, and demonstrates a similar median AT8+ rate of 65%, but the next nearest cell type, Ex10, shows a median AT8+ rate of only 28%. Differential gene expression comparing Ex01 to Ex10 enriched for biological processes such as protein catabolism and synaptic signaling.
Conclusions: This single cell dataset provides a new level of resolution for selective vulnerability by cell type, and allows comparison of closely related neurons that are directly affected by tauopathy. This complements previous work using gene expression to explore resistance to tauopathy on the basis of regional selective vulnerability. Here we identify genes that likely promote resistance to AD tauopathy in excitatory neurons. Further analysis can be broadened to inhibitory and pan-neuronal genes promoting resistance. These targets should then be validated in biological systems.

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P0624 / #2143

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

ACCUMULATION OF M6A IS CORRESPONDING TO TAU PATHOLOGY IN AN APPNL-G-F AND P301S TAU DOUBLE TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: our previous studies discovered that RNA binding protein HNRNPA2B1 functions as a linker connecting oligomeric Tau with N^6-methyladenosine (m^6A) modified RNA transcripts. Levels of m^6A accumulated up to 5-fold in the brains of Alzheimer subjects. The nucleocytoplasmic translocation of m^6A contributes to the integrated stress response in AD. However, the mechanism on how RNA modification was changed in AD is elusive. The study for the pathophysiology of AD has been hampered by the lack of an appropriate model that can recapitulate the integrated features of disease progression, including extracellular amyloid-β deposition, intracellular tau aggregation, neurodegeneration as well as neuroinflammation. In the proposed study we aim to develop a double transgenic mouse model of AD with both AppNL-G-F knock in and P301S Tau over-expression, to uncover the disease mechanism on epitranscriptomic level.
Methods: By the cross-breeding of AppNL-G-F knock in with the heterozygous P301S tau over-expression, we established an APP^{NLGF}/$MAPT^{P301S}$ double transgenic rodent model. The pathology examination was conducted by immuno-labeling and biochemistry method simoutaniously. Novel object recognition and Y-maze were used for assessment of the cognitive function.
Results: We discovered that amyloid-β deposition is accumulated in a time-dependent manner in the APP^{NLGF}/$MAPT^{P301S}$ mice. $APP^{NL\text{-}G\text{-}F}$ potentiated tau pathology in the APP^{NLGF}/$MAPT^{P301S}$ mice. Microglial activation is co-related to tau pathology while $APP^{NL\text{-}G\text{-}F}$ and $MAPT^{P301S}$ displayed synergistic effect in astrogliosis. Neurodegeneration and cognitive dysfunction is co-related to tau pathology in the double trangenic mouse. Surprisingly, the m^6A accumulation and the expression of its regulator proteins (ALKBH5, Mettl3 etc.) are changed in corresponding to tau pathology in APP^{NLGF}/$MAPT^{P301S}$ mouse.
Conclusions: The outcome of this study will provide new insight on brain m^6A representing a novel layer of complexity in gene expression regulation in AD and other related tauopathies.

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P0625 / #1319

POSTERS: B01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

POOLED GENOME WIDE CRISPR SCREENS TO IDENTIFY MODIFIERS OF VULNERABILITY TO TAU AGGREGATION IN HIPSC DERIVED NEURONS

David Schoendorf[1], Juergen Korffmann[2], Christopher Sliwinski[1], Sandra Bieisnger[2], Benjamin Mielich - Suess[2], Christiane Imhof[2], Christopher Untucht[2], Peter Reinhardt[2], Janina Ried[3], Laura Gasparini[1], Miroslav Cik[2], Dagmar Ehrnhoefer[1]
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Aims: One major hallmark of Alzheimer's disease (AD) is the aggregation of tau protein, which correlates with progression of cognitive decline. Nevertheless, Tau aggregates can also be observed sporadically in cognitively normal elderly individuals, independent of neuronal loss. This phenomenon suggests either the presence of additional pathomechanisms, or the loss of protective mechanisms that act synergistically with tau aggregation specifically in AD patients.
Methods: Here, we developed a genome wide CRISPR - mediated knock out screen in human induced pluripotent stem cell (hiPSC) derived cortical neurons. We generated a Microtubule Associated Protein Tau (MAPT) mutant hiPSC line with inducible expression of Cas9, containing a stably integrated genome-wide sgRNA library. Differentiated neurons were treated with recombinant tau aggregates to induce endogenous tau aggregation. To identify genes associated with vulnerability to Tau aggregation, cell pools were collected and subjected to next generation sequencing (NGS) and bioinformatic analysis.
Results: Pathway enrichment analyses of essential genes were in agreement with commonly described cellular essential mechanisms such as mRNA processing and protein synthesis. Unbiased computational analysis of changes induced by tau aggregation highlighted genes regulating processes important to neuronal function and dysfunction such as mitochondrial pathways.
Conclusions: A whole genome pooled CRIPSR screen has been successfully performed in hiPS-derived neuronal model of endogenous Tau aggregation. Follow up studies of top hits may provide insight into pathways that promote the neuronal susceptibility to Tau aggregation in AD.

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P0626 / #2602

POSTERS: B01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

CLINICOPATHOLOGICAL ANALYSIS OF AGING-RELATED TAU ASTROGLIOPATHY AND ITS ASSOCIATION WITH CEREBROVASCULAR PATHOLOGY

Seong-Ik Kim[1,2], Sooyeon Yoo[1,2], Kwanghoon Lee[1,2], Yu-Mi Shim[1,2], Jae-Kyung Won[1,2], Sung-Hye Park[1,2]
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Aims: Aging-related tau astrogliopathy (ARTAG) is an abnormal accumulation of phosphorylated tau protein in astrocytes of the aging brain. We examined the relationship between collectible clinicopathological variables and the distribution of ARTAG lesions. Furthermore, we aimed to verify the hypothesis that the presence of small-vessel cerebrovascular pathology affects the development of ARTAG lesions.
Methods: Pathologically diagnosed Alzheimer's disease neuropathologic change (ADNC; n=6), primary age-related tauopathy (PART; n=6), and chronic traumatic encephalopathy (CTE; n=2) cases were obtained from the Seoul National University Hospital Brain bank. With the aid of AT8 immunohistochemistry, the distribution of granular/fuzzy astrocytes (GFA) and thorn-shaped astrocytes (TSA) were evaluated. Three cases with arteriolosclerosis were also analyzed to determine any correlation between the degree of arteriolosclerosis, perivascular hemosiderin leakage, perivascular dilatation, and the presence of ARTAG lesions in 9 different gyral regions and 4 different basal ganglia structures.
Results: The most common site for the ARTAG lesion was the mammillary body (11/14). TSA of occipital lobe was found more frequently in ADNC (4/6) than PART (0/6). Lobar subpial TSA was mainly observed in the depth of the cortical sulci rather than the crest or lateral part of the gyri. There was no significant correlation between each component of small-vessel cerebrovascular pathology and the presence of ARTAG lesions. In the case of ADNC with a high Braak stage and high CTE, it was unable to distinguish the lesion only with AT8 due to the strong background staining.
Conclusions: ARTAG is a common pathology observed in the aging brain. It has been considered that its development relates to several clinicopathological factors and ARTAG should be differentiated from other tauopathies. We concluded that its association with small-vessel cerebrovascular pathology is uncertain.

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P0627 / #1845

POSTERS: B01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

IDENTIFICATION OF HISTOPATHOLOGICAL AND GENETIC FEATURES OF AGE-RELATED COGNITIVE IMPAIRMENT USING DEEP LEARNING.

Kurt Farrell[1], Andrew Mckenzie[2], Gabriel Marx[1], Daniel Koenigsberg[1], Bergan Babrowicz[1], Mary Sawyer[1], Megan Iida[1], Jamie Walker[1], Timothy Richardson[1], Gabriele Campanella[3], Ann Mckee[4], Thor Stein[5], Thomas Fuchs[3], Charles White[6], John Crary[1]
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Aims: To identify the structural features of brain microanatomy that are robustly associated with cognitive impairment using a weakly supervised multiple instance learning algorithm and translate those results to genetic data using polygenetic risk scores (PRS).
Methods: A cohort of elderly brain donors with tau pathology but no to mild amyloid pathology was assembled with and without antemortem cognitive impairment (n = 367, 349 respectively). A previously described multiple instance learning algorithm was run on digitized whole slide images (WSIs) from the hippocampus and frontal cortex stained for Luxol fast blue, hematoxylin, and eosin. Feature vectors were generated on 256×256 pixel segmented tiles. For WSI classification, we used tenfold Monte Carlo cross-validation to split the data into training (80%), validation (10%), and test (10%) sets. Hue saturation and pixel counting measurements were used to generate quantitative features from the tiles. Donor genotyping data and public summary statistics were used to generate PRSs.
Results: In predicting cognitive impairment in the hippocampus, our model had a mean area under the curve (AUC) on the test subsets of 0.63 (p=0.006) and a mean balanced accuracy of 0.59 (p=0.013). In the frontal cortex, we found a mean AUC of 0.67 (p=0.002) and a mean balanced accuracy of 0.58 (p=0.009). PRSs were used to associate individual genetic risk loads with generated quantitative endophenotypes from WSIs.
Conclusions: Our results identify unanticipated aspects of neuropathology in cognitive impairment and the ability to translate these findings to genetic risk.

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P0628 / #1984

POSTERS: B01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

MICROGLIA IN P301S TAU MICE EXHIBIT MARKERS OF CELLULAR SENESCENCE AND RNA SPLICING FACTOR ALTERATIONS

Matthew Mason[1], Aviva Tolkovsky[1], Suchira Bose[2], Maria Grazia Spillantini[1]
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Aims: Ageing is the principal risk factor for sporadic neurodegenerative diseases. Cellular senescence has previously been reported in mouse models of neurodegeneration, but it remains unclear whether senescent glia are causally involved in the pathogenesis of these diseases. Previously, we observed the onset of a senescence-like phenotype in naïve microglia cocultured with tau aggregate-bearing neurons (Brelstaff, et al. 2021. Sci adv. 10.1126/sciadv.abg4980). Here, we sought to determine whether markers of cellular senescence can be detected in microglia acutely isolated from the brains of transgenic P301S tau mice as well as other markers of accelerated ageing that may be attributed to tau pathology.
Methods: RNA was extracted from microglia acutely isolated from symptomatic 6 month-old P301S mice and age-matched wildtype C57Bl6 mice. The extracted RNA was used to perform candidate-driven qPCR for markers of senescence (P16ink4a, P21), cellular stress (GADD45a, GADD34) and RNA splicing factors (RBFOX2, PTBP2).
Results: Microglia from P301S transgenic mice showed significantly downregulated expression of homeostatic markers P2RY12 and TMEM119. Additionally, microglia from P301S mice showed upregulated GADD45a and GADD34, and the senescence marker P21, supporting our previous results (Brelstaff, et al. 2021. Sci adv. 10.1126/sciadv.abg4980). Interestingly, these microglia also showed significant downregulation of the RNA-binding proteins RBFOX2 and PTBP2, a change typically associated with ageing.
Conclusions: Microglia in the brains of P301S tau mice express markers of senescence and show downregulation of RNA splicing factors. Microglial RNA splicing in the context of tauopathy has not been explored. RNA-sequencing will be performed to characterise the transcriptomes of these microglia and to explore potential differential splicing events arising from the observed downregulation of RNA splicing factors. Alternative splicing may be a novel mechanism for the transduction of genetic risk variants in neurodegeneration.

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P0629 / #429

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

MULTIPLES VITAMIN DEFICIENCY PROMOTES NEURODEGENERATION AND DEREGULATES EPIGENETICS IN MOUSE MODEL OF ALZHEIMER'S DISEASE

Sook Yoong Chia[1], Sarivin Vanan[1], Zhi Wei Zhang[1], Mei Jiang[2], Nagaendran Kandiah[3], Li Zeng[1]
[1]National Neuroscience Institute, Research, Singapore, Singapore, [2]Institute of Stem Cell and Regenerative Medicine, Department Of Human Anatomy, Dongguan, China, [3]Lee Kong Chian School of Medicine, Dementia Research Centre, Singapore, Singapore

Aims: Dietary vitamins are integrally associated with AD pathogenesis. Vitamins deficiency such as B1, D, and B12 have been linked with an increased risk of AD. However, the impact of vitamin deficiency contributes to the early onset or the late stage of AD remains to be elucidated. Moreover, there is a lack of information on the role of multiple vitamin deficiencies (MVD) in AD. Here, we aim to investigate the role of MVD in the early-onset and late stages of AD pathology. Given that nutrition is closely related to epigenetics in AD, we further examine the molecular basis of epigenetic regulation driven by MVD.
Methods: 3xTgAD and wild-type (WT) mice at 3- (young) and 12-month-old (aged) were subjected to a vitamin B_1, B_{12}, and D deficiency diet, followed by administration of a chow diet or single vitamin supplementation. These mice were then examined for body weight, short-term learning memory, and AD pathology. The status of DNA methylation and histone modification has been examined as well.
Results: MVD reduced body weight and impaired short-term memory with increased phosphorylated Tau in young WT and 3xTgAD. Administration of a chow diet containing essential vitamins to MVD-fed mice significantly restored these phenotypes. Similar phenomena were observed in vitamin B_1 supplementation. In aged WT and 3xTgAD, MVD caused inflammation induction, autophagy, and mitochondrial dynamic dysregulation but not in young mice. These phenotypes were reversed by chow diet feeding in WT. Surprisingly, MVD reduced 5hmC and TET levels shed light on the biological understanding between vitamin and epigenetics in AD pathology.
Conclusions: MVD affects brain function and epigenetic status in the brain. Advances in understanding vitamin-epigenome interaction will provide insight into the development of novel preventive and therapeutic approaches to AD.

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P0630 / #2787

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

ANALYSIS OF SUMO-1 PROTEIN RELOCATION IN HUMAN BRAIN TISSUE FROM ALZHEIMER'S DISEASE PATIENTS

Marco Feligioni[1], Ludovica Zaccagnini[1], Annalisa Davin[2], Valentin Medici[2], Tino Emanuele Poloni[2]
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Aims: Sumoylation is a post-translational modification due to the covalent binding of SUMO proteins to specific protein targets. It involves several cellular events, including transcriptional regulation, nucleus-cytoplasmic transposition, and apoptosis. Not surprisingly, some proteins involved in Alzheimer's such as Tau, alpha-synuclein and TDP-43, undergo the SUMOylation process. However, the SUMOylation and SUMO protein level changes in human tissues have never been well determined. So here we propose to evaluate the SUMO proteins, SUMOylated proteins localization in the tissue of Alzheimer's patients using autoptic tissues.
Methods: The presence of SUMO-1 in cortical brain tissue (frontal and temporal) of different phases from Alzheimer's patients was characterized by using: (i) Western blotting analysis to quantify a possible variation of the expression of SUMO-1 and UBC9 (sumo-conjugating enzyme); (ii) Immunohistochemistry assay to verify the localization of the SUMO-1 protein. (iii) Immunofluorescence assay to detect cells in which a change in the expression and localization of SUMO-1 occurs.
Results: Immunohistochemistry DAB staining revealed a relocalization of SUMO-1 from the nucleus to the cytoplasm of some cells of patients with the disease. This leakage is greater in patients with higher disease stage and less or none at all in patients with the mild stage. Immunohistochemistry also appears to show increased SUMO-1 expression where relocation is greatest.
Conclusions: The results obtained with immunohistochemistry show a difference in the expression and localization of SUMO-1 in patients at the different stages. This difference is present only in some cells. This may explain why we have not seen so far an increase in SUMO-1 expression with western blots, which show the total trend of lysed tissue and not specific cells. For this, we use immunofluorescence to identify the cells affected by this variation

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P0631 / #932

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

EX VIVO TAUOPATHY MODEL: ORGANOTYPIC HIPPOCAMPAL SLICE CULTURE FROM ADULT TAU OVEREXPRESSING MICE

Susanna Kemppainen[1], Nadine Huber[2], Roosa-Maria Willman[1], Ana Zamora Martinez[3], Petra Mäkinen[1], Henna Martiskainen[1], Mari Takalo[1], Annakaisa Haapasalo[2], Uwe Himmelreich[3], Mikko Hiltunen[1]
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Aims: Organotypic slice culture models surpass conventional in vitro methods in many aspects. They retain all tissue-resident cell types, tissue hierarchy, and to some extent the connectivity. For studying complex multifactorial neurodegenerative diseases like Alzheimer's disease, it is crucial to maintain cellular crosstalk in an accessible model system. Organotypic slice cultures from postnatal tissue are an established tool in the field, but adult tissue-originating systems are lacking and desperately needed as young potent tissue cannot fully model adult or senescent brain.
Methods: To establish an adult-originating slice culture system for neurodegenerative studies, we made hippocampal slice cultures from 5-month-old tauopathy model P301S mice. We used interface of semi-porous membrane and cultured slices in serum-free culture conditions for two weeks. In addition to characterizing the system, we set out to test efficacy and target engagement of an antibody for hyperphosphorylated tau (pTau) with a nanomaterial conjugate.
Results: Approximately 60 % of slices adhered to membrane and retained intact granular cell layer and GFAP-positive astrocytes during culture. P301S slice neurons expressed pTau throughout granule cell layer and secreted pTau to culture medium whereas wildtype slices did not. Also, LDH release and IL6 secretion was increased in P301S slice medium compared to wildtype controls, indicating elevated cytotoxicity and inflammation. Antibody or controls tested did not influence the aforementioned parameters. With confocal imaging, we could show target engagement of the antibody to pTau-expressing neurons.
Conclusions: This tauopathy slice culture model enables measuring extracellular and intracellular effects of different mechanistic or therapeutic manipulations on tau pathology in adult tissue without the hindrance of blood brain barrier. Even though no therapeutic effect could be shown for the pTau antibody, this system could prove target engagement inside living tissue *ex vivo*.

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POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

EXPLORING THE IMPACT OF MECHANICAL STRESS IN NEURODEGENERATION

Francesco Napoletano
University of Trieste, Department Of Life Sciences, Trieste, Italy

Aims: Mechanical stress has been proposed as a common denominator of different pathological conditions, including neurodegenerative disorders such as Alzheimer's disease. While mechanical signals shape brain development throughout morphogenesis, a role of mechanical forces in neurodegeneration has been suggested by the observed correlation of traumatic brain injury and cerebrovascular hemodynamic stress with the risk of some neurodegenerative disorders. Furthermore, neurodegenerative diseases and brain injury are associated with changes in composition and properties of the extracellular matrix.
Methods: We investigated the role of tissues mechanical alterations in tneurodegenrative pathologies, using *in vivo* models of Alzheimer's disease.
Results: We provide genetic and molecular evidence that alterations in mechanotransduction could impact on neuronal survival and function in stressful conditions.
Conclusions: Our findings help better understand the pathogenesis of neurodegenerative disorders and could lead to the identification of therapeutic targets.

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P0633 / #728

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

PROTEOMICS-BASED DISTINCTION OF PATHOGENIC FROM PHYSIOLOGICAL TAU INTERACTOMES – INSIGHTS INTO TAU FUNCTION AND DYSFUNCTION IN ALZHEIMER'S DISEASE

Marie Neu[1], Iwan Parfentev[2], Andreas Striebinger[1], Hanna Tarhonskaya[1], Dhaval Nanavati[3], Janina Ried[2], Laura Gasparini[1], Dagmar Ehrnhoefer[1]
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Aims: The formation of neurofibrillary tangles consisting of insoluble Tau protein strongly correlates with cognitive decline in Alzheimer's disease (AD). Tau-mediated neuronal dysfunction may arise from a toxic gain of function by Tau aggregates or a loss of physiological functions such as impaired axonal transport or unstable microtubules. Here, we aim to identify proteins that differentially interact with Tau in control or AD brain samples to discover leads for the development of novel biomarkers and therapeutically targetable pathways.
Methods: Brain tissue lysates from AD patients and controls are subjected to parallel immunoprecipitation experiments with total or phospho-Tau antibodies, followed by mass-spectrometry based interactome analyses.
Results: In control brain tissue, a significant enrichment of kinases and synaptic proteins among Tau interactors was observed, confirming the previously published role for Tau at the synapse as well as the importance of physiological Tau phosphorylation events. In AD brains, Tau interactors were enriched for DNA- and RNA-binding proteins as well as factors involved in endocytosis and vesicle transport. Some of these interactors were found with both total and phospho-Tau antibodies.
Conclusions: Our data suggest that altered biochemical and biophysical properties of Tau in AD are associated with changes in the Tau interactome, which may reflect disease-associated functional changes in affected neurons. The use of different antibodies for immunoprecipitation furthermore allows for the comparative analysis of different Tau interactomes within the same brain sample to further dissect the potential functional impact of Tau post-translational modifications.

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P0634 / #2422

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

AN ACCESSIBLE AND SCALABLE BLOOD-BASED ASSAY FOR PTAU217

Stuart Portbury[1], Inge Verberk[2], Sherif Bayoumy[3], Wiesje Van Der Flier[4], Jeroen Vanbrabant[5], Charlotte E. Teunissen[6], Erik Stoops[7], Andreas Jeromin[1]
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Aims: Aims: Establish a robust and scalable fit for purpose plasma-based ultra-sensitive assay utilizing a proprietary monoclonal pTau217 antibody.
Methods: Methods: In partnership with two independent contract research organizations (CROs), ALZpath has developed reagents for pTau217 and evaluated these reagents using various detection antibodies and calibrators across different immunoassay platforms. An ultra-sensitive blood-based ELISA assay, using a peptide calibrator, has been developed on the semi-automated single-molecule array Simoa® platform.
Results: Results: The ALZpath ptau217 Simoa® assay show good precision (inter-day CVs of less than 12 %) and good sensitivity with a functional lower limit of quantification of 0.260 pg/ml. Parallelism/ dilutional l linearity is within the 80-120 % range. The assay performance in plasma (n = 120) and CSF (n = 42), from AD vs. control participants, demonstrated greater than 90% of all samples were detected with a coefficient of variation below 10%. The assay demonstrated a functional (in matrix) lower limit of quantitation (LLOQ) of 0.26 pg/mL and strong linearity within 15% of acceptance criteria. The capability of the ALZPath pTau217 assay to differentiate AD exceeded the AUCs of the commercial Simoa® pTau181 based assay (Bayoumy, *et al AD/PD 2023.*)
Conclusions: Conclusion: ALZpath has successfully developed a scalable reagent with high selectivity for pTau217 and established a fit-for-purpose validated Simoa® assay for pTau217 in blood with robust precision and diagnostic accuracy in AD compared to controls based on clinical diagnosis. The test will be launched for clinical use in Q4 of 2022 as laboratory-developed test (LDT) and advanced to an inv-vitro diagnostic (IVD). Evaluation in independent clinical cohorts with multiple co-morbidities will be reported.

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P0635 / #2376

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

A UNIQUE CASE OF SEVERE CHRONIC TRAUMATIC ENCEPHALOPATHY IN A SPECIAL WARFARE COMBATANT-CRAFT CREWMAN OF THE UNITED STATES NAVY

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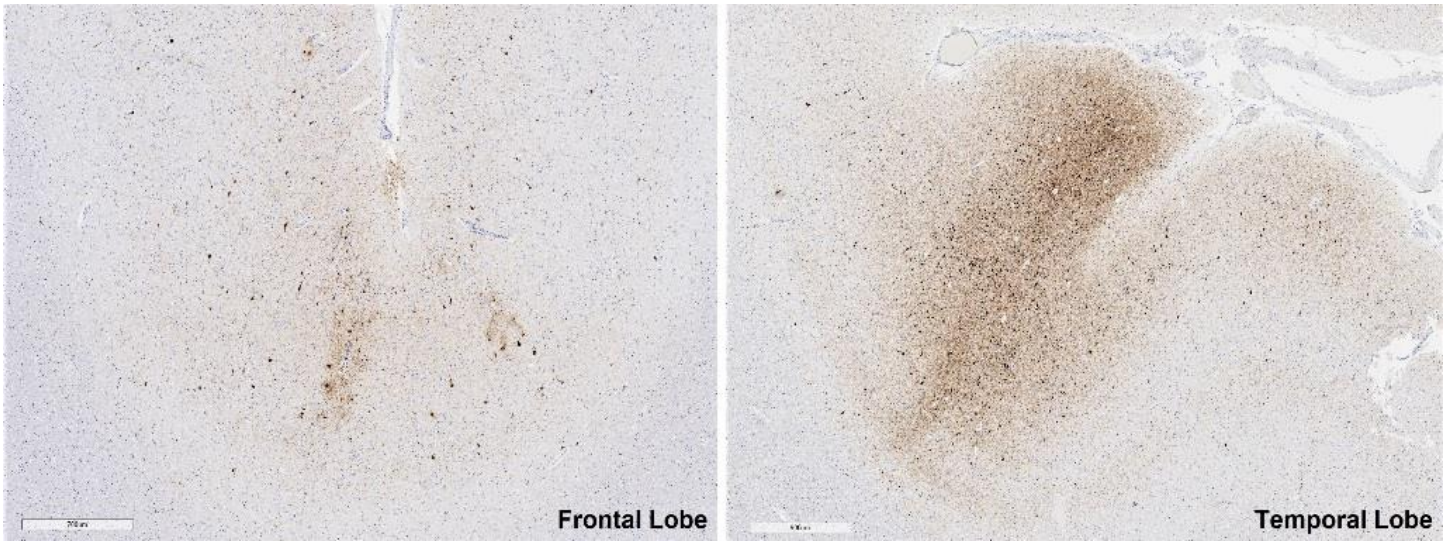
Aims: Chronic Traumatic Encephalopathy (CTE) is an acquired tauopathy that has been observed in those subjected to repeated impact head injury, such as former boxers and American football players. By extension, the assumption has been that repeated head impacts, and related concussions, are closely linked to the pathophysiology of CTE. Recently, we reported that CTE among military personnel is relatively uncommon, usually mild, and most strongly associated with civilian contact sports rather than military activities (Priemer et al. *NEJM* 2022).
Methods: Complete neuropathological examination, including immunohistochemistry for phosphorylated-tau, of the brain of a 44-year-old former baseball player who served for 20 years as a US Navy Special Warfare Combatant-Craft (SWCC) Crewman and who had prominent neuropsychiatric symptomotology.
Results:



Neuropathological examination revealed severe CTE involving multiple lobes of the brain.
Conclusions: We report a case of severe CTE associated with prominent neuropsychiatric symptomatology in a SWCC crewman. SWCC crewmen operate small, specialized boats at high velocities (95+ kilometers/hour) in high seas, and sustain numerous severe "shock forces" as the boats impact with waves. Separate studies show that these wave impacts are associated with 15+ G-forces, and occur up to 150 times per hour. Crewmen do not typically hit their heads, and do not report concussions, but instead receive repeated, severe whiplash-like jostling of their heads. While this report involves a single case, it suggests that CTE may be associated more with repeated brain distortion from non-impact acceleration/deceleration forces, rather than impact itself. The case further emphasizes the importance of sub-concussive events toward CTE development. These observations may provide insights into CTE pathogenesis in the setting of contact sports and beyond. As such, SWCC crewmen deserve increased attention regarding other potential instances of CTE.

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P0636 / #1995

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

NEUROPATHOLOGICAL CONTRIBUTORS TO COGNITIVE IMPAIRMENT IN BRAIN DONORS EXPOSED TO REPETITIVE HEAD IMPACTS

Nicole Saltiel[1,2], Yorghos Tripodis[1], Talia Menzin[1], Aliyah Olaniyan[1], Zachary Baucom[1], Joseph Palmisano[1], Brett Martin[1], Madeline Uretsky[1], Evan Nair[1], Bobak Abdolmohammadi[1], Arsal Shah[1,2], Raymond Nicks[1,2], Robert Stern[1], Victor Alvarez[2,3], Russ Huber[2,3], Jesse Mez[1], Ann Mckee[1,2,3], Michael Alosco[1], Thor Stein[2,3]
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Aims: Exposure to repetitive head impacts (RHI) is associated with cognitive symptoms and risk for multiple neuropathologies. The prevalence of co-morbid pathologies and contributions to cognitive symptoms in people exposed to RHI is unknown. Here, we examined the co-occurrence of 13 neuropathologies and their contributions to cognitive symptoms and dementia in RHI-exposed brain donors.
Methods: Neuropathologists examined brain tissue from 581 RHI-exposed donors and assessed for the presence of 13 neuropathologies, including Alzheimer disease (AD), Lewy body disease (LBD), chronic traumatic encephalopathy (CTE), and limbic TDP-43 (LATE). Measures of independent functioning and cognitive challenges were obtained from informants and medical records. Antemortem dementia was adjudicated via consensus conferences, based on informant-reported clinical presentation. Frequencies of pathological co-occurrence were compared to a simulated distribution assuming no intercorrelation, and each pathology's contribution to variance in dementia status and cognitive scale scores was determined.
Results: The sample age range was 13-97 (mean: 60.0 [20.2 SD]). Of 581 brain donors, 76.2% had at least one moderate-severe neurodegenerative or cerebrovascular pathology. The most common neurodegenerative diseases observed were CTE, LATE, AD, and hippocampal sclerosis. We observed far fewer unique pathology combinations than would be expected if the pathologies were independent (252 vs 278; p=0.004). The greatest contributors to dementia were AD, cortical LBD, hippocampal sclerosis, cerebral amyloid angiopathy, and CTE. Altogether, all neuropathologies accounted for 48% of variance in dementia status.
Conclusions: In this sample of brain donors exposed to RHI, multiple neuropathologies were common and highly correlated. This contrasts with findings from population-based aging studies and may be a result of common exposure to RHI. Cognitive symptoms were associated with multiple neuropathologies. These findings emphasize the role of mixed neuropathologies in cognitive decline associated with exposure to RHI.

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P0637 / #2335

POSTERS: B01.U. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

THE PTAU INTERACTOME IN SPORADIC ALZHEIMER'S DISEASE ACROSS APOE GENOTYPES

Manon Thierry[1], Jackeline Ponce[2], Mitchell Martà-Ariza[1], Arline Faustin[3], Dominique Leitner[1], Geoffrey Pires[1], Evgeny Kanshin[2], Eleanor Drummond[4], Beatrix Ueberheide[2], Thomas Wisniewski[5]
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Aims: *APOE* polymorphism is the major genetic risk factor for sporadic Alzheimer's disease (AD), defined by the abnormal accumulation of β-amyloid (Aβ) and phosphorylated Tau (pTau). Although the various ApoE isoforms are known mostly to differentially modulate Aβ aggregation and clearance, recent data support an influence of *APOE* genotype on pTau accumulation, which correlates better with AD symptom progression. The exact effects of ApoE isoforms on pTau metabolism, however, remain unclear. Localized proteomic methods developed in our laboratory, on *post-mortem* human brain, are an ideal strategy to elucidate these aspects *de novo*.
Methods: Co-immunopurifications against pTau pSer396/pSer404 from frozen frontal cortex were combined with mass spectrometry to map out, for the first time, the pTau interactome across *APOE* genotypes in 10 sporadic AD cases (n=5 $APOE_{3/3}$ and n=5 $APOE_{4/4}$).
Results: A total of 62% and 70% of the proteins previously identified as *bona fide* pTau interactors were respectively enriched in the $APOE_{3/3}$ and $APOE_{4/4}$ pTau immunopurified samples (FC ≥ 1.50, IP_{PHF1} *vs.* $IP_{IgG\ control}$), validating our approach (Drummond *et al*., 2020). In $APOE_{3/3}$ pTau immunopurified samples, 1130 proteins were enriched (FC ≥ 1.50), including 66 proteins absent from the $APOE_{4/4}$ group. A total of 1330 proteins were enriched in $APOE_{4/4}$ pTau immunopurified samples (FC ≥ 1.50), among which 114 proteins were not found in the $APOE_{3/3}$ group. In comparison to the $APOE_{3/3}$ group, 280 proteins were upregulated in the $APOE_{4/4}$ group (FC ≥ 1.50, $APOE_{4/4}$ *vs.* $APOE_{3/3}$), while 215 proteins appeared downregulated (FC ≤ 0.67). Refined interaction and network analyses are pending to complete these observations.
Conclusions: Our proteomic results will be validated in the human brain by histological and biochemical studies, paving the way to the identification of new therapeutic targets for AD.

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P0638 / #290

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

NEUROPROTECTIVE EFFECT OF DA-7503, A NOVEL TAU AGGREGATION INHIBITOR, AGAINST OKADAIC ACID-INDUCED TAUOPATHY IN VITRO AND IN VIVO

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Aims: The objective of this study is to investigate *in vitro* and *in vivo* the neuroprotective effect of DA-7503, a novel tau aggregation inhibitor, on tauopathy induced via okadaic acid (OA), a phosphatase 2A inhibitor.
Methods: Differentiated SH-SY5Y human neuroblastoma cells were treated with OA alone or with DA-7503. For protein analysis, levels of pTau and free tubulin were measured after 3 hours of treatment. Neurite outgrowth was examined using a live-cell fluorescent plasma membrane dye and total neurite length was calculated after 6 hours of treatment. We also evaluated effects of DA-7503 on memory deficits and tau phosphorylation in a tauopathy mouse model. 8-week-old C57BL/6 mice were microinjected with OA 100 ng, and then continuously administered with DA-7503 for 2 weeks. Effects were also examined long-term by administering DA-7503 for 4 weeks from 2 weeks after i.c.v. injection of OA.
Results: *In vitro*, DA-7503 decreased the pTau and free tubulin levels increased by treatment with OA, suggesting that DA-7503 exerts a protective effect against microtubule destabilization. From this, it was hypothesized that microtubule destabilization will have a detrimental effect on neuronal processes. Consistently, OA treatment affected neurite outgrowth in a concentration-dependent manner. The decrease in neurite outgrowth upon OA treatment was attenuated by DA-7503. *In vivo*, oral administration of DA-7503 for 2 weeks significantly prevented spatial memory deficits and significantly reduced pTau levels in the hippocampus. In addition, DA-7503 for 4 weeks from 2 weeks after i.c.v. injection of OA also attenuated OA-induced memory impairment and reduced pTau in the hippocampus.
Conclusions: Our findings indicate the neuroprotective effect of DA-7503 on OA-induced tauopathy *in vitro* and *in vivo*, and highlight its potential as a promising therapeutic drug for tauopathies, including Alzheimer's disease.

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P0639 / #1317

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

TAU PHOSPHORYLATION AT RESIDUE THR217 AND TAU AGGREGATION IN DIFFERENT IN VITRO MODELS

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Aims: Recent studies highlight phosphorylated tau at residue threonine 217 (pThr217) as a new promising plasma biomarker for pathological changes implicated in Alzheimer's disease (AD) and therefore it also gained attention as possible target in AD therapeutics. To provide platforms to screen for possible pThr217-related drugs and assess pThr217 implications in AD we tested the presence and modulation of pThr217 and different other ptau sites in several established *in vitro* models.
Methods: SHSY-5Y cells overexpressing hTau441-P301L as well as primary neurons isolated from PS19 embryos were cultivated and treated with different kinase inhibitors (e. g. CHIR99021), autophagy modulators (e. g. rapamycin) or anti-aggregatory agents (e. g. Anle138) for 4 h, 24 h and 48 h. The level of total tau as well as tau phosphorylated at Thr217, Thr181, Thr231 or Ser396 were evaluated by immunocytochemistry or immunosorbent assays. Tau aggregation was tested for some conditions using a HTRF-based assay.
Results: Tau phosphorylated at Thr217 was detected in both *in vitro* models. In SHSY-5Y-hTau441-P301L cells time-dependent modulation of pThr217 was observed after kinase inhibitor treatments. Currently evaluations in primary PS19 neurons are completed and analyzed.
Conclusions: *In vitro* methods to screen for the activity of compounds are of high relevance for the early stages of drug development. The here presented assays are developed as complementary tools to our transgenic and induced *in vivo* tauopathy models. The presence as well as the capability to modulate pThr217 phosphorylation in these *in vitro* models was shown.

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P0640 / #1383

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

GEBR-7B, A SELECTIVE INHIBITOR OF PHOSPHODIESTERASE 4D, INCREASES PHOSPHORYLATION OF TAU AT SER214 RESIDUE

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Aims: Tau can be phosphorylated by multiple kinases at several sites. Among such kinases, the cAMP-dependent protein kinase A (PKA) phosphorylates tau at Ser214 (pTAU-S214), an event that was shown to reduce the pathological assembly of the protein. Given that the neuronal cAMP/PKA-activated cascade is involved in synaptic plasticity and memory, and that cAMP-enhancing strategies demonstrated promising therapeutic potential for the treatment of cognitive deficits, we investigated the impact of cAMP on pTAU-S214 in N2a cells and rat hippocampal slices.
Methods: To increase the intracellular levels of cAMP we used GEBR-7b and forskolin (FSK). GEBR-7b is a specific inhibitor of the enzyme phosphodiesterase 4D (PDE4D) that hydrolyses cAMP, while FSK is an activator of adenylyl cyclase, the enzyme that synthesizes cAMP from ATP. Tau phosphorylation was analyzed by western blot with high-affinity phosphoepitope recognition antibodies. Amyloid-β (Aβ) peptides and cAMP levels were measured with specific ELISAs.
Results: Our results confirm that the activation of adenylate cyclase increases pTAU-S214 in both model systems and, more interestingly, this effect is mimicked by GEBR-7b, a PDE4D inhibitor with proven pro-cognitive efficacy in rodents. Furthermore, we show that the cAMP-mediated phosphorylation of tau at Ser214 occurs independently of Aβ peptides, at least under physiological conditions.
Conclusions: Although further investigation is needed, our results indicate that PDE4D inhibitors, which have consistently demonstrated memory-enhancing effects in Alzheimer's disease models, increase tau phosphorylation at a serine residue that could prevent protein aggregation into PHFs, an effect that, if confirmed *in vivo*, could endow disease-modifying properties to these drugs.

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P0641 / #2041

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

REPURPOSING ADRENORECEPTOR DRUGS FOR ALZHEIMER'S DISEASE?

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Aims: A few studies have implicated the protective role of hypertension or asthma drugs acting on adrenoreceptors (AR) in Alzheimer's disease (AD), while other studies have associated these drugs with increased risk. Therefore, the role of β AR is controversial and the effects observed could be an off target effect of the various drugs used in the studies. In this regard we investigated whether specific hypertension drugs blocking β1 AR, and asthma drugs activating β2 AR have the potential to affect tau hyperphosphorylation and β amyloid (Aβ) aggregation in order to determine if β AR play a role in AD.
Methods: SHSY-5Y cells were used and tau hyperphosphorylation induced by hypothermia. Cells were incubated with selected drugs acting on the β adrenoreceptors as agonists or antagonists, and tau hyperphosphorylation was followed by western blotting. Aβ aggregation was studied in vitro with the Thioflavin T assay.
Results: The β1 agonist dobutamine, decreased tau hyperphosphorylation, and the β1 blocker Atenolol had marginal effect. Dobutamine, not only showed the most pronounced decrease in tau hyperphosphorylation when used alone, but in combination with atenolol the effect was synergistic to the point where no tau hyperphosphorylation was evident. We attributed this to dobutamine's non specific β2 effect and indeed when formoterol, a β2 agonist was used, it caused a decrease in tau hyperphosphorylation. Dobutamine and atenolol also inhibited Aβ aggregation in vitro.
Conclusions: β2 AR seem to have a protective a role in AD, and some of the drugs tested also inhibit Aβ aggregation making them potential multi target drug ligands. More studies are needed to fully understand the potential protective role of these receptors in AD.

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P0642 / #381

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

ALTERATIONS IN ENDOCYTIC AND MITOCHONDRIAL PATHWAYS SUBSERVE THE NEUROPROTECTIVE, ANTI-AMYLOIDOGENIC ACTION OF CLEAVAGE-SPECIFIC TAU 12A12MAB IN AD MOUSE MODEL

Valentina Latina[1], Anna Atlante[2], Sebastiano Cavallaro[3], Pietro Calissano[1], Giuseppina Amadoro[4,5]
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Aims: Immunotherapy relying on conformational antibodies is one of the most promising approaches for an effective and harmless treatment of Alzheimer's disease (AD). 12A12 is a monoclonal cleavage specific antibody (mAb) which selectively neutralizes the AD -relevant, toxic N-terminal 20-22kDa tau fragment(s) (i.e NH_2htau) without cross-reaction with the normal full-length protein. When systemically-injected into Tg2576 mouse model overexpressing a mutant form of Amyloid Precursor Protein (APP), APPK670/671L linked to early-onset familial AD, this tau mAb successfully neutralizes the NH_2htau accumulating both in the brain and retina and, thus, markedly alleviates the phenotype-associated signs, such as behavioral deficits (spatial memory and orientation) and anatomo-pathological lesions (accumulation of APP/Aβ, tau hyperphosphorylation and truncation). The mechanism(s) of action responsible for 12A12mAb-mediated *in vivo* neuroprotection was investigated.
Methods: Crude synaptosomal preparation, Western Blotting, Transcriptomic analysis
Results: We found out that the administration of 12A12mAb in 6-month-old Tg2576 mice limits the Aβ production by modulating the steady-state expression levels of BIN1 and RIN3, two risk genes coding for crucial adaptator proteins which control the trafficking/maturation of APP /BACE-1 along the endocytic pathway, both in hippocampus and retina. Imbalance in the expression of genes participating to mitochondrial bioenergetics is also significantly normalized in AD mice following immunization with 12A12mAb.
Conclusions: Our results will not only enhance our understanding of the signaling pathways that crucially contribute to the AD pathogenesis, but also will facilitate the discovery of novel targets for improving tau-based treatment strategies for human AD.

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P0643 / #1192

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

SELECTION OF AN ANTI-TAU ANTIBODY CANDIDATE TARGETING PATHOLOGICAL TAU FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Wencheng Liu[1], Ishan Shah[1], Maneesha Paranjpe[1], Vinodh Kurella[1], Li Liu[1], Dillon Kavanagh[1], Jerrah Holth[1], Charlotte Chung[1], Alex Powers[1], Xiao-Qin Ren[1], Yanqun Shu[1], Allen Capili[1], Jay Hou[1], Bernardino Ghetti[2], Kelly Bales[1], Dinah Sah[1], Steve Paul[1], Todd Carter[1]
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Aims: The current hypothesis for the progression of tau pathology in Alzheimer's disease (AD) is that neuron-to-neuron transmission of pathologic tau, including especially trans-synaptic propagation, plays a major role. Our goal is to identify a selective, potent and efficacious anti-tau antibody clinical candidate that blocks pathologic tau spreading in vivo for the treatment of AD.
Methods: Immunization of mice with AD patient-derived PHF-tau (paired helical filamentous tau) as the immunogen yielded 113 anti-tau antibody hits with significant binding to PHF-tau and an absence of detectable binding to wild-type recombinant tau. These antibodies were characterized and prioritized based on affinity, biophysical characteristics, efficacy in animal models of tau spreading, and differentiation from clinically ineffective anti-tau antibodies.
Results: Four anti-tau antibodies were selected (Ab01, Ab03, Ab04, and Human Ab5) with novel sequences and epitopes that fit our target profile based on selectivity, functional inhibition in vitro and in vivo, and developability. Ab01, Ab02, and Ab04 are murine antibodies that target the same C-terminal epitope, whereas Human Ab5 targets the mid-domain of tau. Among these four antibodies, Ab01 demonstrated superior efficacy in the mouse seeding model and is currently undergoing humanization, as well as a dose-response efficacy study that may allow extrapolation to clinical doses.
Conclusions: We plan to leverage the Ab01 antibody for passive immunotherapy for AD. The clinical candidate will be chosen based on selectivity for pathological tau, potency, functional inhibition in vitro, and developability.

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P0644 / #720

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

NOVEL VACCINE CANDIDATES AGAINST MISFOLDED TAU PROTEIN

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Aims: Alzheimer's disease (AD) is thought to be caused by the misfolding of the amyloid beta (Aβ) and tau proteins, which both adopt a beta-sheet rich conformation and form oligomers and amyloid fibrils. Diverse attempts have been made to develop vaccines as prophylactics for AD employing these proteins and peptides in their linear form, but they lacked structural specificity and functionality. Here, we present a novel approach to design vaccine candidates based on the structure of tau fibrils that present the epitopes in a structurally-controlled manner.
Methods: The innocuous HET-s prion that adopts a beta-sheet rich conformation natively was engineered in a structurally-controlled manner to design vaccine candidates based on recent structures of tau fibrils solved by cryo-EM. Constructs were expressed in *E. coli* cells, purified, refolded, controlled for their structural fidelity and injected into wild-type mice. The specificity of the immune responses was tested against non-neurologic controls and Alzheimer disease brain homogenates.
Results: The purified and refolded tau vaccine candidates exhibited the expected self-assembly into amyloid fibrils by negative stain electron microscopy. The antisera from wild-type mice, immunized with these recombinant antigens, were found to be specific for disease-specific antigens in AD brain samples, but did not recognize non-neurologic control samples.
Conclusions: The tau vaccine candidates elicited specific immune responses targeting AD disease antigens. Next, we are going to test their efficacy in a transgenic mouse model of AD and watch for a delay or reduction in the formation of pathogenic assemblies.

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P0645 / #1628

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

TARGETING INTRACELLULAR TAU WITH INTRABODIES

Clara Theunis[1], Dina Rodrigues Martins[1,2], Pieterjan Van Maele[2], Fern Sha[3], Daniel Diamant[4], Rupesh Nanjunda[3], Wilson Edwards[4], Marc Mercken[1], Paul Declerck[2,5]
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Aims: In the context of intracellular protein misfolding and aggregation, such as tau pathology in Alzheimer's Disease (AD), it poses a major therapeutic advantage to target the pathological proteins already inside the cell. This can potentially be done with intrabodies, small antibody moieties that are expressed in neurons after vector-mediated delivery. Intrabodies have the advantage that they can target specific post-translational modification and conformations of the pathological protein
Methods: We used our proprietary monoclonal antibody panel to engineer anti-tau single-chain variable fragments (scFvs). The scFvs were first assessed as recombinant proteins in ELISA to confirm that the tau binding capacity was retained after conversion. Subsequently, they were evaluated for stability and potency to bind tau protein in the cytoplasmic environment of HEK293 cells. Nuclear translocation of the scFv after co-expression with Tau-NLS was evaluated by immunocytochemistry. Finally, a neuronal based seeding assay was used to measure the effect of these scFvs on tau aggregation.
Results: We show here that the scFv format of high affinity antibodies can retain tau binding. The generated constructs were stably expressed in the cytoplasm of cells and maintain capacity to bind tau.
Conclusions: We show that tau targeted intrabodies under the form of scFv can influence tau aggregation without the need to incorporate additional mechanisms to direct the scFv-tau complexes for clearance pathways.

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P0646 / #1861

POSTERS: B02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, PHOSPHATASES, OTHER ENZYMES

IMPACT OF HIGH LEVEL FOREBRAIN EXPRESSION OF ACTIVE TAU KINASE P38GAMMA ON COGNITIVE DYSFUNCTION IN AGED ALZHEIMER'S MICE

Prita Riana Asih, Kristie Stefanoska, Emmanuel Prikas, Arne Ittner
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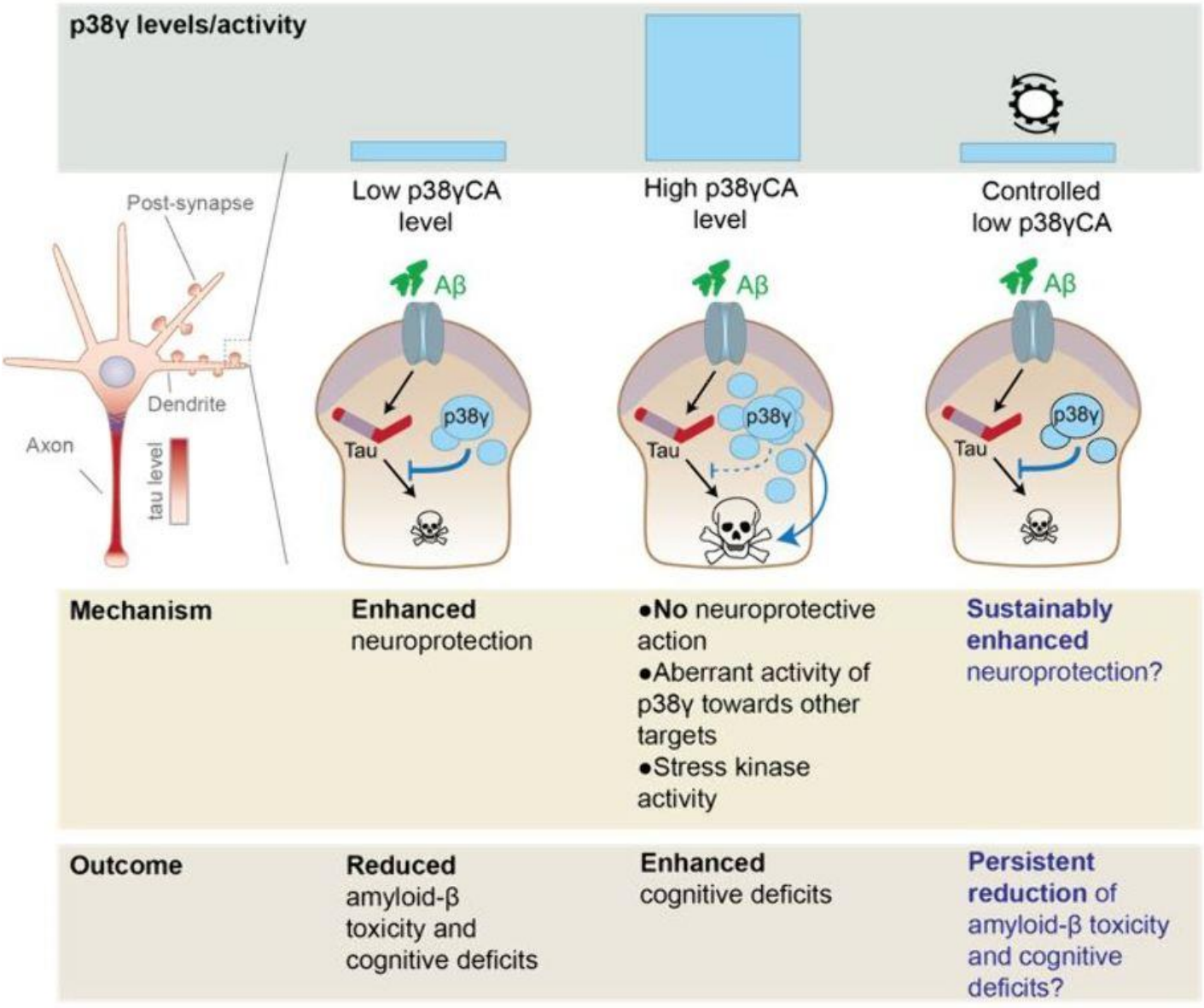
Aims: Alzheimer's disease (AD) is a progressive form of dementia, for which there are no treatments that can effectively improve cognitive deficits. Gene therapy holds promise for treatment of familial and sporadic forms of AD. p38gamma, a member of the p38 mitogen-activated protein (MAP) kinase family, inhibits amyloid-beta toxicity through regulation of tau phosphorylation. We recently showed that a gene therapy approach increasing p38gamma resulted in marked improvement of learning and memory performance in mouse models of AD at advanced stages. Notably, low expression of active p38gamma had beneficial outcomes on cognition. However, the impact of high levels of active p38gamma on neuronal function remain unclear.
Methods: We addressed the outcomes of high levels of active p38gamma on brain function, by direct injection of p38gamma-encoding adeno-associated virus (AAV) into the forebrain of aged mice of an APP transgenic AD mouse model. Two months post-injection, mice were tested on Rotarod, Open Field, and Morris Water Maze. Brain tissue was collected for histology and Western blot.
Results: Strikingly, p38gamma-expressing APP transgenic mice developed no motor impairment. However, their activity was markedly reduced with frequent immobility bouts. Moreover, learning and memory function was markedly impaired compared to control-treated aged APP mice. Notably, target engagement of p38gamma was impaired when excessive kinase levels were expressed. These results suggest that high neuronal levels of active p38gamma emphasize a stress kinase role of p38gamma, perturbing circuit function in motivation, navigation, and spatial learning.
Conclusions: Our work informs on impact of excessive neuronal p38gamma levels which can exacerbate circuit dysfunction. Thus,our future work targets the development of sustainable AD gene therapy based on p38gamma activity that depends on adjustable expression systems with tight control of the vectors, dose, and delivery

mode.


p38γ levels/activity
Post-synapse
Dendrite
Axon
tau level
Low p38γCA level
High p38γCA level
Controlled low p38γCA
Aβ
Tau
p38γ
Mechanism
Enhanced neuroprotection
•No neuroprotective action
•Aberrant activity of p38γ towards other targets
•Stress kinase activity
Sustainably enhanced neuroprotection?
Outcome
Reduced amyloid-β toxicity and cognitive deficits
Enhanced cognitive deficits
Persistent reduction of amyloid-β toxicity and cognitive deficits?

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P0647 / #579

POSTERS: B02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, PHOSPHATASES, OTHER ENZYMES

APPSALPHA RESCUES KINASE DYSREGULATION IN TAU TRANSGENIC MICE

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Aims: Alzheimer´s disease is characterized by hyperphosphorylated tau species and Abeta plaques. Whereas Abeta is produced by amyloidogenic APP processing, processing along the competing non-amyloidogenic pathway results in the secretion of neurotrophic APPsalpha. Here, we studied the potential of APPsalpha to regulate two major tau kinases, GSK3beta and CDK5 in Tau transgenic THY-Tau22 mice.
Methods: The temporal course of pathological tau species was studied using Immunohistochemistry. The activity of GSK3beta and CDK5 was assessed with Western blotting and a sensitive radioactive kinase assay. Stereotactic injection of AAV9-APPsalpha vectors into the hippocampus of THY-Tau22 mice was used to study potential therapeutic effects.
Results: Immunohistochemistry revealed a dramatic increase in pathologically phosphorylated (AT8, AT100) or misfolded tau species (MC1) in the hippocampus of THY-Tau22 mice between 3 and 12 months of age. Using a highly sensitive radioactive kinase assay, we demonstrate an increase in GSK3beta and CDK5 activity in the hippocampus of THY-Tau22 mice. Interestingly, AAV-mediated intracranial expression of APPsalpha efficiently restored normal GSK3beta and CDK5 activity. Western blot analysis revealed upregulation of the CDK5 regulatory proteins p35 and p25, indicating CDK5 hyperactivation in THY-Tau22 mice. Strikingly, AAV-APPsα rescued p25 upregulation to wild-type levels even at stages of advanced Tau pathology. Sarkosyl fractionation revealed increased soluble AT8-Tau and decreased insoluble AT100-Tau species upon AAV-APPsα injection. Moreover, AAV-APPsα reduced misfolded (MC1) Tau species in CA1 pyramidal neurons. Finally, we show that AAV-APPsα normalizes PSD95 expression and spine density deficits of THY-Tau22 mice.
Conclusions: Our findings indicate that APPsalpha has beneficial effects in transgenic mice to mitigate tau-induced pathology. Mechanistically, we show that APPsalpha rescues aberrant GSK3beta and CDK5 activity. This suggests that APPsalpha may have therapeutic potential for patients suffering from AD or primary tauopathies.

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P0649 / #222

POSTERS: B02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

ANTIDEPRESSANT EFFECT OF PHOENIX DACTYLIFERA VIA INVOLVEMENT OF DOPAMINE AND SEROTONIN SYSTEM

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Aims: The present study was designed to evaluate the antidepressant effects of *Phoenix dactylifera* (Ajwa dates). This plant has been extensively used in the Muslim world due to its religious and traditional beliefs like prevention and cure for chronic diseases.
Methods: In this study, the antidepressant activity of methanolic extracts of *Phoenix dactylifera* fruit (PDF) and *Phoenix dactylifera* seed (PDS) were investigated using tail suspension test (TST), forced swimming test (FST), open field test (OFT) and hole board test (HBT) in Sprague Dawley rats. The level of neurotransmitters was determined by HPLC followed by antioxidant enzymes determination along with histopathological investigation.
Results: Both extracts showed good antidepressant activity in all test, however, maximum value was exhibited by PDS (70%) followed by PDF (65%). Quantification of dopamine and serotonin was carried out by HPLC. PDS treatment led to significant ($P<0.05$) rise in the level of dopamine (2-fold) and serotonin (1.8-fold) neurotransmitter in the midbrain region and PDF treatment had 1-fold increase in dopamine and 1.2-fold increase in serotonin respectively. The level of antioxidant enzymes like SOD, POD, CAT, GSH and TBARS in extract group showed approximately 1.5-fold increase for PDS and 1.1-fold increase in PDF. Histopathology results reflected the normal morphology of the cells after treatment with PDS and DPF.
Conclusions: Collectively, present study suggests that *Phoenix dactylifera* can be used as an herbal drug against depression and neurobiological syndromes due to its pharmacological effects. However, further research is needed to identify and isolate the specific components which are responsible for antidepressant activity.

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P0650 / #385

POSTERS: B02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

INHIBITION OF THE PROSTAGLANDIN-E2 RECEPTOR EP2 ATTENUATES ALZHEIMER'S DISEASE RELATED NEUROPATHOLOGY

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Aims: Neuroinflammation has emerged as one of the key hallmarks of Alzheimer's disease (AD), which is known to exacerbate amyloid-β (Aβ) and neurofibrillary tangle pathologies and associated cognitive and behavioral deficits in AD and PD patients. Neuroinflammation is a complex mixture of features such as induction of cytokines, chemokines, and cyclooxygenase-2 enzyme, and activation of glia making it challenging to target with small molecule therapeutics. We recently determined that prostanoid receptor EP2 as a key member in the neuroinflammatory sequelae. We aimed to ask whether prostanoid receptor EP2 plays a role in neuroinflammation and amyloid pathology, and, whether treatment with an EP2 antagonist mitigates neuroinflammation and amyloid-β load in AD mouse model.
Methods: We tested the effect of a potent EP2 antagonist in the 5xFAD/SJL transgenic mouse model of AD. 5xFAD mice (3 months old) and their sex and age-matched non-transgenic littermates were treated for 8 weeks with an EP2 antagonist (50-60 mg/kg/day) in drinking water. These mice were intraperitoneally injected with lipopolysaccharide (LPS) (1 mg/kg/week) for 8 weeks to create a two-hit model in which chronic peripheral and brain inflammation is present.
Results: The brain tissue analysis revealed that only in two-hit male mice the mRNA levels of proinflammatory mediators (EP2, COX-2, iNOS, NOX-2, IL-1β, TNFα, IL-6, IL-4, CCl2) and glial markers (Iba1, GFAP, CD11b, S110B) were significantly reduced by the EP2 antagonist treatment. Interestingly, treatment with the EP2 antagonist also attenuated amyloid deposition in various brain regions assessed by Congo-red positive Aβ-plaques in male 5xFAD mice.
Conclusions: Our data suggest that EP2 antagonism mitigates the neuroinflammation and Aβ pathology in 5xFAD mice. Further investigation is needed to examine whether EP2 antagonism mitigates behavioral deficits in AD mice to promote EP2 selective inhibitors for preclinical and clinical development.

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P0651 / #2372

POSTERS: B02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

AN ASSESSMENT OF CERTAIN PHYTOCHEMICALS AS POSSIBLE THERAPEUTIC OPTIONS TO TREAT ALZHEIMER'S DISEASE

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Aims: 1) To assess the extent to which certain phytochemicals
(PhTs) can inhibit AChE and BuChE. 2) To evaluate their antioxidant potential. 3) To consider their cytotoxicity.
Methods: All PhTs were assayed in vitro over 1–1000 µM to inhibit human AChE, electric eel AChE or horse serum BuChE using an Ellman assay. Antioxidant potential was measured via the ability to inhibit the stable free radical 2,2-Diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing power ability (FRPA) (Fe3+ to Fe2+) evaluated, radical 2, 2` azino-bis-3-ethylbenzthiazoline-6- sulphonic acid (ABTS) scavenging activity, hydrogen peroxide (H_2O_2) scavenging activity, Hydroxyl radical (OH) scavenging activity, lipid peroxidation inhibitor activity. Cytotoxicity was assessed using human neuroblastoma SH-SY5Y cells by the MTT cell viability assay.
Results: Seven phytochemicals displayed potentially useful inhibitory activity against human acetylcholinesterase (hAChE) and were compared with the commercial ChEI galantamine. Most of them showed antioxidant activity with the assays used. All phytochemicals displayed relatively low cytotoxicity to SH-SY5Y cells. In summary, the phytochemicals, most notably 4-O-CQA and Q3-β-D-G and others are potentially beneficial ChEIs with the additional benefits of potent antioxidant and free radical scavenging capacity and low cytotoxicity and may therefore prove valuable compounds for development in the next-generation ChEIs for the treatment of AD.
Conclusions: Since 2001, the FDA-approved second-generation ChEI galantamine hydrobromide has been one of the mainstay treatments for mild-to-moderate AD, and little has changed regarding the drug therapy for AD. Along with phytochemical ChEIs, the potential of Gala was also examined and observed to be the most potent of the natural products.PhTs, most notably 4-O-CQA, Q3-β-D-G, Rutin and Ber are potentially useful ChEIs with the additional benefits of potent antioxidant and free radical scavenging capacity, and low cytotoxicity may therefore prove valuable compounds for the development as the next-generation ChEIs for the treatment of AD.

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P0652 / #1182

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

SMALL-MOLECULE STRUCTURALLY TARGETED ALLOSTERIC REGULATORS OF GLUCOCEREBROSIDASE SHOW NEUROPROTECTIVE PROPERTIES IN A CELL-BASED MODEL OF ALZHEIMER'S DISEASE

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Aims: Glucocerebrosidase (GCase) protein levels and enzyme activity are decreased in sporadic Alzheimer's disease (AD) and overexpression of GCase promotes lysosomal degradation of Aβ1-42. Augmentation of GCase activity may therefore be a potential therapeutic option for the treatment of AD. Gain Therapeutics has applied its innovative proprietary drug discovery platform, Site-directed Enzyme Enhancement Therapy (SEE-Tx®), to the discovery and development of small-molecule structurally targeted allosteric regulators (STARs) that stabilize GCase by binding to an allosteric site, facilitating its maturation and trafficking to the lysosome. In this study we have evaluated the neuroprotective properties of these compounds in primary rat hippocampal neurons challenged with human Tau oligomers (hTauO).
Methods: Primary hippocampal neurons were prepared from E17 Wistar rat brains. At 6DIV, the culture was pre-incubated with compounds for 96 h and then challenged for 24 h with hTauO (5 μM) prepared from recombinant human tau monomers (2N4R, 441 aa). Cell viability was investigated using the MTT assay at 24 h post hTauO challenge (11 DIV).
Results: We report *in vitro* evidence that STAR compounds reduce hTauO-induced neurotoxicity in primary rat hippocampal neurons.
Conclusions: We have demonstrated that our brain penetrant STAR compounds show promising activity against TauO pathology, which has been shown to underlie neurodegeneration and cognitive impairment. Therefore, STAR therapy emerges as a potential disease-modifying, novel pharmacological option for the treatment of AD that warrants further investigation.

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P0653 / #2368

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

TARGETING LYSOSOMAL ACIDIFICATION IMPAIRMENT AND AUTOPHAGY DYSFUNCTION IN TAUOPATHIES

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Aims: Alzheimer's disease (AD) and related tauopathies are a group of neurodegenerative disorders characterized by the presence of tau inclusions in affected brain regions. These tau inclusions such as neurofibrillary tangles have been shown to play a key role in initiating tau misfolding as well as seeding and spreading of tau pathology. Both cellular and mouse models of AD and tauopathies have suggested that endolysosomal autophagy dysfunctions contribute to tau accumulation and disease pathogenesis. While lysosomal acidification impairment has been associated with AD, it has not been clearly established in tauopathies. Our goal is to investigate whether lysosomal acidification impairment and related autophagy dysfunction are present in tauopathy models.
Methods: We investigate whether overexpression of tauP301L or treatment of tau preformed fibrils (PFF) in SH-SY5Y neuronal cells and human iPSC derived primary neurons leads to lysosomal acidification impairments. Additionally, we use acidic nanoparticles (acNPs) as a tool to modulate lysosomal pH and rescue lysosome dysfunction.
Results: We show that overexpression of tauP301L in SH-SY5Y cells or treatment of tau PFF to human neurons results in lysosome alkalization and autophagy dysfunction. Importantly, acNPs restore lysosomal acidification, activate autophagy function, reduce tau accumulation, and rescue tauP301L or tau PFF induced neuronal death. Treatment of acNPs also reduces tau secretion into the cell culture media, suggesting a potential role in preventing the spreading of tau pathology. We are currently studying the effect of acNPs in attenuating the propagation of tau pathology in mice.
Conclusions: Lysosomal acidification impairment and autophagy dysfunction are present in tauP301L overexpressed SH-SY5Y cells and tau PFF treated human neurons. We propose acNPs as a tool to study the mechanism of lysosomal acidification as well as a potential therapeutic for AD and related tauopathies.

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P0654 / #151

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

THE POTENTIAL OF AVANAFIL IN MODULATING TAU PATHOLOGY AND ASTROCYTE EXPRESSION IN STREPTOZOTOCIN-INDUCED ALZHEIMER'S DISEASE MODEL IN RATS

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Aims: Alzheimer's disease (AD) is a neurodegenerative disease. Sildenafil and Tadalafil extend neuroprotection by increasing cGMP levels, decreasing tau, and improving cognitive impairments. This study was undertaken to evaluate the neuroprotective efficacy of Avanafil (AV) in the sporadic AD rat model induced by streptozotocin (STZ).
Methods: Disease was induced by administration of STZ (3 mg/kg bilaterally) intracerebroventricularly. AV was administered for 28 days (AV0.25: 0.25mg/kg, AV0.4: 0.4mg/kg, AV0.55: 0.55mg/kg, orally). At the end of the treatment phase, behavioral parameters (Morris water maze (MWM), Novel Object Recognition test (NOR), Y-maze, and Conditioned avoidance) were performed and brain samples were collected for further biochemical, immunohistochemistry, and histopathological analysis.
Results: The treatment ameliorated the deficits caused due to STZ. It reduced the latency to find the hidden platform in MWM ($P<0.05$) and enhanced the discrimination index in NOR ($P<0.05$) and exploratory behavior in Y-maze (AV0.55: $P<0.05$) in comparison to the disease control group. It reduced the levels of amyloid-β 1-42, total tau ($P<0.001$) and phospho tau ($P<0.0001$), malondialdehyde (AV0.55: $p<0.001$), and catalase ($P<0.05$) and increased the levels of amyloid-β 1-40, neprilysin (AV0.4: $P<0.05$), β-Nerve Growth Factor (AV0.4: $P<0.05$), superoxide dismutase (AV0.4, AV0.55: $P<0.0001$), and glutathione ($P<0.05$). The histopathology showed that treatment ameliorated cell damage by reducing eosinophilia and cell apoptosis. Immunohistochemistry showed increased immunoreactivity to GFAP in comparison to the disease control group.
Conclusions: It can be inferred from the study that AV reduces AD pathologic markers and enhances cognition and thus can be further researched for the treatment of AD.

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P0655 / #1129

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

DESIGN OF SMALL MOLECULE INHIBITORS OF TAU OLIGOMERIZATION

Marcia Taylor, Scott Banfield, Christopher Barden, Kunal Keskar, Crystal Liu, Lucía López Vásquez, Erhu Lu, Ross Mancini, Luzhe Pan, Mark Reed, Kurt Stover, Shengguo Sun, Yanfei Wang, Fan Wu, Arun Yadav, Seung-Pil Yang, Carlos A. Zepeda-Velázquez, Donald Weaver
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Aims: Investigating the hypothesis that pathogenic, or seed-competent monomers are the root cause of toxicity in tauopathies, small molecules targeting the presumed conformation adopted by these monomers were developed. It is proposed that small molecules targeted to a pathogenic conformation prevent the generation of small soluble oligomers. Small molecules were designed to be orally bioavailable, brain penetrant, and well tolerated.
Methods: An in silico platform technology, CCM (Common Conformational Morphology), was used to generate hits against a sub-population of tau monomers. An in vitro assay was developed to test the effect of small molecules on tau oligomerization. Molecules were screened for microsomal stability, permeability, and preliminary toxicity by measurement of cytochrome p450 and human Ether-à-go-go-Related Gene (hERG) inhibition. Pharmacokinetics and tau oligomer levels were determined in the tauopathy model rTg4510 using biochemical and cell-based measurements.
Results: A novel class of molecules were characterized that inhibit in vitro tau oligomerization. Lead molecules had acceptable microsomal stability and were found to be orally bioavailable and brain penetrant. The molecules with increased concentration at the target tissue had a concomitant decrease in dose required for a change in tau oligomers. Molecules were well tolerated and met the target safety profile.
Conclusions: CCM guided discovery of a class of small molecules capable of inhibiting generation of small soluble tau oligomers. Molecules with increased brain exposure had similar decrease in tau oligomer levels at a lower oral dose in the tauopathy model rTg4510. Next steps include screening for translatable biomarkers and continuing IND-enabling studies.

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POSTERS: B02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

TARGETING THE P2Y6 RECEPTOR TO PREVENT MICROGLIAL PHAGOCYTOSIS OF SYNAPSES AND NEURONS

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Aims: There is growing evidence that excessive microglial phagocytosis of synapses and neurons contributes to neurodegeneration. The microglial P2Y6 receptor has been shown to be required for microglial phagocytosis of neurons. We aimed to test here whether inhibition or knockout of the P2Y6 receptor could prevent such excessive microglial phagocytosis of synapses and neurons, as well as neurodegeneration induced by tau, amyloid, LPS or ageing.
Methods: In co-cultures of mouse glia and neurons, we tested whether inhibition or knockout of the P2Y6 receptor prevented synaptic or neuronal loss induced by tau, amyloid or LPS. In vivo, we tested whether the neuronal and memory loss induced by amyloid beta or LPS in mice was prevented in P2Y6 knockout mice. We tested whether crossing P2Y6 knockout mice with P301S TAU mice prrevented TAU induced neuronal and memory loss. And we tested whether, P2Y6 knockout prevented synpatic and memory loss in aged (17 month old) mice.
Results: In co-cultures of mouse glia and neurons, inhibition or knockout of the P2Y6 receptor prevented synaptic and neuronal loss induced by tau, amyloid beta or LPS. In vivo, neuronal and memory loss induced by amyloid beta or LPS in mice was prevented in P2Y6 knockout mice. Crossing P2Y6 knockout mice with P301S TAU mice prrevented TAU induced neuronal and memory loss. P2Y6 knockout prevented synpatic and memory loss in aged (17 month old) mice.
Conclusions: Inhibition or knockout of the P2Y6 receptor prevented loss of synapses, neurons and/or memory induced by tau, amyloid beta, LPS or aging. Thus, P2Y6 may be a good target to prevent neurodegeneration by preventing excessive microglial phagocytosis of synpases and neurons.

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POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

NEURAL PRECURSOR CELLS-DERIVED MITOCHONDRIA AS THERAPY FOR ALZHEIMER'S DISEASE

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Aims: The need to identify potential disease-modifying treatments that can prevent or halt the progression of Alzheimer's disease (AD) is timely and critical. Based on the association between mitochondrial damage and the pathogenesis of several neurodegenerative diseases (NDs), including AD, improving mitochondrial function appears as a good target for treatment. Mitochondrial transplantation therapy (MTT), through supplementation of healthy mitochondria, has been proposed as a therapeutic intervention for NDs. Prior studies demonstrated that supplementation of healthy mitochondria to damaged neurons promotes neuronal viability. Our goal is to analyze the benefit of using healthy mitochondria as a therapeutic approach to treat AD pathology in vivo using an animal model of tau deposition.
Methods: We isolated and characterized mitochondria from mouse neural precursor cells. JC-1 assay was used to assess mitochondrial membrane potenital and TEM for morphological characterization. 7 months old P301L mice were injected intravenously with isolated mitochondria or saline once weekly for 5 months. Mice were then sacrificed and the brains collected for immunohistochemical and biochemical analysis. Immunohistochemical analysis with AT8 antibody was performed on formalin-fixed paraffin-embedded sagittal sections of one hemisphere. Biochemical analysis of the other hemisphere included western blot and ELISA using AT8 antibody and other phosphorylated tau antibodies.
Results: We found a significant reduction in %AT8 burden in the brains of mitochondria-injected compared to saline-injected P301L mice. This reduction was confirmed in biochemical analysis.
Conclusions: We believe that MTT can be developed as an AD therapy. MTT can meet a critical need to develop a disease-modifying intervention for NDs and advance our knowledge about the mechanistic details of mitochondrial dysfunction in AD.

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P0659 / #793

POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

POTENTIAL NEUROPROTECTIVE PROPERTIES OF LIPIDIZED CART PEPTIDE ANALOG IN IN VITRO MODEL OF NEURODEGENERATION

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Aims: Cocaine- and amphetamine-regulated transcript peptide (CARTp) is strong anorexigenic hypothalamic neuropeptide under the direct control of leptin. Due to the suggested link between obesity and Alzheimer´s disease (AD) development, anorexigenic compounds are considered as a potentially neuroprotective tool. Despite therapeutic potential, anorexigenic compound delivery from the periphery to the brain is complicated by their peptidic character. In this study, we aimed to demonstrate the potential neuroprotective effects of our new palmitoylated CARTp analog (palmCART).
Methods: We employed an *in vitro* model of glutamate-induced excitotoxicity using NGF-differentiated PC12 cells. The cells were pretreated with palmCART, and cell viability was measured using CellTiter-Glo® assay. The signaling pathways were further examined by the method of Western blot.
Results: Pretreatment of PC12 cells with the palmCART protected the cells from the glutamate-induced cytotoxic effect manifested by an increased viability compared to cells treated only with glutamate. PC12 cells exposure to palmCART also enhanced the differentiation of the cells into neuronal-like state. Furthermore, glutamate-induced inhibition of PI3K/Akt signaling pathway was restored by palmCART pretreatment.
Conclusions: In summary, palmCART is a potential neuroprotective agent but the exact mechanism of action must be further studied.

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POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

DEVELOPMENT OF NIO752, AN INTRATHECALLY ADMINISTERED MICROTUBULE ASSOCIATED PROTEIN TAU (MAPT) ANTISENSE OLIGONUCLEOTIDE IN PROGRESSIVE SUPRANUCLEAR PALSY AND ALZHEIMER DISEASE

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Aims: *MAPT* mRNA encodes the neuronal protein Tau, which is modified and aggregates in a group of neurodegenerative diseases known as tauopathies. Primary tauopathies such as progressive supranuclear palsy (PSP) are diseases where Tau lesion is the upstream, or only aggregated protein found in the brains of patients. Secondary tauopathies such as Alzheimer Disease (AD) are diseases where the Tau lesion occurs in association with other protein forms (eg. β-amyloid). *We are developing NIO752, a 2'MOE modified gapmer antisense oligonucleotide (ASO) targeting the MAPT mRNA, with the goal of reducing all species of Tau and thereby slowing disease progression in patients with tauopathies.*
Methods: Preclinical PK, PD and safety of NIO752 was assessed in mice and cynomolgus monkeys.
Results: NIO752 robustly reduced all measured forms of Tau *in vitro* and *in vivo*. A single ICV injection of NIO752 into the brain of hTau BAC mice led to a wide distribution and dose-dependent reduction of *MAPT* mRNA and Tau protein. The highest dose resulted in 60-70% reduction, which was enhanced with repeated dosing. Intrathecal administration of NIO752 in cynomolgus monkeys also reduced *MAPT* mRNA by about 60% and Tau protein by ≥30% in brain regions relevant to PSP and AD. Repeated dosing showed a slower elimination phase with persistent exposure in the brain up to 12 weeks. In a 13-week GLP toxicity study in cynomolgus monkeys, NIO752 was well tolerated with repeated IT administration.
Conclusions: The preclinical data supports clinical development of NIO752 in PSP and AD.

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POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

STATIN USE AND TAU DEPOSITION: FOUR YEARS FOLLOW-UP

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Aims: There are contradictory findings regarding the effect of statin drugs on atau deposition as one of the main hallmarks of Alzheimer's disease (AD). We aimed to longitudinally investigate the therapeutic and preventive role of statin drugs by examining the brain tau protein deposition and metabolism rate in AD, mild cognitive impairment (MCI), and healthy controls (HC).
Methods: The data of 828 subjects including 178 HC, 492 MCI, and 158 AD individuals were obtained from ADNI. The baseline and longitudinal [^{18}F] AV1451 PET standard uptake value ratios (SUVR) measures were investigated among statin users and non-users.
Results: Our results showed that there is no significant difference in baseline tau deposition between statin users and non-users among HC, MCI, and AD subjects. There was a significant difference in tau deposition change after two and four years (from baseline) between statin users and non-users within HC subjects (p=0.014). The change of tau deposition at four years from baseline was -1.5±5.3% for statin users and 1.9±7.2% for non-users. Moreover, there was also a significant difference in tau deposition change at four years from two years visits between statin users and non-users of the HC group (p=0.024). The change was -4.1±5.2% and 0.7±4.9% for statin users and non-users respectively. There was no significant difference in tau deposition change after two years and four years in MCI and AD patients.
Conclusions: The present longitudinal analysis revealed that statins could reverse the tau deposition in subjects without cognitive impairment over extended periods of follow-up. However, once the clinical symptoms of cognitive impairment appear, statins fail to reduce tau deposition; in other words, statins seem to be preventive rather than a therapeutic agent.

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P0662 / #824

POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

A COMPUTATIONAL APPROACH TO UNDERSTAND CELLULAR CROSSTALK IN AN IPSC-DERIVED TRICULTURE MODEL OF AD

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Aims: Modelling cellular crosstalk during neurodegeneration in Alzheimer's disease (AD) by identifying cell -cell interactions (CCIs) in an *in vitro* triculture model of neurons, astrocytes and microglia derived from human induced pluripotent stem cells.
Methods: Intraneuronal tau aggregation was modelled by treating the triculture with tau paired helical filaments (PHF). Using single cell RNA-sequencing, we determined cellular subpopulations and examined PHF treatment-induced cellular crosstalk changes. We identified CCIs using the LIANA framework in combination with OmniPath, a cellular signaling database, and validated findings in two independent human post-mortem brain tissue data sets.
Results: We identified 5870 CCIs (CCI score < 0.05) in the triculture, 2728 of them were confirmed in both human data sets. 211 of these confirmed CCIs were exclusively identified in the PHF-treated dataset and could indicate tau aggregation specific crosstalk. Moreover, CCIs were found associated with AD progression in both human datasets that showed significant correlation with several pathological determinants such as APOE status, Braak stage, total tau, and total amyloid plaque numbers and were also validated in the PHF-treated subset of the triculture dataset.
Conclusions: These observations underscore the potential of the triculture system to model AD relevant cellular interactions *in vitro*. Leveraging in silico CCI analyses to characterize this multicellular system will aid our understanding of underlying mechanisms of Alzheimer's disease.

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P0663 / #280

POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

IN VITRO MODELLING OF INTRANEURONAL TAU AGGREGATION IN A HIPSC-DERIVED CO-CULTURE SYSTEM OF NEURONS, ASTROCYTES AND MICROGLIA

Julian Roewe[1], Yasmin Riesinger[1], Heyne Lee[1], Lamiaa Bahnassawy[1], David Schoendorf[1], Ezgim Sahin[1], Shringarika Singh[1], Yashna Paul[2], Venus Thomanetz[1], Christopher Untucht[1], James Soper[3], Astrid Wachter[2], Janina Ried[2], Dagmar Ehrnhoefer[1], Robert Talanian[3], Knut Biber[1], Thomas Wassmer[1], Miroslav Cik[1], Peter Reinhardt[1]
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Aims: Establish a co-culture protocol of human induced pluripotent cell-derived (hiPSC) neurons, astrocytes and microglia suitable to investigate the effect of astrocytes and microglia on neuronal tau aggregation *in vitro*.
Methods: We optimized conditions for co-culturing hiPSC-derived neurons, astrocytes and microglia. The sequential process of the co-culture protocol regimen allows the induction of intraneuronal tau aggregation by the addition of exogenous tau paired helical filaments (PHF) or lentiviral genetic modification. Culture composition and pathological tau aggregation was examined by high content imaging. To shed light on cellular state and responses to Tau pathology of neurons, astrocytes or microglia we performed single cell RNA sequencing.
Results: The protocol results in a robust co-culture system of neurons, astrocytes and microglia. Homeostatic phenotype of microglia is increased by neurons and astrocytes present during cell differentiation. Intraneuronal tau aggregation is inducible in the co-culture protocol as shown by immunocytochemistry staining with a tau aggregate-specific antibody. Single cell sequencing of PHF-treated cultures reveal moderate changes of the transcriptomes of all three cell types. Differentially expressed genes in PHF-treated neurons are associated with the organization of synapses, and other processes, demonstrating changes of substantial neuronal pathways.
Conclusions: Cell-cell interaction is an important factor during development of Alzheimer's disease. The impact of microglia and astrocytes on tau aggregation is an area of active investigation. The described protocol will help to model and characterize the effects of microglia and astrocytes during this process in a controllable human *in vitro* system.

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P0664 / #1398

POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

TARGETING INSULIN SIGNALLING IN THE BRAIN WITH A NOVEL INSULIN MIMETIC TO AMELIORATE ALZHEIMER'S PATHOLOGY.

Amy Woodfield[1,2], Imran Khan[1,2], Erik Helmerhorst[1,2], Philip Newsholme[1,2], Giuseppe Verdile[1,2,3]
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Aims: Impaired insulin signalling plays a key role in the pathogenesis of Alzheimer's disease including driving amyloid-beta (AB) and tau hyperphosphorylation (pTau). The therapeutic potential of intranasal insulin has been explored in clinical trials. This study begins to explore a novel mimetic of insulin with a focus on modulating neuronal insulin signaling and pTau levels.
Methods: For *in vivo* analysis, normal chow or high fat fed human Tau (hTau) mice were administered intranasally vehicle, insulin or the insulin mimetic daily for 7 days. Brain tissue underwent analysis for total Tau (tTau) and pTau, insulin signaling, neuronal viability and inflammatory markers. For *In vitro* analysis, differentiated wild-type or APP over-expressing SHSY5Y cells were treated with vehicle, insulin or the insulin mimetic. Changes in tau and insulin signalling proteins assessed using Western Blot and AB production assessed using AB ELISA.
Results: The insulin mimetic was well tolerated with no adverse effects *in vivo*. In normal chow fed mice (cortex), insulin promoted a trend to reduced pTau-S202/T205 ratio, in males this association was significant. In high fat mice (cortex), insulin was associated with reduced pTau-S396 ratio. In females, both insulin and mimetic significantly reduced pTau-S396 ratio. No significant changes in insulin signalling or inflammatory markers were observed.
Conclusions: Intranasal insulin mimetic delivery lead to no adverse effects *in vivo*. Surprisingly, no change in insulin signaling was observed with insulin or mimetic *in vivo*, potentially reflecting duration or frequency of treatment. This is being explored *in vitro*. Insulin and the mimetic, however, led to reduced brain pTau levels. *In vitro* experiments continue to explore effects on neuronal pTau and AB levels. These studies represent initial analysis of the insulin mimetic to determine its potential for further exploration.

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P0665 / #2351

POSTERS: B02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

CURRENT APPROACHES IN PARKINSON'S TREATMENT: ESTABLISHMENT OF PARKINSON'S DISEASE MODEL IN 3D NEURONAL CELL LINE AND INVESTIGATION OF THERAPEUTIC EFFICACY OF THE NANOCARRIER SYSTEM

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Aims: Neurodegenerative diseases have started to attract attention due to their increasing prevalence day by day. Parkinson's Disease (PD) is today's second most common neurodegenerative disease. In the known pathology of Parkinson's disease, the loss of dopaminergic neurons in the substantia nigra of the brain occurs as a result of the accumulation of the (α)-synuclein component formed by the accumulation of Lewy bodies in specific genes and damaged neurons. The treatment and early diagnosis possibilities of Parkinson's disease, one of the most common neurodegenerative diseases, are minimal. For this reason, the condition needs to be investigated in more detail. There are in vitro and in vivo models in research. However, both types of research have their difficulties. Therefore, new models are needed. In this study, we aimed to develop a 3D culture medium with hydrogel-based bioink in neuron cells and then induce Parkinson's disease through neurotoxin. It was aimed to investigate the therapeutic efficacy of the nano-sized exosome-based formulation developed later.
Methods: Then 2-Dimensional (2D) and 3-dimensional (3D) culture mediums were created with the dopaminergic neuroblastoma cell line (SH-SY5Y), and these culture mediums were induced to Parkinson's model. The therapeutic efficacy was investigated by Live&Dead analysis, processing these analysis images in the trainable Weka Program program, and finally by immunostaining method. According to the results; The neuroprotective effect of dopamine-loaded exosomes has been proven in 2D and 3D culture mediums induced in the PD model.
Results: At the end of 1 week, it was determined that the cells took a spheroidal form. Findings revealed that dopamine-loaded exosomes protect cells against 6-OHDA.
Conclusions: Accordingly, we predict that exosome-based treatment methods will be a promising approach to treating Parkinson's.

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P0666 / #2565

POSTERS: B03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

CYTOSOLIC ENTRY OF TAU-SPECIFIC ANTIBODIES IS INCREASED BY THE ADDITION OF TAU AGGREGATES

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Aims: Tau immunotherapies have shown in pre-clinical and cell culture models to reduce the level of aggregated tau protein. One possible mechanism of protection of these antibodies could be via the cytosolic, high-affinity IgG receptor and E3 ubiquitin ligase, TRIM21. Tau:antibody complexes bind to TRIM21 upon lipofectamine-mediated entry in HEK293 cells, which results in efficient proteasomal degradation of tau aggregates (McEwan et al., 2017). However, it is unknown whether or how antibodies can enter the cytosol of neurons, either alone or in combination with their substrate, to engage with TRIM21.
Methods: The 11 amino acid HiBiT tag was attached to light chain of recombinant AP422, a phospho-tau antibody and 9C12, a control antibody targeted to adenovirus. Entry of antibodies to mouse primary neurons modified to express LgBiT in the cytosol was measured over 48 hours. The effect of complexing antibodies with tau was investigated by pre-incubating 50nM of HiBiT tagged antibodies for 1 hour with 250nM of tau assemblies which were either of recombinant origin or brain-derived.
Results: HiBiT-tagged antibodies reconstituted the luciferase enzyme in a concentration-dependent manner *in vitro* when mixed with recombinant LgBiT. Both AP422-HiBiT and 9C12-HiBiT alone entered poorly to primary mouse neurons in a 48 hour period. However, the pre-incubation of the antibodies with their respective substrates (i.e. tau or adenovirus) resulted in a substantial increase in antibody entry.
Conclusions: Extracellular tau aggregates have membrane-crossing abilities which can facilitate the transport of tau antibodies into the cytosol of neurons by 'piggybacking'. Once in the cytosol, antibodies can engage TRIM21, which may result in proteasomal degradation of tau:antibody complexes and inhibition of seeded aggregation. Future work will probe the entry pathways involved, as well as the temporal kinetics of TRIM21-mediated degradation.

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POSTERS: B03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: TAU CLEARANCE

A PLACEBO CONTROLLED RANDOMISED CONTROLLED TRIAL OF SODIUM SELENATE AS A DISEASE MODIFYING TREATMENT FOR PROGRESSIVE SUPRANUCLEAR PALSY

Lucy Vivash[1], Cassandra Marotta[1], Kelly Bertram[2], Andrew Evans[3], John O' Sullivan[4], Thomas Kimber[5], Stephen Tisch[6], Simon Lewis[7], Terence O'Brien[1]
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Aims: There are no disease-modifying treatments that arrest or reverse tau hyperphosphorylation in tauopathies. Through its action in upregulating protein phosphotase 2 (PP2A), sodium selenate has been shown to reduce levels of total-tau, phosphorylated-tau and hyperphosphorylated-tau in animal models of disease associated with increases in tau as well as early phase clinical trials. This study is a placebo-controlled, randomised controlled trial of sodium selenate as a treatment for the primary tauopathy, progressive supranuclear palsy (PSP).
Methods: Up to 70 patients with probable PSP (Richardson's syndrome) will be recruited (expected withdrawal rate 30%), and randomised to treatment with sodium selenate (15 mg tds) or placebo (1:1) over 52 weeks. This is a multisite clinical trial (6 sites total, 4 currently active). The primary study outcome will be change in MRI volume composite (frontal lobe+midbrain-3rd ventricle) over 52 weeks of treatment. Secondary outcome measures will include change on the PSP rating scale, clinical global impression of change, and change in midbrain mean diffusivity.
Results: To date, 13 patients have been screened, resulting in 2 screen fails, 9 randomisations and 2 awaiting randomisation. Of the 9 patients randomised, 1 has completed the study, 1 withdrew early (due to an adverse event) and 7 remain on treatment. Baseline characteristics of the randomised patients are: Age mean 62.3 years (range 47-73), male (n=5) and PSPRS total score: mean 37.1 (range 28-56). To date safety has been good with no serious adverse events related to treatment.
Conclusions: Recruitment is ongoing and is expected to complete in March 2024, with last patient last visit in June 2025.

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POSTERS: B03.M. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

TWINRCT: LEVERAGING EXTERNAL DATA, ARTIFICIAL INTELLIGENCE, AND COVARIATE ADJUSTMENT

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Aims: Describe a novel Twin Randomized Controlled Trial (TwinRCT™) that uses external data and disease-specific deep learning models (prognostic model) to optimize the covariate adjustment process, enabling gains in sample size reduction and/or power.
Methods: We explain attainable advantages of a TwinRCT over using Analysis of Covariance with single covariates. We built a deep learning model that was trained on historical Alzheimer's disease (AD) data. The prognostic model was locked prior to obtaining the data from an additional study to apply the Prognostic Covariate Adjustment, or PROCOVATM , procedure. The variance of the treatment effect was estimated (i) without covariate adjustment, (ii) with adjustment for single covariates, (iii) with adjustment for multiple covariates, and (iv) with a TwinRCT.
Results: The variance of the treatment effect for change in AD Assessment Scale - Cognitive Subscale 11 (ADAS-Cog11) was 1.07 without adjustment for covariates. Adjusting for baseline ADAS-Cog11 (single covariate) reduced the variance of the treatment effect to 1.02 while adjusting for Apolipoprotein E4 (APOE4+/-) did not reduce the variance (1.07). Adjusting for both baseline ADAS-Cog11 and APOE4+/- (multiple covariates) was comparable to adjusting for baseline ADAS-Cog11 alone (1.02). Adjusting for the optimal covariate with TwinRCT achieved the lowest reduction in variance (0.92). This variance reduction would allow for a 24.6% reduction of the control arm for prospectively designing a clinical trial.
Conclusions: TwinRCTs enable a more accurate estimation of the treatment effect, increase statistical power, and reduce the sample size of for example AD clinical trials.

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P0670 / #2587

POSTERS: B03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

4 MA TDCS IMPROVES WALKING ABILITY IN PSP: A PILOT STUDY OF TWO CASES

Durjoy Lahiri[1], Carlos Roncero[2], Howard Chertkow[1]
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Aims: The objective is to examine if tDCS can improve gait speed in people living with Progressive Supranuclear Palsy (PSP). There is no current treatment for PSP. One study from Roncero-Chertkow lab has looked at the effects of tDCS on motor function in PSP. Although tDCS is known to work through modulating spontaneous activity of neural network in cortex,certain technical modifications while applying tDCS can allow for the stimulation, and subsequent modulation, of sub-cortical brain structures adequately as well.
Methods: An 84 year lady with moderately severe PSP for 5 years and an 80 year gentleman with moderately severe PSP for 3 years (both walker-dependant), underwent two rounds of stimulation, two months apart, each consisting of twelve tDCS sessions over three weeks. In the first week of both rounds, sham tDCS was given to establish a pre-stimulation baseline, while one of two real tDCS montages was given in weeks two and three of each round. tDCS was given at an intensity of 4 mA over two anode electrodes placed over the left and right deltoid muscles, and two cathode electrodes placed just ahead of the motor cortex on both sides (C3 & C4). Primary outcome measure was gait time which is the time required to walk the length of the gait mat for 4 times (24 meters).
Results: Significant improvement in gait time compared to baseline (26.84% and 30.63% right after second round and 18.82% and 40.2% after 2 weeks without stimulation, for cases 1 and 2 respectively) was noted after second round. In both the rounds, they demonstrated improvement in cadence, stride length and stride velocity.
Conclusions: These results suggest tDCS can provide a significant improvement in walking ability of people with PSP.

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POSTERS: B03.Q. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

CLINICALLY IMPORTANT CHANGES IN PROGRESSIVE SUPRANUCLEAR PALSY: CGI-C WORSENING AND EFFECT ON PSPRS, SEADL AND RBANS

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Aims: The PSPRS, RBANS and SEADL are widely-used scales as key endpoints in progressive supranuclear palsy (psp) in clinical trials; however, the magnitude of change required in these measures for a clinically meaningful effect is unclear. A sensitive approach would be to determine what degree of change on a specific rating scale would be considered clinically meaningful for the physician who treats the patient. Using data from two global multinational studies with psp subjects, we sought to identify the mean score change in PSPRS, RBANS and SEADL when the CGI-C rating indicates clinical worsening.
Methods: We investigated clinically important changes on the PSPRS, RBANS and SEADL when subjects were identified as minimal and moderately worsening using the CGI-C. Clinically important changes were defined as mean change of PSPRS, RBANS and SEADL in subjects rated for the first time as "minimally worse" or "moderately worse" on CGI-C at 6 and 12 months since baseline. Data from these scales was analyzed for baseline, 6 and12 months for 863 subjects with psp enrolled in two multinational double-blind, placebo-controlled clinical trials.
Results: The mean changes for minimal worsening in PSPRS, SEADL and RBANS for CGI-C of 5 were respectively: -4.42±7.29 (d=0.46), 7.79±14.69 (d= -0.46) and 1.75±5.89 (d=-0.16). The mean changes for moderately worsening in PSPRS, SEADL and RBANS for CGI-C of 6 were respectively: -5.73±8.03 (d=1.14), 10.27±16.11(d=-1.01) and 1.75±5.87 (d=-0.31).
Conclusions: This study corroborates other findings of clinically important changes measurable on the PSPRS over six months and additionally demonstrates clinically meaningful changes measurable over six and twelve months mostly on the SEADL and PSPRS.

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POSTERS: B04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

BRAIN ATROPHY PROGRESSION IN PRE-CLINICAL FAMILIAL ALZHEIMER'S DISEASE

Christina Tremblay[1], Shady Rahayel[1], Andrew Vo[1], Natasha Rajah[2], Sylvia Villeneuve[2], Alain Dagher[1], The Prevent-Ad Research Group[2]
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Aims: Alzheimer's disease (AD) includes a long period of presymptomatic biochemical and brain structural changes. Different risk factors are associated with the development of this pathology, including having a family history of AD or carrying an apolipoprotein E e4 allele (*APOe4*). However, the pattern of atrophy progression in people with a family history of AD (FHAD) remains unclear. Here we used structural MRI from three databases (Montreal Adult Lifespan Study, ADNI and PREVENT-AD). The ADNI and PREVENT-AD dataset had follow-up data that allowed for longitudinal analysis of atrophy progression in FHAD compared to individuals without familial AD (Control group).
Methods: We created atrophy maps using deformation-based morphometry (ANTs longitudinal pipeline) applied to T1-weighted MRI for three groups with similar age, education and men/women proportion at baseline (Control: N=116, FHAD: N=153, AD: N=156). The Cammoun atlas (463 regions) was used for parcellation. A method for hamonizing longitudinal multi-scanner imaging (longComBat) was applied. The atrophy progression was compared between the three groups with linear mixed models (FDR corrections) controlling for sex, education, body mass index, *APOe4* genotype and *APOe4* interaction with age. Posthoc comparisons were computed between the Control, FHAD and AD groups.
Results: In AD, we found that atrophy significantly increases with age in 28 regions, mostly part of the insula, cingulate cortex, temporal and parietal lobe. Eight of these regions also showed a significant atrophy progression in the FHAD group: the right fusiform gyrus, precentral gyrus and posterior cingulate cortex, the left insula, postcentral gyrus and superior parietal lobule, and the bilateral isthmus of the cingulate.
Conclusions: Asymptomatic individuals at risk for AD show early neurodegenerative changes in regions also affected in AD. This work can help determine the presymptomatic neurodegenerative landscape in AD.

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P0673 / #1490

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

A/T/N/C DYNAMICS AND THEIR PROGNOSTIC VALUES IN A MEMORY CLINIC POPULATION

Cecilia Boccalini[1,2], Federica Ribaldi[3], Ines Hristovska[1], Annachiara Arnone[1], Debora Peretti[1], Daniela Perani[2], Giovanni Frisoni[3], Valentina Garibotto[4,5]
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Aims: To examine the independent and combined association among neuroimaging Alzheimer's disease (AD) biomarkers (amyloid, A; tau, T; neurodegeneration, N) and cognitive performance (C) and decline.
Methods: A total of 94 participants ranging from cognitively unimpaired to demented with Mini-Mental State Examination (MMSE) (C), tau-PET (T), amyloid-PET (A), FDG-PET (N), and structural MRI (N) scans were recruited from the Geneva Memory Center. For 64 subjects longitudinally followed (average=2years), the cognitive decline was assessed as MMSE annual rate of change. Neuroimaging analyses were performed in AD-related regions. Additional whole-brain voxel-wise analyses were performed for tau-PET and FDG-PET. Linear regression models were applied to correlate AD biomarkers with C and cognitive decline. Mediation analyses examined whether associations between baseline T and C and cognitive decline were mediated by N. We assessed prognostic values of AD biomarkers by applying linear mixed-effects models and Cox proportional hazards regression.
Results: Among biomarkers, the FDG metabolism in lateral temporal regions had the strongest association with C ($p=0.551$; $p<0.001$), followed by T in the same regions ($r= -0.487$; $p<0.001$). Neocortical T was associated with the cognitive decline ($r=-0.602$; $p<0.001$) showing the strongest association. Accordingly, T positivity predicted longitudinal cognitive decline better than N, A and C, and it represented the strongest risk factor (hazard ratio=35.17; 95% confidence interval: 6.39-192.43). N, assessed by both FDG and MRI, mediated the baseline association between T and C, but not the longitudinal one.
Conclusions: Our results are consistent with T and N synergistically contributing to cognitive impairment. However, N drives concurrent C while neocortical T drives cognitive decline. The superior value of T for predicting cognitive changes compared to other neuroimaging biomarkers supports tau-PET as a prognostic tool in memory clinics.

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P0674 / #2441

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

DATA-DRIVEN APPROACH FOR FEATURE SELECTION FOR AUTOMATED VISUAL TAU-PET STRATIFICATION

Alejandro Costoya-Sánchez[1], Jesús Silva-Rodríguez[2], Pablo Aguiar[1], Alexis Moscoso[3]
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Aims: Visual interpretation of [^{18}F]flortaucipir (FTP) PET scans according to recently approved FDA guidelines remains a time-consuming task. Approaches for automated FTP PET scan classification are at risk of bias due to producing overfitted, non-generalizable models. The aim of this study is to use a data-driven approach to investigate quantitative tau-PET features that might be used for an automated, low-dimensionality classification model while avoiding overfitting.
Methods: We included individuals from the Alzheimer's Disease Neuroimaging Initiative who had undergone FTP PET and MRI scanning as our validation cohort (N=895). FTP PET scans were visually interpreted by one reader (AM) according to approved FTP visual interpretation guidelines. Standardized uptake value ratio (SUVR) values were quantified for FreeSurfer cortical output regions of interest (ROI). Regional SUVRs were used as input features for a multi-class Support Vector Machine (SVM) classification model. Feature selection was then performed using Recursive Feature Elimination (RFE).
Results: RFE selection showed that a small subgroup of regional SUVR values corresponding to temporal, occipital, parietal, precuneus, frontal and cerebellum cortical regions provided most of the information used for the SVM classification model.
Conclusions: Our study shows that a few selected regional SUVR values could be used as input for a generalizable, automated FTP scan classification model that reproduces time-consuming visual interpretations. Moreover, the ROIs selected by the RFE method largely coincided with the regions used for the visual interpretation pipeline, reinforcing the interpretability of an automated stratification model based on these features.

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P0675 / #1921

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

ASSOCIATIONS BETWEEN RETRIEVAL AND ENCODING INDICES AND TAU IN EARLY AND LATE PET-BRAAK STAGES

Jaime Fernandez-Arias
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Aims: Extracellular tau and intracellular amyloid-beta are the neuropathological hallmarks of Alzheimer's disease (AD). Episodic memory decline is a classical early sign of this pervasive disease that has been shown to relate to tau load in the medial temporal lobe (MTL) and neocortical regions in the AD spectrum. Encoding failure has been suggested to cause AD-related memory decline, but the debate is far from settled. We sought to explore whether these associations are driven by retrieval or encoding deficits using a PET-Braak staging approach.
Methods: Tau PET ([18F]-MK6240) was acquired for 146 cognitively unimpaired elderly, 40 MCI Abeta+ patients and 32 AD Abeta+ patients. Participants were segregated into two groups based on tau PET-Braak staging (group 1=Braak I-III; group 2=Braak IV-VI). Episodic memory was assessed using encoding and retrieval indexes derived from the Rey Auditory Verbal Learning Test. Voxel-wise analyses were conducted. Covariates were global amyloid, age, sex, education and APOE genotype.
Results: Voxel-wise analyses revealed that encoding deficits are associated to tau bilaterally in perirhinal (PRC) and entorhinal cortices (EC) and in the right hippocampus (HC), while retrieval deficits relate to tau in right PRC, EC and HC in participants from group 1. Only encoding deficits seemed to be associated to tau in group 2, where a clear lateralization on the left was observed predominantly in posterior neocortical regions.
Conclusions: Our findings support the narrative that memory impairment in the preclinical and clinical AD spectrum is due to encoding deficits, since most of our Braak IV-VI participants are cognitively impaired. In early stages of tau accumulation, where the vast majority of participants are cognitively unimpaired, both retrieval and encoding deficits are observed. We also found that these processes may be lateralized across the brain.

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P0676 / #1851

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

TAU PET POSITIVITY REVEALS ALZHEIMER'S DISEASE RELATED COGNITIVE DECLINE

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Aims: The relatively low positive prognostic value of β-amyloid (Aβ) Positron Emission Tomography (PET) in predicting future cognitive status in Alzheimer's disease (AD) continuum, underlines the need of new biomarkers. We aim to assess the prognostic accuracy of a tau PET biomarker to predict clinically relevant cognitive decline.
Methods: A subset of 335 individuals [cognitively unimpaired (n=217), cognitively impaired (n=118)] with baseline Aβ and tau PET scans and a follow-up ≥ 2 years, was selected from the Alzheimer's Disease Neuroimaging Initiative dataset. Based on the Alzheimer's Disease Assessment Scale–Cognitive Subscale and linear mixed-effects models, we defined the annual rate of cognitive decline of all individuals. Gaussian mixture modelling, was next used to cluster them into fast (FD) and slow decliners (SD). The accuracy of tau PET to discriminate between these cognitive decline profiles was tested. Furthermore, we investigated the prevalence of non-AD comorbidities in individuals with discordant status between Aβ and tau biomarkers.
Results: Aβ(+)FD showed the highest tau PET uptake independently of baseline cognitive status, compared to the other groups [Aβ(-)FD/SD, Aβ(+)SD]. Baseline tau PET uptake could determine Aβ(+)FD with an accuracy of 85% (composite temporal region of interest) and is linearly related to the annual rate of cognitive decline in Aβ(+). The tau positive T(+) individuals were the subgroup of those Aβ(+) with the highest prevalence of FD. In relation to Aβ(+)T(+)FD (28/41, 68%), Aβ(+)T(-)FD (13/41, 32%) showed higher frequency of cerebrovascular risk factors and comorbid depression.
Conclusions: High tau PET uptake can define cognitive decline driven by AD neuropathology. Tau PET imaging shows better combined diagnostic and prognostic accuracy than Aβ PET. The introduction of tau PET in memory clinics could better determine the best candidates recruited in clinical trials.

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P0677 / #2353

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

DEVELOPMENT OF A HIGHLY SENSITIVE TAU TRACER 18F-SNFT-1 FOR IMAGING EARLY TAU PATHOLOGY IN ALZHEIMER'S DISEASE

Nobuyuki Okamura[1,2,3], Ryuichi Harada[2,4], Pradith Lerdsirisuk[3], Yuki Shimizu[3], Yuka Yokoyama[3], Yiqing Du[3], Michinori Ezura[5], Hiroyuki Arai[2], Yukitsuka Kudo[2], Shozo Furumoto[3]
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Aims: For the assessment of early tau burden in Alzheimer's disease (AD) continuum, it is important to improve the sensitivity and reduce the off-target binding of tau PET tracers. The purpose of this study is to characterize the binding profiles of a novel tau tracer ^{18}F-SNFT-1, by the comparison of other reported tau tracers.
Methods: *In vitro* binding assays were performed to measure the binding affinity of SNFT-1 to tau aggregates and monoamine oxidase (MAO) enzymes. Receptor binding screen assays were also performed to check for off-target binding of SNFT-1. In vitro autoradiography was performed to evaluate the binding selectivity and sensitivity of ^{18}F-SNFT-1 on medial temporal brain sections from individuals with low (II) and high (VI) Braak stages and compared with other tau tracers (MK-6240, PM-PBB3, PI-2620, RO6958948, JNJ-64326067, and flortaucipir).
Results: SNFT-1 showed high binding affinity (K_D = 0.6 nM) to tau-rich AD brain homogenates, while it showed low binding affinity to MAO-A and MAO-B (IC_{50} > 1,000 nM). Receptor binding screen assays of SNFT-1 also confirmed no remarkable interaction with various receptors, ion channels, and transporters. Autoradiographic analyses showed that ^{18}F-SNFT-1 selectively binds to tau deposits in medial temporal cortex. In the entorhinal cortex of Braak stage II brain sections, the specific binding signal of ^{18}F-SNFT-1 was greater than that of other tau tracers including MK-6240 and flortaucipir.
Conclusions: ^{18}F-SNFT-1 is a promising tau PET tracer, which has potential to enable longitudinal assessment of age-related tau pathology in the human brain.

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P0678 / #1133

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

18F-PI2620 TAU-PET TRACER AND NEUROFILAMENT LIGHT CHAIN AS PROGNOSTIC BIOMARKERS IN AMYLOID-NEGATIVE CORTICOBASAL SYNDROME

Carla Palleis[1,2], Nicolai Franzmeier[3], Leonie Beyer[4], Brigitte Nuscher[2], Endy Weidinger[1], Alexander Bernhardt[1], Sabrina Katzdobler[1], Boris-Stephan Rauchmann[5], Robert Perneczky[5], Christian Haass[2], Matthias Brendel[4], Johannes Levin[1], Günter Höglinger[2,6]
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Aims: The aim of the study is to evaluate neurofilament light chain (NFL) in plasma, a marker for neuro-axonal damage, and the next generation tau-PET tracer ^{18}F-PI2620 as potential prognostic markers in corticobasal syndrome (CBS) with clinical diagnosis of probable 4-repeat (4R) tauopathy.
Methods: The Munich CBS cohort is part of the longitudinal observational biomarker study "Activity of Cerebral Networks, Amyloid and Microglia in Aging and Alzheimer's Disease (ActiGliA)". Only amyloid-negative CBS patients that met the diagnostic criteria of probable 4R-tauopathies (Movement Disorders Society PSP-criteria or Armstrong CBD-criteria) were included. Baseline visit contained clinical assessment, blood sampling, and ^{18}F-PI2620-PET. Disease severity was assessed by PSP rating scale (PSPRS) at baseline and during follow-up visits. NFL plasma levels at baseline were determined on the Simoa® Quanterix platform. A linear mixed effects model for global "tau expansion" from z-scores of ^{18}F-PI2620 Standardized uptake value ratios (SUVr) and NFL plasma levels was applied to the longitudinal PSPRS scores.
Results: 21 CBS patients were examined longitudinally (mean: 1.8±0.57 years) after baseline. PSPRS worsened significantly over the observation period ($p<0.001$, baseline PSPRS =22.2±14.1, rate of change per year=6.5±4.5). Higher Tau-PET Z-scores (> tau median) were associated with a more severe clinical deterioration (linear mixed model: interaction Tau-PET x follow-up time, b/SE=0.03/0.01, $p=0.015$). Worse clinical performance was also seen for high NFL levels (> NFL median) in plasma (linear mixed model: interaction NFL x time from baseline, b/SE=0.16/0.05, $p=0.002$).
Conclusions: Both tau ligand ^{18}F-PI2620 and plasma NFL are potential prognostic biomarkers in CBS with probable 4R-tauopathy.

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P0679 / #1906

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

TAU PET CONCENTRATIONS IN EARLY BRAAK REGIONS INCREASE ACROSS THE AD CONTINUUM

Guilherme Povala[1], Pamela Ferreira[1], Bruna Bellaver[1], João Pedro Ferrari-Souza[1,2], Firoza Lussier[1], Douglas Leffa[1,3], Cécile Tissot[1,4], Joseph Therriault[4], Andrea L. Benedet[5], Mira Chamoun[4], Gleb Bezgin[4], Stijn Servaes[4], Jenna Stevenson[4], Nesrine Rahmouni[4], Ann Cohen[1], Oscar Lopez[1], Dana Tudorascu[1], William Klunk[1], Victor Villemagne[1], Thomas Karikari[1,5], Eduardo Zimmer[2,6], Pedro Rosa-Neto[4], Tharick Pascoal[1]
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Aims: To determine whether a single brain region can track early and late Braak stages for monitoring clinical trials across the AD spectrum.
Methods: We stratified 387 individuals from the McGill TRIAD cohort with [^{18}F]MK6240 tau-PET Braak stages using four classes (Braak 0, Braak I-II, Braak III-IV, and Braak V-VI). Voxel- and regional-wise analysis assessed the brain regions that better captured the Braak stage scheme variance.
Results: Voxel-analysis suggest that the transentorhinal cortex (Braak I) best explains the entire Braak staging variance, differentiating patients in early (Braak 0 to I-II) and late (Braak III-IV to V-VI) Braak stages (Fig. 1A-B) (R-squared = 0.754), which was confirmed by ROI-wise analysis (Fig. 1C). Larger composite brain region comprising entorhinal and hippocampus (Braak II) cortices also stratified Braak stages with high accuracy (R-squared = 0.619). On the other hand, late Braak regions could not differentiate individuals in the early stages of tau accumulation (Braak 0 to I-II).

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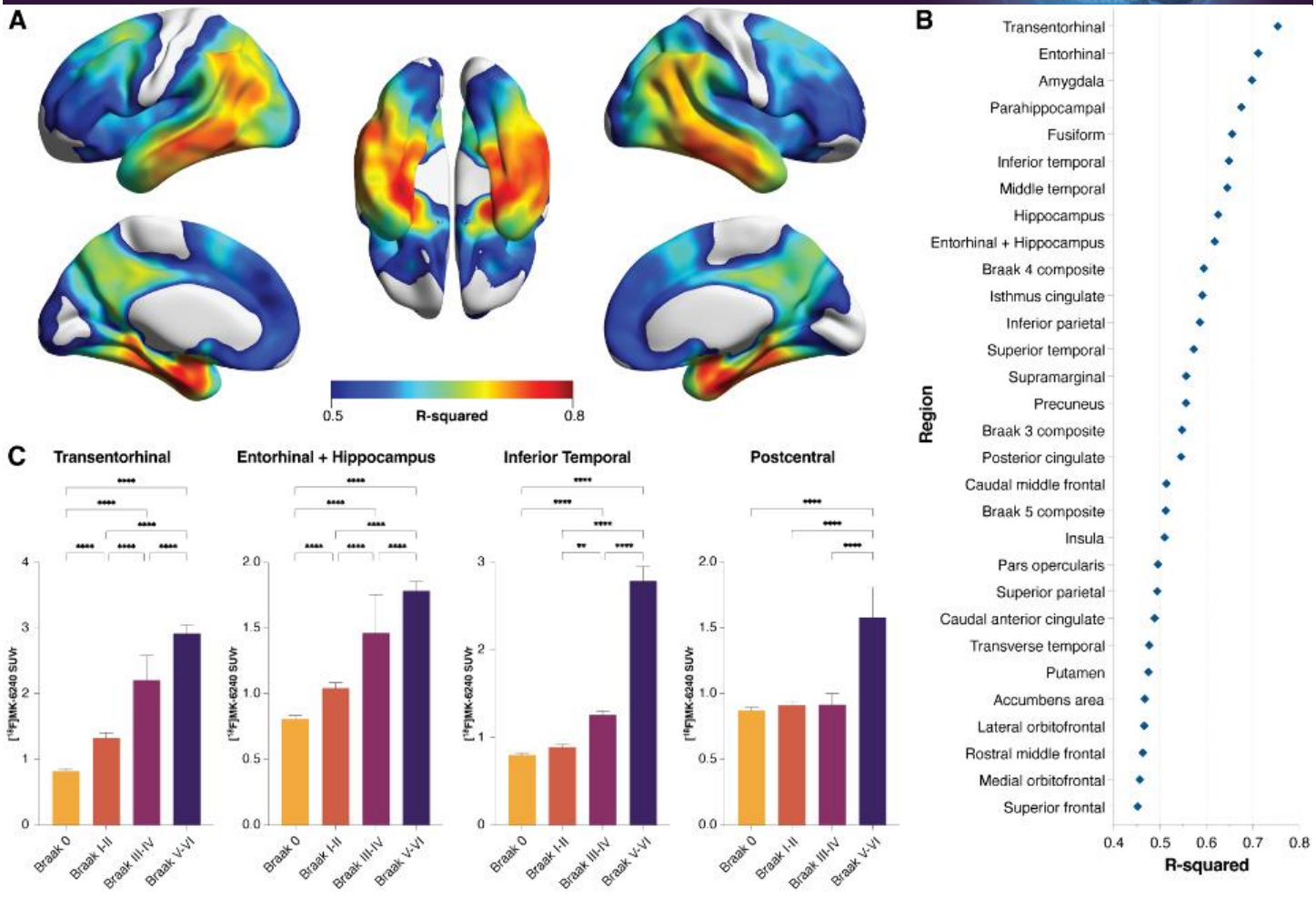

Figure 1. Association between SUVr values and Braak stagings. **A** Voxel-wise linear regression association between [^{18}F]MK6240 tau-PET and Braak staging using sex and age as covariates. **B** Regional R-squared for the association between [^{18}F]MK6240 tau-PET and Braak staging. **C** Performance of brain regions using the averaged R-squared stratifying the individuals in Braak 0, Braak I-II, Braak III-IV, and Braak V-VI.

Conclusions: Our results suggest that regions confined to the mediobasal temporal cortex best discriminate Braak stage using [^{18}F]MK6240 tau-PET and therefore have a higher potential to be used in clinical trials. Our results exemplify that adding late Braak stage regions to a composite ROI decreases the sensitivity of tau PET biomarker to identify early tau accumulation, whereas using early Braak regions can depict both early and late tau accumulation.

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P0680 / #1704

POSTERS: B04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

CONNECTING COGNITIVE SCORES AND TAU-PATHOLOGY IN NFV-PPA

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Aims: The nonfluent-agrammatic-variant of primary progressive aphasia (**nfv-PPA**) is a rare disorder from the spectrum of frontotemporal lobar degeneration characterized by a continuous decline of grammatical speech abilities. Patients frequently present with agrammatism, apraxia of speech and impaired comprehension of syntactically complex sentences. On the one hand, many cognitive scores cannot be captured due to limited speech abilities, on the other, it is still unknown which cognitive scores are suitable to mirror the severity of neuropathology in nfv-PPA patients. Therefore, the aim of this study was to investigate the associations between cognitive scores and Tau-pathology in nfv-PPA patients.
Methods: 15 patients diagnosed with nfv-PPA according to the Gorno-Tempini-Criteria were examined using various cognitive scores (CDR, MMSE, FRSBE, DSFT, DSBT, BNT15, CFT, LFT, AAT, AC) and [^{18}F]-THK5351-ᴛ-PET. Subsequently, Standard-Uptake-Volume-Ratio (**SUVr**) was voxel-wise calculated and correlated with the cognitive scores (**Cluster-Size > 600 voxels**, $\mathbf{q_{FDR\text{-}corrected} < 0.05}$).
Results: For the Aachen-Aphasia-Test (**AAT**) subtest „**Reading-Aloud** “, a highly significant correlation between cognitive score and the SUVrs of two large cortical brain areas could be ascertained. One area is located on the left brain hemisphere (**Maximum-Location (x/y/z): -26/18/54mm**) and mainly consists of the left middle frontal gyrus (**29.64%**), inferior parietal gyrus (**13.48%**), precentral gyrus (**9.36%**) and postcentral gyrus (**7.32%**). The other one is located on the right brain hemisphere (**Maximum-Location (x/y/z): 52/34/18mm**) and predominantly involves the right middle frontal gyrus (**16.72%**), precentral gyrus (**16.27%**), superior frontal gyrus (**10%**) and inferior frontal gyrus (**9.14%).**
Conclusions: Assumed that Tau-PET-SUVr is a suitable biomarker for the Tau-pathology in the affected brain regions, the AAT-Reading-Aloud subtest appears to be a reliable predictor for the severity of Tau-pathology in nfv-PPA patients.

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P0681 / #1772

POSTERS: B04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

APOE4 IS A KEY PLAYER IN THE EARLY ACTIVATION OF MICROGLIA IN ALZHEIMER'S DISEASE

João Pedro Ferrari-Souza[1,2], Firoza Lussier[1], Douglas Leffa[1], Joseph Therriault[3], Cécile Tissot[1,3], Bruna Bellaver[1,2], Pamela Ferreira[1], Maura Malpetti[4], Yi-Ting Wang[3], Guilherme Povala[1], Andrea L. Benedet[5], Nicholas Ashton[5], Mira Chamoun[3], Stijn Servaes[3], Gleb Bezgin[3], Min Su Kang[3], Jenna Stevenson[3], Nesrine Rahmouni[3], Vanessa Pallen[3], Nina Poltronetti[3], John O'Brien[6], James Rowe[4], Ann Cohen[1], Oscar Lopez[7], Dana Tudorascu[1], Thomas Karikari[5], William Klunk[1], Victor Villemagne[1], Jean-Paul Soucy[8], Serge Gauthier[3], Diogo Souza[2], Henrik Zetterberg[5], Kaj Blennow[5], Eduardo Zimmer[2], Pedro Rosa-Neto[3], Tharick Pascoal[1]
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Aims: To investigate whether *APOE*ε4 carriership is associated with microglial activation in individuals across the aging and AD spectrum.
Methods: We studied 118 individuals that were across the aging and AD spectrum (79 cognitively unimpaired [CU], 23 with mild cognitive impairment [MCI], and 16 with AD dementia) with [^{18}F]AZD4694 Aβ PET, [^{18}F]MK6240 tau PET, [^{11}C]PBR28 microglial activation PET, and magnetic resonance imaging (MRI), as well as *APOE* genotyping. *Postmortem* data from the Allen Human Brain Atlas was used to assess the cerebral physiological distribution of *APOE* mRNA expression.
Results: We found that *APOE*ε4 carriership was associated with increased microglial activation mainly in early Braak-staging regions within the medial temporal cortex, and this effect of *APOE*ε4 was independent of Aβ and tau deposition (**Figure 1**). Furthermore, microglial activation mediated the Aβ-independent effects of *APOE*ε4 on downstream tau accumulation, neurodegeneration, and clinical impairment (**Figure 2**). Interestingly, the brain distribution of *APOE* mRNA expression predicted the topography and magnitude of *APOE*ε4 effects on [^{11}C]PBR28 uptake observed in our population, suggesting that the deleterious effects of *APOE*ε4 occur at the level of gene expression (**Figure**

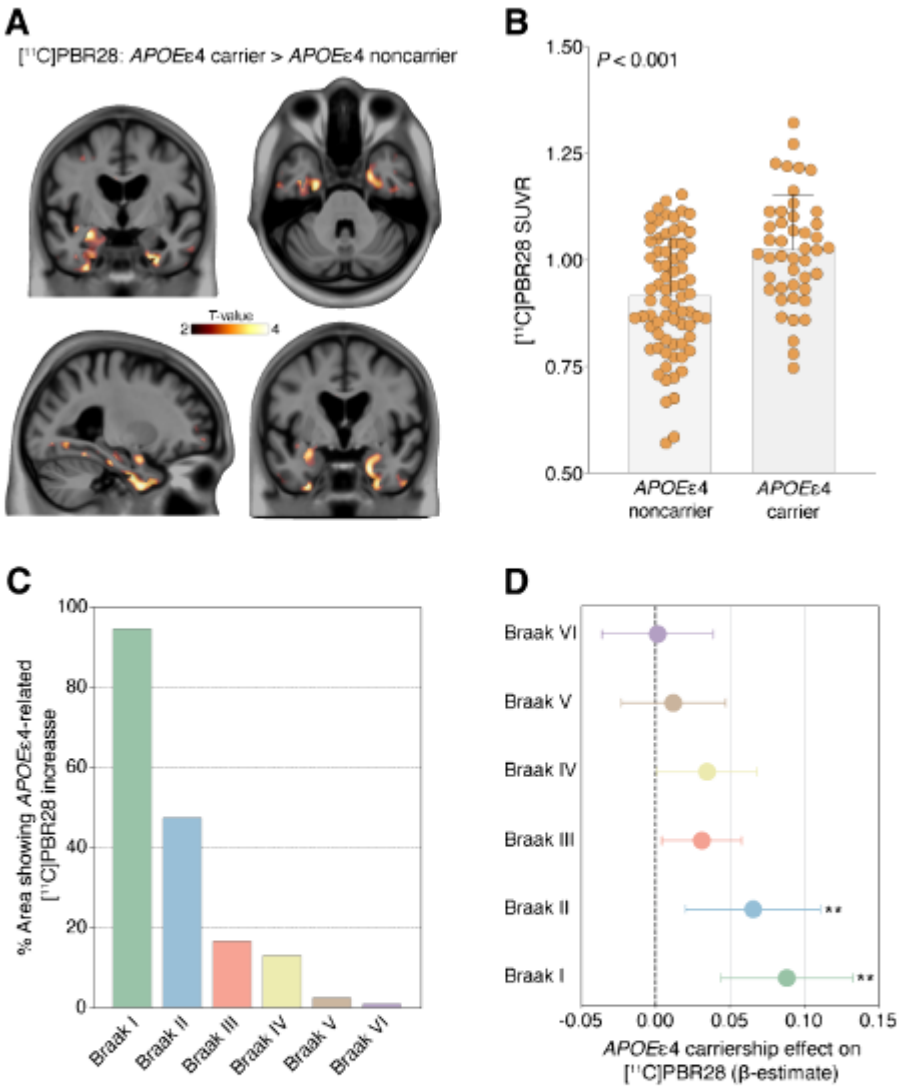

Fig. 1. *APOE*ε4 carriership is associated with microglial activation in early Braak regions. (**A**) *T*-map shows the result of voxel-wise linear regression testing the association of *APOE*ε4 carriage status (noncarrier or carrier) with [11C]PBR28 SUVR accounting for age, sex, and clinical diagnosis (CU, MCI, or AD). Results survived random field theory correction for multiple comparisons at $P < 0.05$. (**B**) Bars show the mean and standard deviation of [11C]PBR28 SUVR in *APOE*ε4 noncarriers and carriers. Imaging biomarker values were extracted from the peak *T*-value cluster of the voxel-wise analysis (*T*-value ≥ 4.7). *P*-value indicates the result of regression analysis accounting for age, sex, and clinical diagnosis. (**C**) Bars represent the spatial extent of the *APOE*ε4-related microglia activation across Braak regions. Values were calculated by determining the percentage of voxels per Braak region having an association (*T*-value > 2) between *APOE*ε4 carriership and [11C]PBR28 in the voxel-wise analysis. (**D**) β-estimates with 95% CI represent the strength of the regional association between *APOE*ε4 status and [11C]PBR28 SUVR across Braak regions from ROI-based linear regressions. Models were adjusted for age, sex, and clinical diagnosis. Estimates that survived Bonferroni correction at $P < 0.05$ are indicated with a double asterisk.

3).

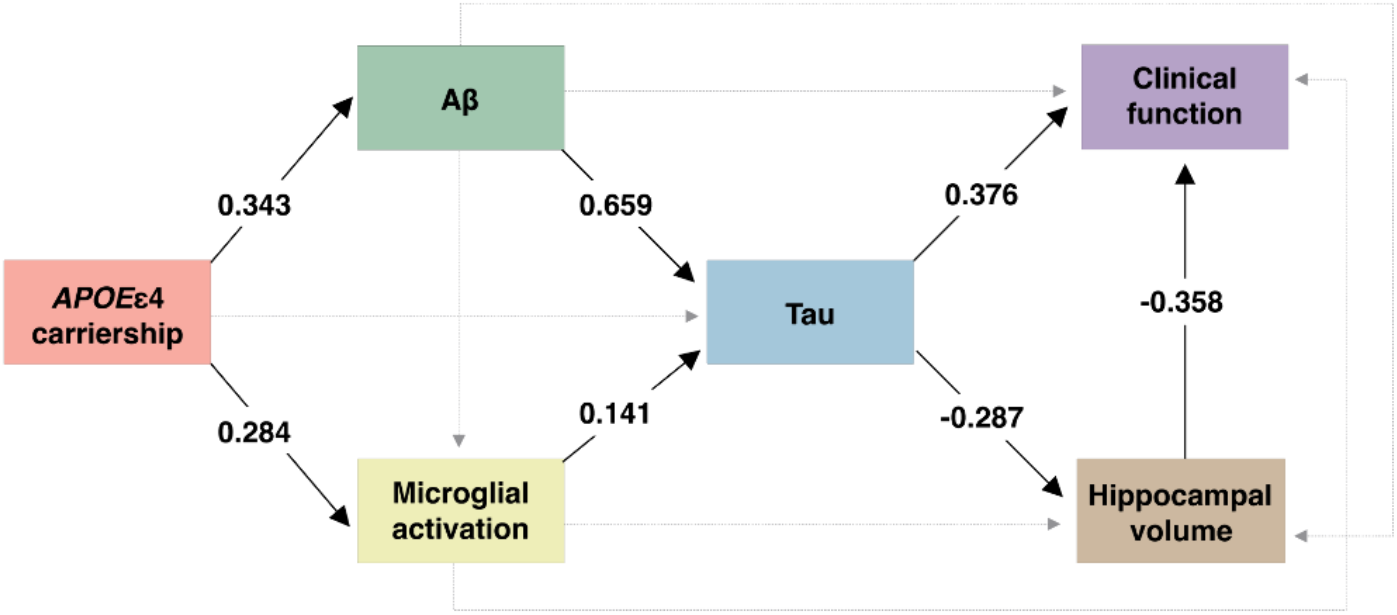

Fig. 2. *APOE*ε4 contributes to AD progression independently of Aβ by activating microglia. The values presented in the figure are structural equation model β-estimates testing the associations between *APOE*ε4 status, microglial activation PET, Aβ PET, tau PET, hippocampal volume, and clinical function. Given that the β-estimates presented in the figure are standardized, the effects can be directly compared. Solid lines represent significant associations, whereas dashed lines represent non-significant effects. All associations were adjusted for age and sex. Associations involving hippocampal volume and clinical function were also adjusted for years of education. Aβ pathology was measured with global [^{18}F]AZD4694 SUVR, microglial activation with Braak I-II [^{11}C]PBR28 SUVR, and tau pathology with Braak I-II [^{18}F]MK6240 SUVR. Clinical function was assessed with the clinical dementia rating scale sum of boxes score.

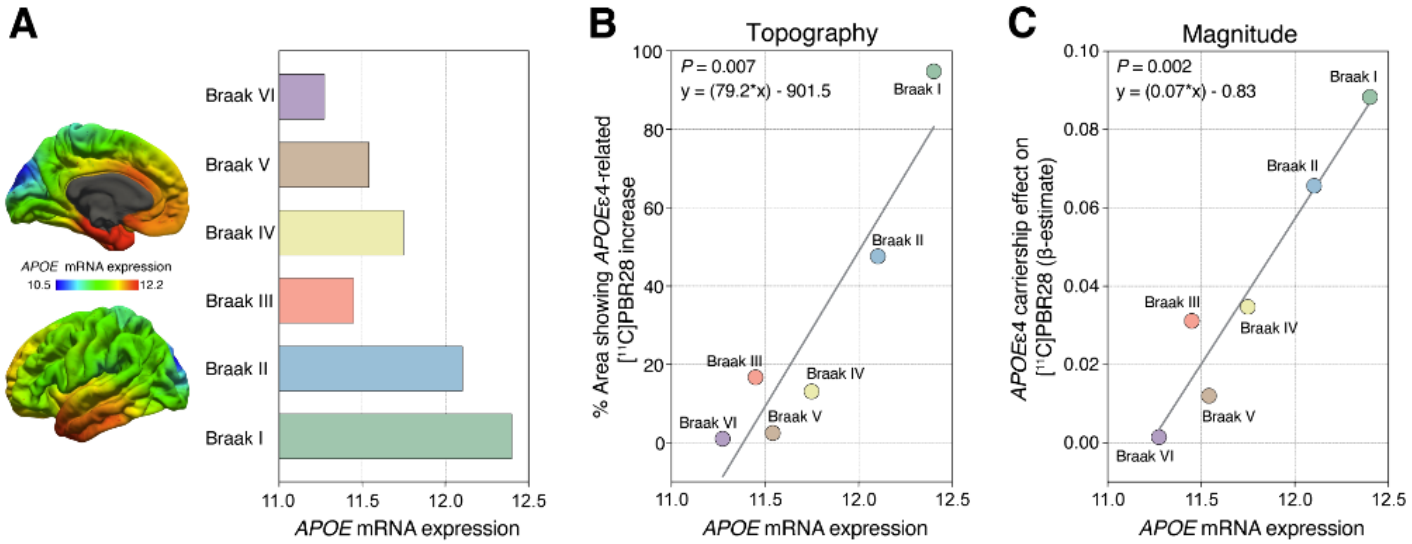

Fig. 3. The brain levels of *APOE* gene expression predict *APOE*ε4-related [11C]PBR28 SUVR increase. (**A**) Brain map of the topographical distribution of *APOE* mRNA expression in 6 CU individuals obtained from the Allen Human Brain Atlas (left). Average intensity values of *APOE* mRNA expression in each Braak region (right). (**B**) Regression analysis testing whether Allen *APOE* gene expression patterns predict the percentage of the area showing *APOE*ε4-related [^{11}C]PBR28 SUVR increase across Braak regions in our population. (**C**) Regression analysis testing whether the Allen brain *APOE* gene expression patterns predict the magnitude/strength of the association between *APOE*ε4 and [^{11}C]PBR28 uptake across Braak regions in our population.

Conclusions: These results support a model in which *APOE*ε4 carriership has Aβ-independent effects on AD pathogenesis by activating microglia in brain regions associated with early tau deposition. Our findings provide a rationale for the development of novel AD therapies targeting the interplay between ApoE and neuroinflammation.

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POSTERS: B04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

ENHANCED MACHINE LEARNING APPROACH TO DIAGNOSING ALZHEIMER'S DISEASE AND MILD-COGNITIVE IMPAIRMENT BASED ON TRIPLET FUNCTIONAL BRAIN NETWORKS AND APOE GENE

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Aims: To improve classification, diagnosis, and performance accuracy and to better understand the pathological mechanisms behind the brain dysfunction associated with Alzheimer's, it is essential to develop interpretable and precise imaging biomarkers from functional brain networks.
Methods: The APOE gene has three alleles in humans: Ɛ2, Ɛ3, and Ɛ4. While having the Ɛ2 allele is beneficial but having the Ɛ4 allele increases the chance of developing AD. *APOE* is a crucial lipid transporter that controls several crucial physiological mechanisms and is vital for the growth, preservation, and restoration of the CNS. For computer-aided analysis we included 35 cognitively healthy controls (HC), 33 AD, and 61 people with MCI, we created four alternative prediction models and suggested data exploratory methods (DET) in this study. To find the robust feature classification into the MCI, AD, and HC classes in prior models, three-layered important DET, such as feature correlation, removal, and hyper-parameter optimization, were thoroughly investigated multimodal information to uncover interpretable and discriminative biomarkers from functional networks and APOE Ɛ4 gene.
Results: For AD vs. HC, this diagnostic classification system has a 91.71% accuracy rate. Similarly, for less commonly reported classification group in state-of-art methods MCIs vs MCIc we achieved 83.13% accuracy. Results for the integration of features further indicate that our suggested method has a high rate of accuracy.
Conclusions: The potential features for disease diagnosis are evaluated for both brain networks and genetic features. Persons with MCI and AD can be distinguished from HC more precisely by successfully integrating important brain networks and genetic information using techniques like feature selection. These findings have confirmed the clinical relevance of the suggested approaches for the detection of AD.

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POSTERS: B04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

EARLY DETECTION OF ALZHEIMER'S DISEASE: ASSOCIATION OF NEUROIMAGING WITH MULTIMODAL MACHINE LEARNING ALGORITHM

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Aims: In early stages of AD, people experience memory problems often referred to the age-related physiological reduction of cognitive capabilities, and as a consequence of it AD in early stages can be undetected. Appropriate methods are required to develop strategies for early detection of AD. The conventional approach based on cognitive testing is not accurate enough and should be integrated with reliable biomarkers to allow a correct diagnosis. Increasing evidence suggests that markers, such as Voxel-based morphometry (VBM), extracted from Magnetic Resonance Imaging (MRI) may allow a correct diagnosis of AD. VBM shows brain neuro-structural changes providing useful information about brain morphology and allowing to track the neurodegeneration.
Methods: Non-invasive methods such as computer aided diagnosis systems (CADS) have been proposed as a complement of imaging techniques to improve AD diagnostics. CADS with good performance can provide accurate information of early stages of brain neurodegeneration. Computer methods in neuroscience represent a useful way to use huge and complex datasets, the potentialities of six different supervised classifiers for identifying reliable CADS using MRI obtained from subjects diagnosed for AD at different stages are presented.
Results: The classifiers used produced good results in terms of accuracy and precision; however, considering the different classification accuracy metric, the gradient boosting technique seems to have a better potential classifier than others.
Conclusions: Our study showed that it is possible to predict individual dementia of older adults with a screening of MRI data by ML classifiers using the demographic information and pre-existing conditions of the patient to enhance the classification accuracy. More detailed subject data and clinical features should be investigated in future studies to produce more sophisticated prediction models.

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P0684 / #407

POSTERS: B04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

MAPT GENE EXPRESSION AND AMYLOID-PET ENHANCE CONNECTIVITY-BASED PREDICTION OF REGIONAL TAU ACCUMULATION IN ALZHEIMER'S DISEASE

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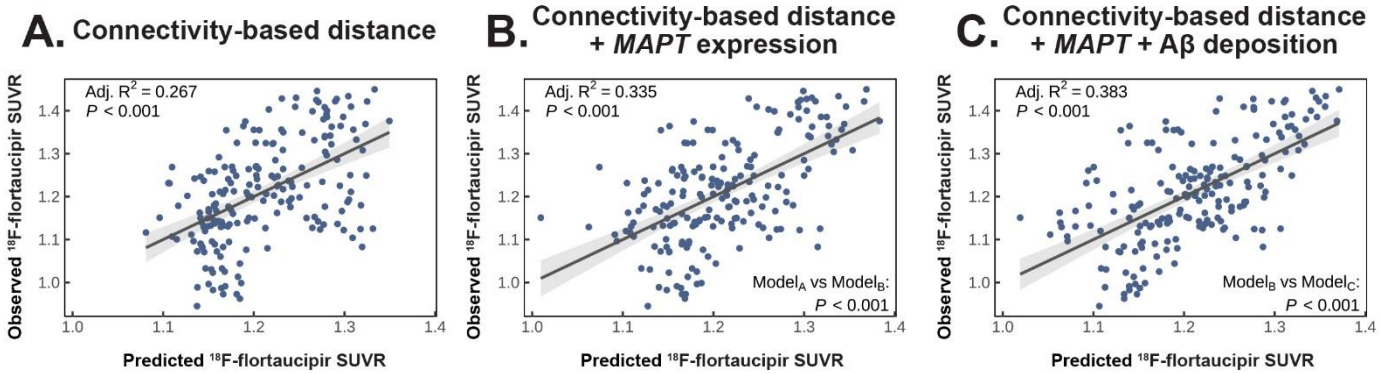
Aims: Fibrillar tau pathology spreads preferentially between closely connected regions of functional networks in Alzheimer's disease (AD). Yet local molecular properties such as gene expression profiles and amyloid deposition may also contribute to individual spreading patterns of tau. We aimed to test whether local brain properties could enhance the connectivity-based prediction of regional tau levels in AD.
Methods: Here, we combined connectomics with transcript mapping of *MAPT*, *i.e.*, the tau-encoding gene, and patient-level regional amyloid-PET to explain regional vulnerability to tau pathology in AD. We included 611 participants encompassing 321 Aβ negative cognitively normal (CN), and 290 Aβ positive participants within the AD spectrum, in whom both ^{18}F-flortaucipir tau-PET and ^{18}F-florbetaben/^{18}F-florbetapir amyloid-PET were collected. All scans and the *MAPT* gene expression map were transformed to MNI space and parcellated by the 200-ROI Schaefer brain atlas. In stepwise spatial regression analyses, we added in addition to epicenter-based functional connectivity-based distances (*Franzmeier et al. Sci Adv 2020*), 1) ROI levels of *MAPT* gene expression obtained from the transcriptomic Human Allen Brain Atlas, and 2) patient-level amyloid-PET ROI levels as predictors of tau-PET ROI values.
Results: Compared to epicenter-based connectivity (adjusted R^2 = 0.27, p < 0.001), adding *MAPT* gene expression increased the proportion of explained variance in regional tau-PET to 0.34 (p < 0.001), and the proportion was further increased to 0.38 when adding subjects' regional amyloid PET levels (p < 0.001, Figure 1).



Conclusions: Fully integrated connectomics and molecular properties including atlas-based *MAPT* expression and regional amyloid PET enhance the explained variance of regional level of tau-PET by 11% to 38%, thus yielding a promising tool to define patient-tailored regional tau-PET outcome variables in clinical trials targeting tau in AD.

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P0685 / #2538

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

HIGH PRECISION MEASUREMETNS OF EXOSOME-BOUND AMYLOID BETA IN PLASMA FOR THE IDENTIFICATION OF ALZHEIMER'S DISEASE PATIENTS

Ji Yoon Kang[1], Roy Soumi[1], Kyung-Sik Shin[2]
[1]KIST, Center For Brain Technology, Seoul, Korea, Republic of, [2]Bioxonics, Research, Seoul, Korea, Republic of

Aims: Exosome-based biomarkers in plasma have been noticed as a reliable biomarker especially in blood-based AD diagnosis, but the assay of rare proteins is hard for conventional ELISA. Hence this paper suggests an ultrasensitive microbead-based electrocheimcal sensor in microwell (μBECS) for detecting exosome-bound Aβ in plasma as a biomarker for Alzheimer's disease (AD).
Methods: The limit of detection (LOD) of μBECS was tested with dimer $A\beta_{40}$ diluted from 10 fg/mL to 1 ng/mL. The surface of magnetic bead was immobilized with capture antibody and the detection antibody was attached by HRP(horseradish peroxidase). The substrate for peroxidase was TMB, and the reduction current was measured at -0.2V. The feasibility exosome-bound Aβs for identification of AD was tested with 30 patients and 30 normal controls enrolled in this study.
Results: The μBECS could detect down to 100 fg/mL of dimer $A\beta_{40}$ that is two orders less than the limit of detection of conventional plate ELISA assay. The dynamic range of μBECS was about 5 decades and the sensor respnse was logarithmically linear. The current range of working microelectrode was from 0.5 to 10 nA. The levels of exosome-bound Aβs in plasma of AD patients was higher than normal control. The plasma levels of exosome-bound Aβs identified Alzheimer's disease with an area under the ROC curve (AUC) of about 0.9. Higher exosome-boudnd Aβ level in plasma of AD than that of NC was opposite tendency with plasma $A\beta_{42/40}$ ratio in CSF. There are some controversial issues in assessing the level of Aβ in plasma as well as that on exosome.
Conclusions: This study showed that the exosomal Aβs measured by highly accurate electrocheimcal sensor could be a promising biomarker for the diagnosis Alzheimer's disease.

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P0686 / #2545

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

STUDY OF PATHOLOGICAL AMYLOID IN SERUM OF PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: To investigate the pathological amyloid in the serum of AD patients and the change of peripheral profile blood cells of AD
Methods: All clinical protocols and experiments were carried out under the guidelines of Tianjin General Hospital. Statistical evaluations were performed using the T-test followed by the calculation of two-tailed p values to determine the significance between groups. Computations were carried out with SPSS Version 20.0.
Results: Determination of the degree of amyloid in the serum of healthy volunteers and pH 7.4 PBS buffer was measured by ThT solution, and the fluorescence intensity in serum was significantly higher than in PBS control ($p<0.05$). Coomassie brilliant blue ThT-stained gels were no different from the healthy volunteers combined with AD patients, multiple protein regions, and several gel zones which indicated the presence of amyloid aggregates in the serum. There were significant differences in levels of RBC, HGB, HCT, LY%, and LYM between AD patients and control groups. Using the RP-HPLC method to analyze the peak spectrum characteristics of amyloid fibrils, and were found the clinical significance of serum pathological amyloid components in AD patients and healthy volunteers. We detected differential peaks of albumin dynamic changes in the blood serum of patients with AD and healthy volunteers, but a direct correlation between serum albumin and AD pathology remains uncharacterized. The characterization of differential Albumin dynamic changes may contribute to the development of blood-based biomarkers for AD.
Conclusions: The pathological amyloid in the serum of AD patients was significantly higher than that of healthy volunteers. This study explored the extraction conditions for the isolation of pathological amyloid by the HPLC method for further study. The application of peak in clinical lays the foundation

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P0687 / #1530

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ALZHEIMER'S DISEASE BLOOD BIOMARKERS IN OUT-OF-HOSPITAL CARDIAC ARREST

Nicholas Ashton[1], Andrea L. Benedet[2], Marion Moseby-Knappe[3], Lana Grötschel[1], Juan Lantero-Rodriguez[1], Thomas Karikari[1], Niklas Nielsen[3], Tobias Cronberg[3], Henrik Zetterberg[1], Kaj Blennow[4]
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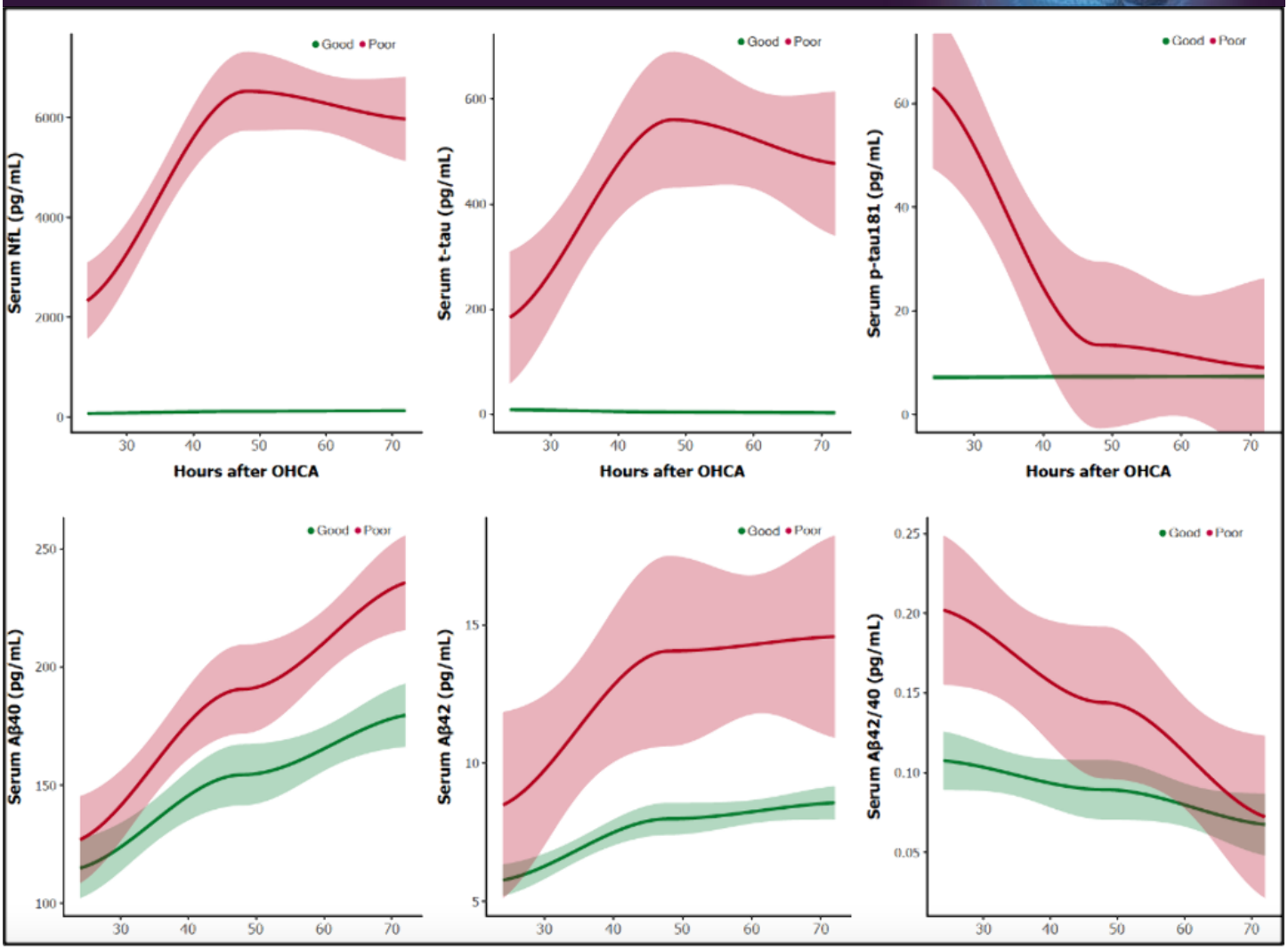
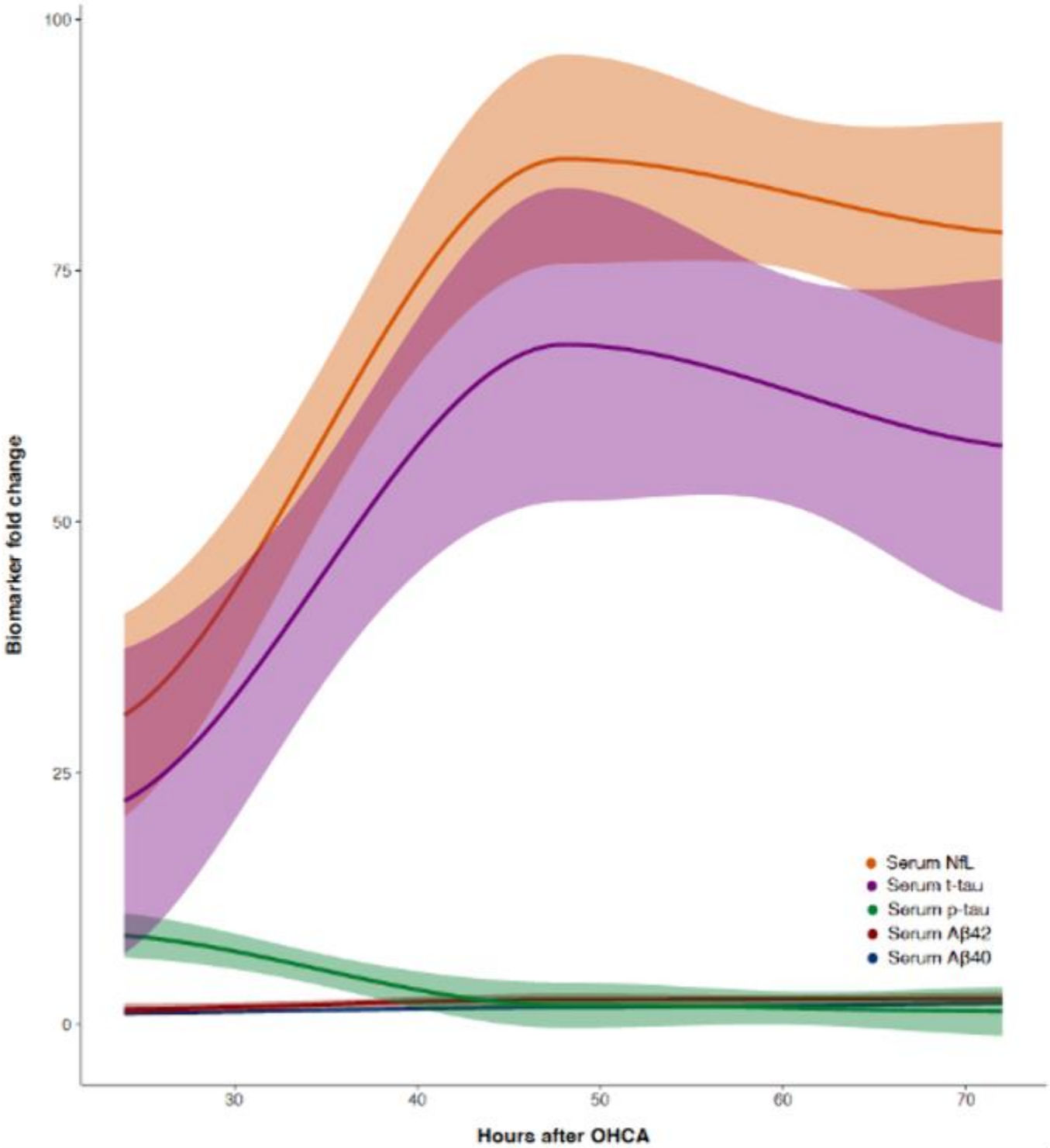
Aims: Blood levels of phosphorylated tau (p-tau) and amyloid-β peptides (Aβ) are promising peripheral biomarkers of Alzheimer's disease (AD) pathology. However, their possible alteration after acute neurological conditions is not known. We measured AD blood biomarkers following acute ischemia and compared their performance and trajectories with neural injury markers.
Methods: In 757 participants from the randomized Target Temperature Management (TTM) After Out-of-hospital Cardiac Arrest trial, evenly distributed between good neurological outcome (≤CPC2) and poor outcome (≥CPC3) at 6-month follow-up, we measured serum p-tau, Aβ42, Aβ40, NfL and t-tau 24 hours (h), 48h, and 72h after cardiac arrest using Single molecule array technology.
Results: Serum p-tau levels were significantly elevated 24h after cardiac arrest, relating to poor neurological outcome. However, the increases of p-tau (fold-change=8.8) in poor neurological outcome at 24h were not of the same magnitude as neural injury markers NfL (fold-change=30.8) and total tau (fold-change=22.2) compared with good neurological outcome. At later timepoints (48–72h), the levels and prognostic value of p-tau deteriorated and normalised to the good neurological outcome group. In contrast, NfL and t-tau remained high and had good diagnostic performance (AUC>0.9). Serum Aβ concentrations increased in most patients, with Aβ42 relating more to clinical outcome.


Good Poor
Serum NfL (pg/mL)
Hours after OHCA
Serum t-tau (pg/mL)
Hours after OHCA
Serum p-tau181 (pg/mL)
Hours after OHCA
Serum Aβ40 (pg/mL)
Serum Aβ42 (pg/mL)
Serum Aβ42/40 (pg/mL)



Conclusions: AD blood biomarkers have different dynamics after cardiac arrest. The rapid increase and decrease of p-tau may relate to an opening of the blood brain barrier with the release of the interstitial fluid to the blood, following hypoxic-ischemic brain injury. However, NfL and t-tau reflect neural injury and have larger changes and prolonged changes in poor outcome patients. Slower but continual increases of Aβ peptides after cardiac arrest indicate activation of amyloidogenic processing in response to ischemia, with Aβ42 relating more to neurological outcome.

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P0688 / #555

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

SINGLE-MOLECULE METHODS FOR THE DETECTION AND CHARACTERISATION OF TAU AGGREGATES IN BIOLOGICAL SAMPLES

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University of Cambridge, Department Of Chemistry, Cambridge, United Kingdom

Aims: Hyper-phosphorylation and aggregation of tau is a common pathological hallmark of neurological disorders such as Alzheimer's disease and Pick's disease. However, the role of tau aggregates in the pathogenesis and pathophysiology of these disorders remains a topical area of research. Their low abundance and high heterogeneity make tau aggregates challenging to study, a challenge that can be met using single-molecule techniques. We therefore aimed to develop biophysical tools to address this.
Methods: We have developed two complementary antibody-based techniques: a single-molecule pull-down (SiMPull) and a single-molecule array (SIMOA) assay. SiMPull uses TIRF microscopy to quantify specifically captured single particles and allows morphological characterisation at super-resolution. SIMOA is an ultra-sensitive immunoassay that uses bead-based technology to achieve a digital readout of molecules of interest.
Results: Here, we report the adaptation of SiMPull to the analysis of tau aggregates using homogenised brain tissue from Alzheimer's disease patients alongside age-matched controls. Using this assay, we found a two-fold difference in the aggregate number and detected long aggregates (>300 nm) only in disease samples. We also adapted the SIMOA assay for the quantification of tau aggregates. We show the compatibility of both assays with various biological samples, including human serum, and a variety of conformation- and phosphorylation-specific antibodies associated with AD pathology.
Conclusions: Our results provide a proof-of-concept for two reliable, sensitive, specific, and efficient methods for the detection and characterisation of tau aggregates in biological samples. The high specificity, sensitivity and suitability for high-throughput application make these assays a promising tool for the early detection of disease-associated aggregate pathology. Together, they enable the quantitative characterisation of tau aggregate particles in unprecedented detail.

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P0689 / #936

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

BIOMARKER-RELATED PHOSPHO-TAU 181 SIGNALS LOCALIZE TO AXONS OF MYELINATED NEURONS BUT NOT UNMYELINATED NEURONS IN APP KNOCK-IN MOUSE

Yu Hirota[1,2], Yasufumi Sakakibara[1], Kyoko Ibaraki[1], Kimi Takei[1], Risa Nishijima[1], Michiko Sekiya[1,3], Koichi Iijima[1,3]
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Aims: Tau phosphorylated at Thr181 (p-tau 181) in cerebrospinal fluid and blood is a sensitive biomarker for preclinical and early stage of Alzheimer's disease (AD). An increase in p-tau 181 level well predicts Aβ pathology before neurofibrillary tangle formation, though the relationship between p-tau 181 and Aβ-mediated brain pathology is less well understood. We have recently reported that p-tau 181 signals are detected in the axonal structures and represent axonal abnormality around Aβ plaques in the cortex of *App* knock-in mouse model of Aβ amyloidosis (*App*^{NLGF} mice). However, a neuronal subtype(s) responsible for these p-tau 181-positive axons remain elusive. In this study, we aimed to determine which neuronal subtype expresses p-tau 181 in the axons.
Methods: To investigate the localization of p-tau signals in the brains of aged (24-month-old) *App*^{NLGF} and wild-type mice, we prepared frozen brain sections and co-immunostained with antibodies against p-tau 181 and myeline basic protein (MBP), the glutamatergic neuronal vesicle marker vesicular glutamate transporter 1 (VGLUT1), the GABAergic neuronal vesicle marker vesicular GABA transporter (VGAT), the cholinergic neuronal vesicle marker vesicular acetylcholine transporter (VAChT), or the noradrenergic neuronal vesicle marker norepinephrine transporter (NET).
Results: Histochemical analyses revealed that p-tau 181 signals were not overlapped with axons of unmyelinated cholinergic nor noradrenergic neurons, but well co-localized with those of myelinated GABAergic neurons.
Conclusions: This study suggests that p-tau 181 signals may represent axonal abnormality of myelinated GABAergic neurons induced by Aβ plaques.

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POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

COMPARISON OF DIAGNOSTIC PERFORMANCE OF CSF BIOMARKERS WITH PLASMA P-TAU181 CONCENTRATIONS IN PREDICTING ALZHEIMER'S DISEASE IN PATHOLOGICALLY CONFIRMED CASES

Pankaj Kumar[1], Mary Encarnacion[2], Ali Mousavi[2], Ian Mackenzie[3], Veronica Hirsch-Reinshagen[3], Ging-Yuek R Hsiung[4], Hans Frykman[5]
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Aims: The CSF detection of amyloid-beta (Aβ), Ttau, and tau phosphorylated at threonine-181(p-tau181) make them a valuable biomarker for diagnosis of Alzheimer's Disease (AD). The novel technologies accurately measuring biomarkers in blood offer a unique advantage for use in clinical testing and trials. This study compares the performance of plasma p-tau181 with CSF biomarkers in predicting AD in pathologically confirmed cases.
Methods: Among samples of EDTA plasma of patients who had been referred to the UBC Hospital Clinic for dementia assessment between 2008 – 2018, we examined 22 cases who had pathological confirmed diagnosis. The concentrations of plasma ptau-181 levels were measured on the SIMOA platform, and the CSF biomarkers were assayed by INNOTEST FUJIREBIO immunoassay.
Results: The concentrations of plasma p-tau181 in AD patients were about 7-fold than in non-AD cases. Similarly, CSF p-tau181 levels, in AD cases were more than twice of cases without AD. Moreover, CSF Ttau was more than twice as higher in cases with AD compared to non-AD cases. In addition, the average of CSF Aβ1-42 in non- AD cases was about twice more than the average of Aβ1-42 in AD cases. The receiver operating characteristic (ROC) analysis demonstrated an area under the curve (AUC) of 0.96, 0.86, and 0.63 for plasma p-tau181, CSF p-tau181, and CSF Ttau respectively.
Conclusions: The plasma p-tau181 concentrations in AD cases were significantly higher than non – AD cases. The plasma p-tau181 showed higher performance compared to CSF p-tau 181 and Ttau and Aβ1-42. These findings should be further verified by prospective longitudinal collected samples with more heterogeneous participants.

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POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

NEUROPATHOLOGICAL CHANGES ACROSS THE ALZHEIMER'S DISEASE CONTINUUM: THE MAVERICK ROLE OF AMYLOID-BETA 40

Caterina Motta[1], Martina Gaia Di Donna[1], Chiara Giuseppina Bonomi[1], Agostino Chiaravalloti[2], Alessandro Martorana[1]
[1]University of Rome Tor Vergata, Memory Clinic, Rome, Italy, [2]University of Rome Tor Vergata, Department Of Biomedicine And Prevention, Rome, Italy

Aims: Objectives: To explore Alzheimer's disease (AD) neuronal damage in patients with pathological cerebrospinal fluid (CSF) Aβ42 value (A+) with negative CSF tau biomarkers (T- N-). We stratified patients according to CSF Aβ42/Aβ40 in those with normal (R-) and pathological ratio (R+) and we evaluated the burden of AD pathology (p-tau/Aβ42) and the glucose brain metabolic pattern, highlighting differences and overlaps with healthy control subjects (HC) and full-blown AD patients (A+T+).
Methods: Methods: 163 patients evaluated with neurological/neuropsychological examination and CSF analysis. Patients were stratified in 98 A+T- (52 A+T-/R-, 46 A+T-/R+)and 65 A+T+. CSF samples of 40 HC (A-T-) were analyzed. A subgroup of 26 patients A+T-, 20 A+T+ and 14 HC underwent FDG-PET scan.
Results: Results: CSF levels of Aβ42 were significantly lower in A+T-/R-, A+T-/R+ and A+T+ patients with respect to A-T- ($F=560.9;p<0.001$). CSF levels of Aβ40 were lower in A-T- and A+T-/R-, higher in A+T-/R+ and even higher in A+T+ patients($F=50.75;p<0.001$). The levels of p-tau and p-tau/Aβ42 resembled those of Aβ40 with lower values in A-T- and A+T-/R-, higher in A+T-/R+ and highest in A+T+ (p-tau:$F=192;p<0.001$ - p-tau/Aβ42:$F=131.9;p<0.001$). A positive correlation between p-tau and Aβ40 was found in A-T- and A+T- groups ($p<0.01$), but not in A+T+. A+T-/R- patients showed significant hypometabolism in bilateral temporo-parietal lobes ($p<0.01$) with respect to controls. A+T-/R+ showed significant hypometabolism in left frontal areas ($p<0.01$) as compared to A+T-/R-, but no differences were found with A+T+ patients.
Conclusions: Conclusions: Among A+T- patients those with pathologic Aβ42/40 showed higher levels of p-tau and p-tau/Aβ42, suggesting more pronounced neuronal damage in the presence of higher Aβ40 levels. The different patterns of brain hypometabolism related to Aβ42/40 status confirm the subtle progression of amyloid related damage even before the detectability of tau pathology.

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P0692 / #1472

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

A NOVEL INDIRECT LC-MS/MS METHOD TO QUANTIFY PS396 TAU LEVELS IN CSF

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Aims: To quantitively measure the levels of tau phosphorylated at serine-396 (pS396-tau) in CSF from humans and mouse models expressing human tau, using a novel mass spectrometry approach. Furthermore, to demonstrate treatment response from our pS396 specific antibody, hC10.2, on this biomarker in the preclinical setting.
Methods: Due to multiple post translational modifications in the tau protein a conventional bottom-up mass spectrometry analysis would require quantification of many different signature peptides. Here, we instead used an indirect LC-MS/MS method to specifically measure two peptides, one situated in the microtubule binding domain (MTBD) and the other covering the S396 epitope. By this indirect method we can determine the fraction carrying a phosphorylation at S396. The method was used to quantify the two tau peptides in human CSF and in rTg4510 CSF at different stages of pathology progression and after treatment with Lundbeck's pS396 specific antibody, hC10.2.
Results: The method was validated for analysis of total tau and pS396-tau in human CSF from healthy controls, MCI and Alzheimer's Disease patients. In rTg4510 mice, we demonstrate that pS396-tau in CSF increase with age and pathology progression, while the MTBD peptide concentration on the other hand decreases with age. In addition, treatment with our hC10.2 antibody, result in a lowering of the pS396-tau peptide concentration in CSF from rTg4510 mice.
Conclusions: The method was demonstrated to quantitively measure two different peptides of human tau in CSF in clinical and preclinical samples. By the indirect method we could also readily measure the concentration of pS396-tau and a treatment response using our hC10.2 antibody in preclinical studies. The method will be of great value to prof central target engagement in the clinical setting.

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P0693 / #1827

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

TRAUMATIC AXONAL INJURY UNDERLIES THE PROGRESSION OF BRAIN ATROPHY

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Aims: Traumatic axonal injury (TAI) and brain atrophy are observed after traumatic brain injury (TBI). Using diffusion tensor imaging (DTI), T_1-weighted structural volumetry, and advanced proteomic techniques, we examined (*1*) whether TAI was progressive; (*2*) whether TAI accelerates the progression of age-related brain atrophy; and (*3*) tested whether neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), total-tau (T-tau), and ubiquitin c-terminal hydrolase-L1 (UCH-L1) measured in serum predict progression of TAI or brain atrophy.
Methods: Patients with TBI were prospectively assessed at 30, 90, and 180 days, and 1, 2, 3, 4, and 5 years after TBI. Diffusion weighted images and structural MR were acquired on a 3T Siemens Biograph MR scanner.
Results: In patients with TBI, TAI was progressive, and accelerated brain atrophy was observed in grey matter, subcortical grey matter, and white matter, and was independent of age, sex, and education. Increased DTI measures of TAI at baseline were independently associated with accelerated brain atrophy. Lastly, increased serum NfL and GFAP at baseline were independently associated with accelerated rates of progression of TAI and brain atrophy over five years. Longitudinal changes in serum NfL followed closely the changes in DTI estimates of TAI and MRI-measured brain atrophy. The relationship between baseline levels of T-tau and UCH-L1 and changes in brain atrophy or TAI over time was variable and weak.
Conclusions: A single TBI results in white matter disruption, which progresses for many years. TAI may accelerate age-related brain atrophy. Furthermore, these findings suggest that serum NfL or GFAP can be used as non-invasive biomarkers to assess progression of TAI or neurodegeneration following TBI.

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POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

ACUTE TRAUMATIC ENCEPHALOPATHY (ATE) - NOVEL BLOOD BIOMARKER COMBINATIONS AND THE ORIGINS OF TBI-RELATED CHRONIC NEURODEGENERATION.

Timothy Van Meter[1], Nazanin Mirshahi[1], Sally Boyd[1], Johanna Leinmueller[1], Maggie Barton[1], Gerry Shaw[2], Ina Wanner[3], Ramon Diaz-Arrastia[4], Damon Kuehl[5]
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Aims: Clinical grade antibodies were produced and tested in combinations to identify biomarker signatures that provide discrimination of neural injury stages, and the transition from ATE to neurodegeneration.
Methods: Custom antibodies were identified though robust immunization and screening processes which characterize candidates for target specificity and clinical discrimination. Custom MT3, GFAP, ALDOC, vWF, NF-L, BDNF, Tau, NRGN, SNCA, and FABP7 assays were studied. Longitudinal cohorts of brain injured patients from acute TBI and sports related concussion were collected with neurocognitive testing and outcomes and/or vascular or white matter MRI studies. Biofluids were studied by immunoassays, compared with controls. Results were analyzed in R-Studio with custom algorithms and descriptive statistics.
Results: Subjects 65 and older with TBI were found to have altered profiles of vascular and white matter astrocyte biomarkers that have not been previously described, compared with younger subjects. Several of these were shown to have signal profiles dependent on proteolytic cleavage states, which may be age and injury dependent. Furthermore, Alzheimer's related modifications were identified (e.g., cleavage of ALDOC, NRGN) that may provide distinct signatures between acute brain trauma changes and chronic neurodegeneration in geriatric patients.
Conclusions: Commonly studied biomarkers such as NF-L and Tau, and more novel biomarkers, continue to evolve and the reported data are highly dependent on the epitopes targeted. Therefore, the tools for clinical discrimination rely on improved binding agents. Chronic neurodegeneration as a consequence of TBI, may be indicated by a transitional biomarker profile in some subjects with ATE, and can potentially be monitored by identifying the appropriate follow up time points after injury. Identifying the transition from post-injury repair to neurodegenerative process initiation months after injury may provide optimal windows for therapeutic interventions.

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P0695 / #745

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

SECERNIN-1 IS A CANDIDATE CEREBROSPINAL FLUID BIOMARKER OF ALZHEIMER'S DISEASE CORRELATING WITH TAU PATHOLOGY

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Aims: Secernin-1 (SCRN1) is present in plaque-associated dystrophic neurites and has been shown to co-localize with neurofibrillary tangles in patients with Alzheimer's disease (AD), but not corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) or Pick's disease (PiD), suggesting that it may be useful as a biomarker to distinguish AD from other tauopathies. The aim of this study was to develop a mass spectrometric method to measure SCRN1 in CSF and evaluate its potential as a biomarker of AD.
Methods: Based on a previous proteomic study, the tryptic peptide SCRN1 (EPAAEIEAALGMDLVR) was selected as target for a method based on parallel reaction monitoring. CSF samples were spiked with the stable isotope labelled peptide standard followed by trypsin digestion. Samples were analysed by nano-LC-MS using high-resolution orbitrap mass spectrometry. We analyzed three cohorts; a discovery cohort comprised of biochemically characterized AD (n=25) and control (n=28) samples; one clinical cohort from Gothenburg, consisting of patients with Parkinson's disease (PD) (n=38), multiple system atrophy (MSA) (n=31), PSP (n=20), CBD (n=8) as well as healthy controls (n=37), and one from the US comprising patients with pathology-confirmed AD (n=17) and pathology-confirmed AD plus comorbidities (n=37).
Results: CSF SCRN1 was significantly increased in AD compared with controls in both the discovery cohort as well as the Gothenburg and US cohorts (p<0.01, fold change = 1.4) but not in CBD, PSP, PD or MSA. SCRN1 distinguished AD patients from controls with ROC-AUC=78%. It strongly correlated with CSF total-tau (R=0.78, p=1.1*10^{-13}) and phospho-tau (R=0.64, p= 3.2*10^{-8}). In addition, CSF SCRN1 levels gradually increased across Braak stages and negatively correlated with MMSE score (R=-0.27, p=0.04).
Conclusions: CSF SCRN1 is a candidate biomarker of AD strongly correlating with tau pathology.

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P0696 / #267

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

UTILIZING RABMAB® TAU ANTIBODIES FOR TARGETING DIFFERENT PTM SITES AIDING THE IDENTIFICATION OF AD SUBJECTS

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Aims: Characterization and comparison of multiple pTau biomarker assays for use in CSF and plasma matrices with the potential to identify AD patients.
Methods: Novel assays were developed using commercially available rabbit monoclonal capture antibodies with high binding affinities. Assay performances were conducted in a discovery cohort incorporating soluble brain extracts, CSF and plasma and a Phase 0 AD cohort with matching CSF and Plasma samples was used to compare the performance of antibodies binding to pTau181, pTau217 and pTau231.
Results: In CSF, Tau proteins phosphorylated at different PTM-sites show a very strong positive correlation (Spearman R's of >0.90) with each other. Interestingly, also the very C-terminal pTau396 correlated well with the other analyzed pTau assays. However, strong correlations were observed only for some distinct pTau assays in plasma. Notably, the more C-terminal modifications of pTau262/263 and pTau396 showed a reduced correlation with other PTM sites. In CSF, all assays discriminated AD from Control subjects, while in Plasma only 5 assays did so. In a larger Phase 0 cohort with matching CSF/Plasma, the group discrimination of amyloid positivity within the MCI population (AUC of 0.88 and 0.95 for pTau231 and pTau217, respectively) and correlation performance were confirmed.
Conclusions: Blood-based phospho-Tau biomarkers have great potential to aid the diagnosis of patients with underlying AD pathology, to simplify both clinical and pre-clinical study designs, reduce patient burden and animal use, as well as enabling the continuous monitoring of the effect of potential therapeutic drug candidates.

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P0697 / #517

POSTERS: B04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

EXECUTIVE FUNCTION AND VISUOSPATIAL DEFICITS CHARACTERISE PARKINSON'S DISEASE MILD COGNITIVE IMPAIRMENT – AN ELECTROPHYSIOLOGICAL STUDY

Aoife Sweeney[1], Barry Devereux[2], Charlie Ong[3], John Mckinley[4], Seamus Kearney[4], Karen Doherty[4], Julia Foy[3], David Craig[5], Bernadette Mcguinness[6], Anthony Passmore[1]
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Aims: Cognitive impairment is prevalent in Parkinson's disease (PD), with up to half of patients developing dementia within 10 years. The presence of mild cognitive impairment in PD (PD-MCI) is associated with increased risk of developing dementia. Electroencephalography (EEG) is an inexpensive and non-invasive tool which can be used to assess cognition. In this study, the feasibility of using a dry-EEG headset to assess cognitive impairment in PD was investigated.
Methods: 47 PD patients and 37 age and sex-matched controls were recruited to complete a comprehensive battery of neuropsychological and EEG tasks. EEG tasks measured executive function, language, memory and visuospatial domains. Resting state EEG was also recorded. Differences between groups were assessed using randomisation tests with false discovery rate corrections. Random forest, support-vector machine and logistic regression machine learning models were also employed.
Results: Half of PD participants were classified as having PD-MCI according to the Movement Disorders Society criteria. Participants with PD-MCI had were significantly more likely to be male, had a longer disease duration and had higher levels of apathy. Two-thirds of PD-MCI patients were impaired in at least three cognitive domains. Machine learning models selected neuropsychological and EEG measures of visuospatial and executive function domains as being the most sensitive for participant discrimination.
Conclusions: The findings of this study show that cognitive impairment is prevalent in PD. The addition of EEG recordings enhanced discrimination between cognitively normal and PD-MCI participants at an early stage. The most discriminative features selected by the support vector machines model are in agreement with the dual syndrome hypothesis of cognition (Kehagia et al., 2013) and those identified in a ten year follow-up study (Williams-Grey et al., 2013).

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P0698 / #858

POSTERS: B04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

SPECTRAL GRAPH MODELING OF ALZHEIMER'S DISEASE NEUROPHYSIOLOGY

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Aims: Alzheimer's disease (AD) is the most common form of dementia, progressively impairing memory, cognition, as well as behavior. While various neuroimaging studies of the human brain have revealed functional abnormalities in patients with AD, how neuronal functions are impaired remain unclear. We employed a spectral graph-theory based model (SGM) to identify abnormal biophysical markers of neuronal activity in AD.
Methods: SGM is an analytic model that describes the coupled excitatory and inhibitory activity of local neuronal subpopulations, and the long-range excitatory macroscopic activity, for every brain region. It is parameterized by a small set of global parameters which we inferred for a well characterized clinical population of AD patients and a cohort of age-matched controls.
Results: We estimated model parameters that best captured the regional MEG frequency spectra of AD patients and controls (Fig 1A). Patients with AD have significantly elevated long-range excitatory neuronal time constant (τ_G) compared to controls ($p < 0.0001$; Fig 1B). τ_G is also the most important feature for accurate classification of AD from controls (AUC = 0.88; Fig 1C, D). Lastly, higher τ_G is positively correlated with Clinical Dementia Rating – Sum of Boxes ($p = 0.0007$; Fig 1E) and is negatively correlated with Mini Mental State Exam score ($p = 0.0001$; Fig 1F).
Conclusions: These results indicate that abnormal spectral signatures in combination with SGM can reliably depict altered excitatory neuronal activity in AD patients, which are significantly associated with cognitive deficits. This is intriguing given that tau pathology that is allied to cognitive deficits in AD preferentially affects excitatory neurons in neuropathological studies. Our findings provide critical insights about potential mechanistic links between abnormal neural

oscillations and their cellular correlates in

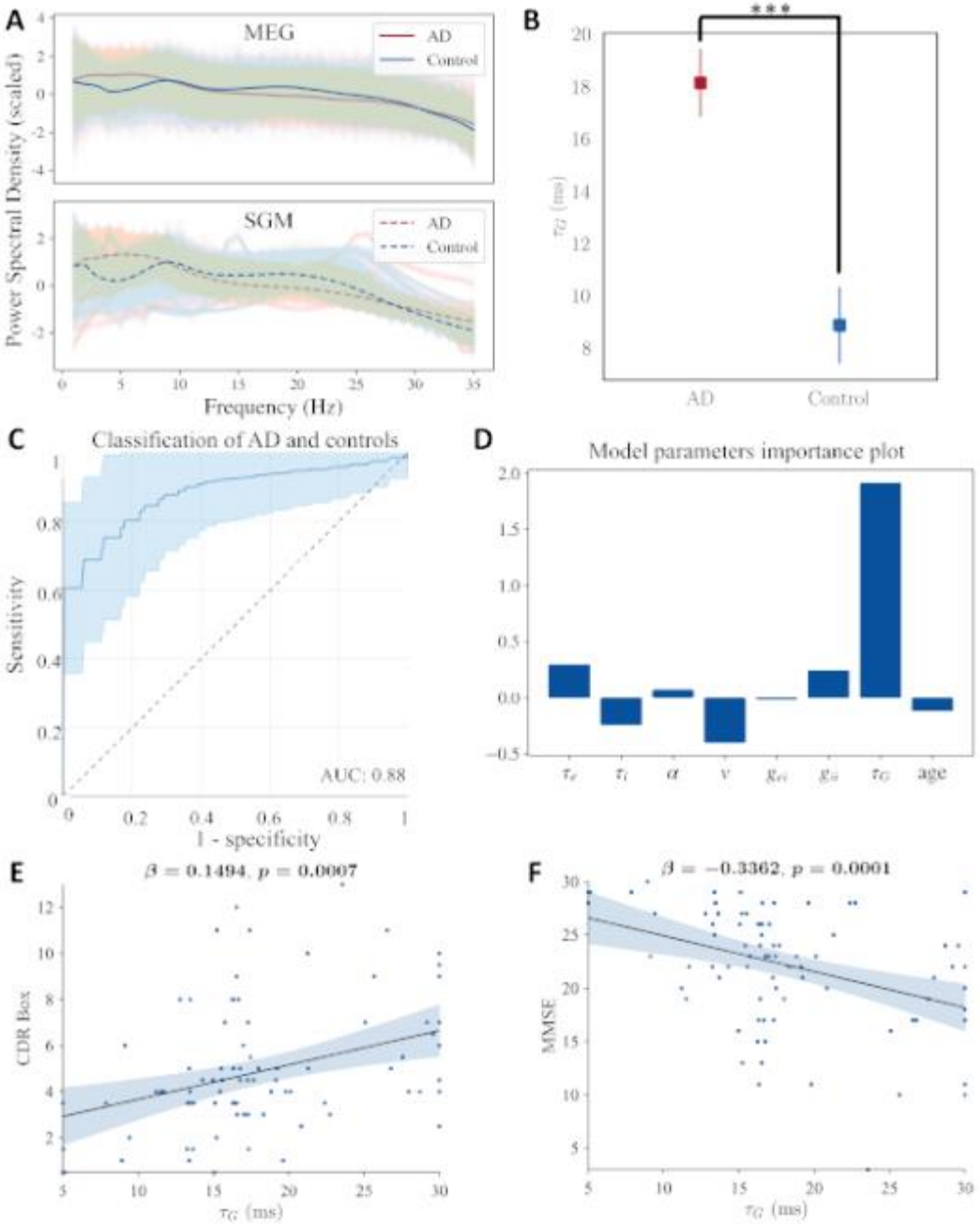

Fig. 1: A: Plot of scaled power spectral density versus frequency for empirical MEG recordings of AD and control (top) and for the modeled spectra after inferring the model parameters (bottom). **B:** Box plot comparing the excitatory time constant (τ_G) in AD and controls. **D:** ROC curve from held out test data for classifying AD versus controls. **E:** Importance plot of model parameters as features of the classifier from the **D**. **E:** Scatter plot showing the trend of association of τ_G with Clinical Dementia Rating – Sum of Boxes (CDR Box) and **F:** Mean Mental State Exam (MMSE).

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P0699 / #1410

POSTERS: B04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

NOVEL COGNITIVE BIOMARKERS FOR EARLY DIAGNOSIS AND MONITORING OF PROGRESSIVE SUPRANUCLEAR PALSY

Maksymilian Brzezicki[1], Günter Höglinger[2], George Tofaris[1], Nagaraja Sarangmat[1], Marko Bogdanovic[1], Simon Simon Prangnell[1], Tim Buchanan[3], James Fitzgerald[4], Chrystalina Antoniades[1]
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Aims: Objectives: To develop a new objective cognitive tests measuring executive function deficits and their progression in Progressive Supranuclear Palsy (PSP)
Methods: Methods: In this longitudinal study, 27 PSP, 51 idiopathic Parkinson's Disease (PD), and 21 Healthy Control (HC) participants were each assessed at five visits at three monthly intervals. Verbal fluencies were assessed with a novel cognitive measure, "strategy adherence", derived from an algorithmic analysis of the method used by a subject completing a computerised version of the well-known cancellation task.
Results: Results: Strategy adherence dropped from 52% to 11% in 12 months, whilst the HC and PD stayed at 100% and 94% respectively. Conventional cognitive measures (MMSE, MoCA) were insensitive to PSP progression in this short timeframe. The PSP rating scale showed significant change from baseline only at visit 5. For diagnosis of PSP, the semantic and phonemic fluency score achieved a ROC area under the curve of 0.91. After addition of the cancellation score, a resultant "combined cognitive score" increased this to 0.93.
Conclusions: Conclusions : The decline in group level performance in PSP strategy adherence was both large and rapid, constituting a strong signal of progression. A potential disease modifying drug could be shown to successfully retard the progression of the cognitive effects of PSP in a short period of time. Verbal fluency and cancellation are simple and inexpensive tasks that discriminate PSP from PD as well as any more expensive test. The real value of the cancellation task however lies in its ability to demonstrate whether patients can devise and follow a problem-solving strategy. This ability is irreversibly lost during PSP progression and at the group level this is a promising potential progression marker.

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P0700 / #2544

POSTERS: B04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

RELATIONSHIP BETWEEN TAU DEPOSITION AND NEURO-INFLAMMATION IN THE POSTMORTEM PARIETAL CORTEX AND ANTEMORTEM COGNITIVE PERFORMANCE

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Aims: 1. Characterize the distribution and density of neuroinflammation and tau in parietal cortex of subjects who died with Alzheimer's disease dementia (AD), mild cognitive impairment (MCI), and controls. 2. Determine the relationship between marker density and antemortem cognitive performance.
Methods: Freshly frozen samples of postmortem parietal cortex (N=36, 18 men, 18 women; 6 controls, 6 MCI, and 6 AD per sex) were obtained from the Washington University brain repository. Less than 18 month prior to death, all subjects were administered the Mini Mental State Exam (MMSE), and twenty-five subjects were also administered a more comprehensive cognitive screen, the Cognitive Abilities Screening Instrument (CASI).Consecutive cryostat sections were incubated with [3H]PK11195 or [18F]T807 to assess neuroinflammation (TSPO) and tau deposit density, respectively, using published methods.
Results: Diagnosis of AD was associated with a significant increase in grey matter of tau and TSPO relative to controls ($p<0.003$ and $p<0.015$). TSPO density, but not tau, was also higher in MCI relative to controls ($p<0.03$). There was a moderate and statistically significant positive correlation between tau and TSPO ($R=0.42$; $p<0.0005$). MMSE scores were negatively correlated with tau density ($R=0.79$, $p<0.0001$), with a weaker, though statistically significant, correlation for TSPO ($R=0.37$, $p<0.025$). Similarly, high tau density was negatively correlated with CASI scores ($N=25$, $R=0.6$, $p<0.0015$) which also displayed a weaker but statistically significant correlation with TSPO ($R=0.44$, $p<0.03$).
Conclusions: Tau density in parietal cortex is a sensitive and specific marker of AD diagnosis and cognitive performance measured with both MMSE and CASI. TSPO is increased in MCI as well as AD and shows moderate and statistically significant correlation with antemortem cognitive performance. This is the first study to demonstrate relationships between the CASI and post-mortem tau and inflammatory burden.

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P0701 / #2455

POSTERS: B04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

DIAGNOSTIC VALUE OF PLASMA BIOMARKERS IN CONTROLS, SCD AND MCI SUBJECTS

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Aims: Alzheimer's disease (AD) is the most common cause of dementia, and a challenging disease for the development of plasma biomarkers. Blood samples are the most common biofluids collected for the classical medical diagnosis. We assessed the diagnostic potential of a number of plasma biomarkers for the detection of early stages of AD.
Methods: 110 participants were recruited at the NYU Alzheimer Disease Research Center. This cohort includes n=32 with normal cognition (NL), n=60 with subject cognitive decline (SCD), n=18 with mild cognitive impairment (MCI). Comprehensive neuropsychological and magnetic resonance imaging evaluations were conducted for all patients. Plasma biomarkers assays (total tau [t-tau], neurofilament light [NfL], glial fibrillary acid protein [GFAP], ubiquitin carboxyl-terminal hydrolase L1 [UCH-L1], and pTau181 were measured using the SIMOA SR-X a novel technology that employs highly sensitive immunoassays with a limit of detection (LOD) under 100 fg/ml
Results: The levels of NfL, t-Tau, GFAP and UCH-L1 were measured using the Neurology 4-plex A. NfL levels showed a significant difference between NL and MCI (p=0.0265 Mann whitney test). The level of NfL was also significantly different between SCD and MCI (p=0.0421 Mann Whitney test). GFAP showed statistically significant differences between NL and SCD, and NL and MCI (p=0.0409 and p=0.0259, respectively). In addition, ptau181 levels showed a significant difference between SCD and MCI (p=0.0238). Correlation of these biomarkers with brain imaging and cognitive measures is underway.
Conclusions: Biomarker levels of NfL, GFAP and pTau 181 in plasma samples showed some significant differences between the three groups of subjects. Plasma biomarkers can be useful for the diagnosis of diagnosis of AD related pathology at early stages.

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P0702 / #1176

POSTERS: B04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

DEVELOPMENT OF A HIGH-THROUGHPUT DRUG SCREENING ASSAY FOR ALZHEIMER'S DISEASE AND TAUOPATHIES

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Aims: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder affecting over 44 million adults worldwide and represents an estimated economic burden of over $605 billion dollars. Presently, there is no cure and current therapies have largely focused on amyloid -beta despite evidence that tau pathology better correlates with cognitive impairment. AD and other tauopathies are characterized by the misfolding and aggregation of the tau protein as intracellular aggregates. Compelling evidence suggests that this pathological protein spreads throughout anatomically connected regions of the brain via a prion-like mechanism in which pathological forms of the protein trigger the corruption of natively folded protein, incorporating them into growing amyloid fibrils in what is often described as a seeding-nucleation mechanism. Preventing the aggregation of tau represents a promising therapeutic target. Here, we present a novel high-throughput assay for the screening of small molecules with potential to inhibit pathological tau protein misfolding and aggregation.
Methods: We first developed and optimized a Tau seed amplification assay (SAA) for the sensitive and specific detection of pathological tau species in postmortem human AD brains relative to control brains. Currently, we are screening known anti-prion and anti-amyloid molecules. Hits will be validated utilizing cellular and animal models of tau spreading.
Results: Our results indicate that the Tau SAA can serve as a robust, high-throughput screening assay to identify compounds that inhibit and/or prevent the pathological aggregation of Tau protein. Furthermore, through the screening of FDA approved compounds, we can potentially identify promising small molecules for further assessment.
Conclusions: Through modification of the Tau SAA technology, we have created an in vitro drug screening method that can be used to identify compounds that inhibit the prion-like misfolding, aggregation, and spreading of Tau.

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P0703 / #1291

POSTERS: B04.K. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

USING THIOPHENE-BASED LIGANDS TO DISTINGUISH DISTINCT TAU FILAMENT STRUCTURES

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Aims: The structures of tau filaments in different tauopathies have been reported, and a structure-based classification of these diseases has been suggested. Our research group develops thiophene-based fluorescent ligands that bind to protein aggregates. In this study, we have investigated if we can use our ligands to distinguish different tau filament structures associated with distinct tauopathies.
Methods: Cases of Alzheimer's disease (AD), chronic traumatic encephalopathy, primary age-related tauopathy, progressive supranuclear palsy (PSP), corticobasal degeneration, MAPT +3 and Pick's disease (PiD) were included in the analysis. The cases were the same that were used previously for the structural studies of tau filaments. Brain sections were prepared and stained with a variety of thiophene-based ligands known to have different binding properties. The specificity of the ligands was confirmed by performing co-staining with antibody against phosphorylated tau, three repeat tau (3R) or four repeat tau (4R).
Results: Ligand HS-84 was binding to tau pathology in all included tauopathies and showed co-localisation with the antibodies. B-TVBT4 demonstrated labelling of tau aggregates in AD, but in non-AD tauopathies, the number of b-TVBT4 positive tau inclusions was low, in particular in the 3R tauopathy PiD. HS-276 and HS-334 showed no staining of tau pathology in AD. However, in the 4R tauopathy PSP, both ligands were labelling tau inclusions, for which HS-334 seemed to be selective.
Conclusions: We have identified ligands that bind to distinct tau filament structures. When applied on tauopathy brain sections, a variation in staining patterns could be seen, indicating that the combination of ligands can be used to distinguish different tau filament structures.

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P0704 / #274

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

A 3D HUMAN CO-CULTURE TO MODEL NEURON-ASTROCYTE INTERACTIONS IN TAUOPATHIES

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Aims: The aim of this study is to establish a physiologically relevant and robust model representing 3D neuron-astrocyte interactions and tau aggregation.
Methods: Human neurons were obtained from a doxycyclin-inducible hiPSC line stably expressing rtTA/Ngn2 (Frega et al. 2017) and co-cultured in 96-well plates with primary human astrocytes (ScienCell #1800) for 4 weeks. Neurons and astrocytes were suspended in a GelTrex extracellular matrix. Overexpression of tau containing one or two frontotemporal dementia (FTD)-associated mutations (P301L: FTDtau[1] and P301L+S320F: FTDtau[1+2]) fused to EGFP was performed by lentiviral transduction of neural progenitors.
Results: We established a novel 100-200 µm thick 3D human neuron/astrocyte co-culture model of tau pathology, comprising homogenous populations of hiPSC-derived neurons and primary human astrocytes in microwell format. Using confocal, electron and live microscopy, we validate the procedures by showing that neurons in the 3D co-culture form pre- and postsynapses and display spontaneous calcium transients within 4 weeks. Astrocytes in the 3D co-culture display bipolar and stellate morphologies with extensive processes that ensheath neuronal somas, spatially align with axons and dendrites and can be found perisynaptically. The complex morphology of astrocytes and the interaction with neurons in the 3D co-culture mirrors that in the human brain, indicating the model's potential to study physiological and pathological neuron-astrocyte interaction *in vitro.* Finally, we successfully implemented a methodology to introduce seed-independent intraneuronal tau aggregation in the 3D co-culture, enabling study of neuron-astrocyte interaction in early tau pathogenesis.
Conclusions: These data provide proof-of-concept for the utility of this rapid, miniaturized, and standardized 3D model for cell type-specific manipulations, such as the intraneuronal pathology that is associated with neurodegenerative disorders.

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P0705 / #1478

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

INVESTIGATING TAU ISOFORM- AND SORTING-SPECIFIC INTERACTORS BY USING VIRUS-BASED TURBOID PROXIMITY LABELLING

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Aims: Aggregation of aberrantly localized Tau in the somatodendritic compartment of brain neurons is the pathological hallmark of Alzheimer's disease (AD) and other tauopathies. Several mechanisms are proposed to mediate the axonal Tau enrichment under healthy conditions but their contributions are still elusive. Further, regulatory motifs and domains of Tau as well as interacting factors of Tau that govern the sorting process, e.g. within the axon initial segment (AIS), are understudied. We aim to identify changes in the Tau interactome and Tau-intrinsic factors that control or influence the sorting success.
Methods: We combine the state-of-the-art proximity labelling technique TurboID, a BioID-derivative that was not yet used in neuronal context, and inducible lentiviral expression vectors for the use in hiPSC-derived glutamatergic neurons. Utilizing fusion constructs of sorting-deficient Tau versions and the biotin ligase BirA, this approach may unravel sorting-dependent binding partners involved in anterograde and retrograde regulation of Tau transit
Results: Preliminary data showed that we were not only successful in applying TurboID to the hiPSC-derived neurons but we also could show efficient axonal targeting of the BirA-Tau fusion constructs, a critical prerequisite for further investigations. In the next step, we successfully obtained profound interactome data for BirA fused to 0N3R-Tau, 0N4R-Tau and the non-sorting Nterm-Tau construct.
Conclusions: The ongoing analyses may provide valuable insight into the isoform- and sorting-specific interactors of the Tau protein, and thereby point at promising targets for further studies to counteract sorting deficits as seen in disease conditions. The TurboID method also enables various advanced assays. Combined with laser microdissection microscopy, it may even allow to obtain compartmentalized, i.e. AIS-specific interactome data. By coupling Tau isoforms to BirA, the technique is also useful for studying isoform-specific differences in the interactome.

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P0706 / #1429

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

THIOPHENE LIGAND BTVBT2 AS A TOOL FOR CAPTURING TAU ACCUMULATION IN THE RETINA OF AD PATIENTS AND MOUSE MODELS

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Aims: Amyloid deposits and hyperphosphorylated tau accumulation have been identified in the retina of Alzheimer's disease (AD) patients and transgenic AD mice. Our main objective is to evaluate the use of the thiophene-based optical ligand bTVBT2 to capture tau accumulation in the retina of AD patients and AD mouse models.
Methods: To evaluate the affinity of bTVBT2 for different phospho-tau conformations, hippocampi samples from AD patients were stained with bTVBT2 combined with antibodies against p-tau Ser202/Thr205 (AT8), p-tau Ser202 (CP13), p-tau 312-322 (MC1), p-tau Thr217 (p217), p-tau Ser396/Ser404 (PHF1), p-tau Thr231 (T231), p-tau Thr181 (T181), and total tau. The colocalization of bTVBT2 signal with different tau markers was measured with ImageJ. Thereafter, cellular localization of bTVBT2 in the retina of AD patients, as well as of Tm2 (APP NL-F) and dKI (APP NL-G-F / MAPT) mice was analyzed by immunostaining against cell-specific markers, such as Iba1 and GFAP, in combination with bTVBT2. Confocal z-stacks were acquired to analyze the localization of bTVBT2 inside cells.
Results: In the human brain, bTVBT2 was mainly restricted to dystrophic neurites associated to amyloid plaques. The bTVBT2 signal colocalized partially with all investigated tau antibodies, with a higher proportion of overlapping with total tau, PHF1 and MC1. In the retina, bTVBT2-positive signal was detected inside microglia of AD, Tm2 and dKI retinas.
Conclusions: Our study suggests that bTVBT2 binds to tau structures engulfed microglia in retina, and it may thus be a potential future tool to monitor AD pathology in the retina.

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P0707 / #524

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

THE AXON INITIAL SEGMENT IS ALTERED IN A TAU DEPENDENT MANNER IN THE HIPPOCAMPUS, CORTEX AND AMYGDALA IN MICE

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Aims: The axon initial segment (AIS) which is located at the proximal part of the axon, generates action potentials. It contributes to the molecular identity of the axon also enabling enrichment of tau within the process. Tau plays a major role in neurodegenerative diseases, like Alzheimer's disease. Therefore, our objective was to investigate potential influence of tau on the structure and position of AIS.
Methods: AnkyrinG was used as a marker of the AIS, and laser scanning micrographs were analyzed for the length of the AIS and the distance from the cell body. AIS structure and position was analyzed during process formation in primary hippocampal cultures and in young (3M old) and aged (1Y old) TauKO mice, compared to the control strain. In adult mice AIS was also analyzed in the cortex and amygdala.
Results: AIS was longer in the neurons of the hippocampal primary culture from TauKO mice compared to controls. After introducing full length tau or tau lacking the N-terminal domain to the primary neuronal cells, we found that the AIS length in TauKO mice was restored to the level of the controls. However, tau was not affecting the position of AIS. Interestingly, we observed a shorter AIS in the adult TauKO mice compared to control, which reached significance in all of the four brain regions at 3M of age.
Conclusions: Our data shows that AIS is altered in TauKO mice and exogenously introduced tau restores the AIS structure, suggesting a critical role of tau in the organization of AIS.

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P0708 / #1810

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

DYSREGULATION OF MAPT EXPRESSION IN PROGRESSIVE SUPRANUCLEAR PALSY HUMAN BRAIN AND IPSC-DERIVED MIDBRAIN ORGANOIDS

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Aims: Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by pathological accumulation of tau protein. While rare kindreds harbor autosomal dominant mutations in the *MAPT* gene, the majority of cases are sporadic. *MAPT* mutations that increase alternative pre-mRNA splicing of exon 10 cause familial PSP through accumulation of tau with four microtubule-binding domain repeats (4R). Here, we explore if this mechanism plays a role in sporadic PSP.
Methods: Publicly available RNA-seq data were analyzed alongside a novel replication cohort. Differential gene expression was performed using RSEM, and splicing analysis was conducted using LeafCutter. Gene levels were normalized to cell population estimates derived from deconvolution analysis. Findings were validated on a single-cell level using immunohistochemistry and novel tau isoform-specific mRNA *in situ* hybridization probes. HiPSC-derived midbrain organoids grown from sporadic PSP patient skin cells were generated in suspension spinner flasks through pharmacological directed differentiation, and maintained for 4 months.
Results: RNA sequencing data revealed total levels of *MAPT* and 4R tau were increased in cases compared to controls. Whole transcriptome regressions identified gene candidates that may influence tau splicing. PSP and control organoids displayed a cytoarchitectural pattern consistent with the developing midbrain. PSP organoids recapitulated disease-relevant features including increased high molecular weight p-tau, a higher ratio of p-tau:total tau, and increased levels of 4R-tau.
Conclusions: These findings indicate that sporadic PSP is associated with increased levels of 4R tau mRNA in key brain regions that may play a role in driving the accumulation of pathological tau protein aggregates in this disorder. PSP patient-derived organoids recapitulate key disease-relevant features, including elevation of toxic tau proteoforms. This sporadic PSP organoid model will provide insight into cell-type specific drivers of neurodegeneration that underlie sporadic tauopathy.

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P0710 / #2486

POSTERS: B06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: POSTTRANSLATIONAL MODIFICATIONS

AUTHENTIC SITE-SPECIFIC PHOSPHORYLATION OF FULL-LENGTH TAU BY GENETIC ENCODING OF PHOSPHOSERINE.

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Aims: Microtubule associated protein tau is abnormally phosphorylated at specific sites in the brain of patients with tauopathies. We aimed to introduce authentic, site-specific phosphorylation on full-length recombinant tau to investigate the role of single phosphorylation sites in tau aggregation.
Methods: We used an engineered bio-orthogonal aminoacyl-tRNA synthetase/$tRNA_{CUA}$ pair (Rogerson et al., 2015) which directs the incorporation of a phosphoserine in place of an amber stop codon (TAG) expressed in *E.coli.* We introduced a TAG stop codon in place of a serine residue at positions S202, S396, S404, or S422, and co-transformed this plasmid with a high-copy number plasmid (PKW2-SepRS-EF-Sep) containing 1) a tRNA molecule (pSer tRNA(B4)CUA) which directs phosphoserine incorporation in place of an amber stop codon, 2) an aminoacyl tRNA synthetase (SepRS(2)), which attaches phosphoserine to the cognate tRNA molecule, as well as 3) an elongation factor (EF-Sep) optimized for directing the aminoacyl tRNA synthetase/tRNA pair to the ribosome for translation. Full-length, recombinant 0N4R tau with a 6xHis tag on the C-terminus was purified with a HisTrap column followed by size exclusion chromatography.
Results: Co-transformation of 0N4R S202TAG, S404TAG, or S422TAG plasmid with PKW2-SepRS-EF-Sep resulted in readthrough of the TAG stop codon to the C-terminal 6xHis tag. Phosphorylation state was validated by western blotting with phospho-specific tau antibodies, mass spectrometry, and/or Phos-tag SDS-PAGE.
Conclusions: We demonstrate that tau can be authentically site-specifically phosphorylated at disease relevant sites, using a method which bypasses the limitation of using phosphomimetics such as glutamate or aspartate substitutions. Future experiments will investigate the effects of single-site phosphorylation on tau aggregation.

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P0711 / #825

POSTERS: B06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

USING FLOW CYTOMETRIC PROXIMITY LIGATION ASSAYS TO DETERMINE INTERACTIONS BETWEEN AMYLOID BETA, TAU OLIGOMERS AND LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 1

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Aims: Alzheimer's Disease (AD) is characterized by three neuropathological hallmarks: amyloid plaques, neurofibrillary tangles, and neurodegeneration ($A^+T^+N^+$). Oligomers of the proteinaceous components of the plaques and tangles, amyloid beta (AβO) and tau (tauO), respectively, are recognized as the true toxic species of the disease. Understanding the mechanism by which these oligomers enter the synapse to induce toxicity is imperative and represents a promising therapeutic target. Previous work from our lab has demonstrated that tauO can outcompete AβO from a protein substrate at the synapse. Low-density lipoprotein receptor-related protein 1 (LRP1) is a tau monomer transporter; therefore, it is logical to hypothesize that LRP1 is also acting as a transporter of tauO at the synapse. This work sought to ascertain the interaction of and differences between AβO and tauO at LRP1 in synaptosomes from human control, $A^+T^+N^+$ patients, and $A^+T^+N^-$ individuals.
Methods: We use flow cytometric proximity ligation assays to investigate exogenous AβO and tauO interaction with LRP1 in synaptosomes isolated from human control hippocampal tissues. The interaction of endogenous tau at LRP1 was examined in synaptosomes isolated from human control, $A^+T^+N^+$ patients, and $A^+T^+N^-$ individuals' frontal cortex.
Results: The presence of 0.5 μM exogenous tauO significantly decreases the interaction of 2.5 μM AβO at LRP1. Mean and median fluorescence data from PLA-positive synaptosomes is highest for $A^+T^+N^-$ individuals, followed by $A^+T^+N^+$ patients, and lowest in control subjects.
Conclusions: The above data suggests that tauO and AβO compete for the binding site of LRP1 and that generally, $A^+T^+N^-$ individuals' LRP1 engages endogenous tau more efficiently than both control and $A^+T^+N^+$ patients, possibly leading to differences in uptake of endogenous tau and confirming distinct molecular characteristics between $A^+T^+N^+$ patients and $A^+T^+N^-$ individuals. **Funding:** NIA 1R01 AG073133

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P0712 / #1428

POSTERS: B06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

PROTEIN SYNTHESIS IN PROTEINOPATHIES

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Aims: Alzheimer's disease (AD) and Frontotemporal lobar degeneration (FTLD) are characterised at the cellular level by aggregates composed of hyperphosphorylated microtubule-associated Tau protein. In AD, we have shown that the *de novo* protein synthesis of microtubule-associated protein Tau is induced by amyloid-beta via a Tau-dependent mechanism (Li & Götz, EMBO J 2017).
Methods: To investigate if and how Tau itself could alter protein synthesis, we have used bio-orthogonal labelling combined with proteomic analysis to tag and identify newly synthesised proteins in mouse models of FTLD (Evans et al., EMBO J 2019).
Results: Our results revealed a marked decrease in the synthesis of proteins associated with microtubule physiology, endocytosis, mitochondria and ribosomal functions. Validation of these results in human FTLD samples confirmed a significant inverted correlation between the decrease in ribosomal protein synthesis and an increase in pathological accumulation of Tau. More recently, we have identified the projection domain of Tau to be involved in alterations of ribosomal biogenesis and thus, protein translation and synthesis (Evans et al., Acta Neuropathol Commun 2021).
Conclusions: Taken together, we have revealed novel aspects of neuronal physiology in relation to pathological Tau accumulation. Currently, we apply bio-orthogonal labelling to investigate the protein synthesis changes induced by the presence of amyloid-beta in microglia, the immune cells of the brain parenchyma.

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P0713 / #1703

POSTERS: B06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

TRANSCRIPTOMIC CHANGES IN C. ELEGANS AND HUMAN ALZHEIMER'S DISEASE WITH MIXED TAU AND TDP-43 PATHOLOGY

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Aims: Alzheimer's disease (AD), the most common aging-associated neurodegenerative dementia disorder, is defined by the presence of amyloid beta (Aβ) and tau aggregates in the brain. However, more than half of patients also exhibit aggregates of the protein TDP-43 as a secondary pathology. Clinically, AD patients with secondary TDP-43 pathology have more severe cognitive impairment, more rapid cognitive decline, worse brain atrophy, and a shorter disease course. TDP-43 is already implicated in neurodegenerative disease as the major pathological protein aggregate in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP), two other devastating neurodegenerative diseases. In patients with mixed Aβ, tau and TDP-43 pathology, TDP-43 dysfunction may synergize with neurodegenerative processes in AD, worsening disease.
Methods: Using *C. elegans* models of mixed pathology in AD, we have shown that TDP-43 specifically synergizes with tau but not Aβ, resulting in enhanced neuronal dysfunction, selective neurodegeneration, and increased accumulation of pathological tau. To identify cellular responses to mixed tau and TDP-43, we are evaluating transcriptomic changes at multiple time-points preceding frank neuronal loss in *C. elegans*, and assessing similarities and differences in gene expression from human AD brain with co-pathological TDP-43.
Results: We find significant expression and splicing changes in genes including those implicated in immune function, RNA metabolism, synaptic integrity, and lipid catabolism.
Conclusions: Characterizing transcriptomic changes resulting from mixed tau and TDP-43 pathology and determining their underlying contributions to disease processes is critical for understanding mixed pathology AD.

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P0713a / #2818

POSTERS: B06.I. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

IDENTIFICATION AND CHARACTERISATION OF SPLICE VARIANTS OF THE TAUOPATHY-INDUCED GENE GROWTH ARREST DNA DAMAGE INDUCIBLE 45 ALPHA (GADD45A)

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Aims: Previous work in the lab showed that the DNA damage response protein Growth Arrest DNA Damage induced 45a (Gadd45a) is selectively induced in *in vivo* murine models of tauopathy. The gene promotes DNA repair, cell death and modulates cell signalling and has 4 alternatively spliced transcripts generated by exon skipping. This post-transcriptional control gives rise to 4 protein isoforms, the presence and function of which have yet to be investigated in neuronal systems in the context of health or tau pathology.
Methods: PCR-amplification of Gadd45a cDNA was performed from HeLa cells, human brain samples (incl. progressive supranuclear palsy patients) and human neuronal-like cells. Myc-tagged constructs of the transcripts were then generated to allow investigation of isoform localization and function, using apoptotic cell death as a read-out.
Results: We have identified a 5th Gadd45a splice variant which generates a novel protein isoform with a distinct C-terminus. We then show that this, and 3 other Gadd45a splice variants, are present in human brain samples and neuronal-like cells. These isoforms show distinct sub-cellular localization, including varying nuclear localization and the generation of punctate cytosolic staining. To begin to investigate function, we assessed apoptotic cell death which is differentially affect by these isoforms.
Conclusions: A novel transcript of the tauopathy-induced gene Gadd45a has been identified, which is present in the adult human brain and neuronal-like human cells. This, and 3 previously reported Gadd45a transcripts, show distinct cellular localization and differentially affect cell death, highlighting the potential significance of the induction and splicing of the variants in the context of neurodegeneration. We next aim to investigate whether these interact with pathological tau and the functional consequences of this. We thank the Alzheimer's Society for funding this work.

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P0714 / #2015

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

CHARACTERIZATION OF A NOVEL TRANSGENIC MOUSE MODEL EXPRESSING 4 REPEAT (4 R) TRUNCATED TAU.

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Aims: A wide range of preclinical models of Alzheimer's disease (AD) have thus far been developed and employed to study underlying disease mechanisms. Majority of these transgenic models express mutated form of tau which do not reflect the epidemiologically prevalent sporadic form of AD tau pathology. Rendering the present models inefficient to recapitulate human AD tau pathology. To this end, we illustrate the molecular and behavioral characteristics of a novel R4m/7 transgenic mice line expressing human truncated 4R tau, encompassing residue 151–391, that develops genuine tangle-like pathology similar to that of AD tau pathology.
Methods: We characterized R4/m7 transgenic mice by standard immunohistochemistry procedures using anti-phospho tau dependent antibodies. For proteomic analysis we extracted sarkosyl soluble and insoluble tau fractions from the brainstem of 6, 12 and 15 month old animal. The extracts were analyzed by standard Western blot using pan- and phospho-tau antibodies. Behavioral studies were performed using sensorimotor impairment assessment tools.
Results: This model reliably recapitulated histopathological features of human AD tau patholgy, such as presence of neurofibrillary tangles, pre-tangles and neuropril threads. The pathology was predominantly located in the brain stem. The life span of the transgenic mice is approximately 15.5 months while sufficient pre-tangles formation was observed at the age of 10-12 months. The sarkosyl insoluble fraction comprised of endogenous and truncated tau protein, where behavioral changes were seen at the age of 10 months.
Conclusions: We suggest that this novel transgenic mouse model may prove itself useful to study tauopathies. Furthermore, this model can be utilized in the preclinical studies to test various therapeutic modalities of AD and other related tauopathies. **This work is supported by APVV-20-0331, APVV-19-0585, APVV-20-0585, and VEGA 2/0127/22grant.**

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P0715 / #822

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

CHARACTERIZATION OF A NOVEL FKBP51-HSP90 INTERACTION DEFICIENT MOUSE MODEL.

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Aims: 1. Assessment of stress resilience in *FKBP5^{mut}* mice and wild type littermates. 2. Assessment of glucocorticoid signaling pathway in neurons, microglia and MEF isolated from wild type and *FKBP5 ^{mut}* mice. 3. Assessment of effect of FKBP51-Hsp90 interaction inhibition on tau pathology.
Methods: Comparison of blood HPA axis biomarkers of different genotypes under basal conditions and acute stress. Comparison of different genotypes in behavioral tests under basal conditions and acute stress. Dexamethasone treatment of cells. qPCR and Western blot assessment of glucocorticoid-induced genes. Crossbreeding of *FKBP5^{mut}* and tau Tg4510 mice. Immunohistochemical investigation of FKBP51 mutation effects on brain tau pathology. Behavioral tests to investigate the effects of FKBP51 mutation on cognitive impairment of Tg4510 mice.
Results: Using proximity ligation assay, we have proved lack of FKBP51-Hsp90 interactions in *FKBP5^{mut}* mice. Behavioral assessment of *FKBP5^{mut}* mice at 2-3 months of age indicated lack of behavioral abnormalities at basal conditions. After acute stress *FKBP5^{mut}* mice exhibited significantly lower levels of corticosterone compared to wild type indicating stress resilience. Upon dexamethasone treatment of cells isolated from wild type and *FKBP5^{mut}* homozygous mice we have observed previously unknown post-translational modification of FKBP51 in wild type but not in mutant cells. Identification of the modification type and site will shed a light on the molecular details of FKBP51-regulated glucocorticoid signaling. We have set-up crossbreedings between *FKBP5^{mut}* and Tg4510 mice. At the age of 4-5 months, we will perform behavioral tests to investigate the effects of FKBP51 mutation on cognitive impairment of Tg4510 mice. After that, we will perform immunohistochemical investigation of brain tau pathology. Total tau and hyperphosphorylated tau will be assessed with respective antibodies.
Conclusions: *FKBP5^{mut}* mice is a useful model in stress and AD-related biology studies.

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P0716 / #1324

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

BEHAVIORAL CHARACTERIZATION OF THE PS19 MOUSE MODEL OF ALZHEIMER´S DISEASE

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Aims: Tau is a microtubule-associated protein and a primary component of neurofibrillary tangles – one of the major pathological hallmarks of Alzheimer´s disease. PS19 transgenic mice overexpressing the disease-associated P301S tau mutation, are shown to present strong tauopathy-related brain pathologies. Here, we characterize the PS19 mice behaviorally and electromyographically for their cognitive and motor deficits, activity, and compound muscle action potential (CMAP).
Methods: PS19 mice at an age of 2 to 6 months are tested for cognitive deficits using the Y-maze, Morris water maze, novel object recognition and fear conditioning test. Activity and motor deficits are evaluated in the open field, wire hanging, and clasping test. Additionally, electromyography (EMG) is performed to measure CMAP.
Results: Our results will provide an extensive characterization of PS19 animals across different ages that will not only focus on cognitive deficits but also on motor disturbances. Up to our knowledge, this will be the first evaluation of myopathy in this mouse model using EMG.
Conclusions: Together with already published data, our results will further support the value of the PS19 mouse as a valid animal model to investigate the deleterious effects of increased mutant tau and to test novel drug agents.

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P0717 / #1307

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

A MULTI-OMICS ANALYSIS OF THE THY1-HTAU.P301S TAUOPATHY MODEL DURING DISEASE PROGRESSION

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Aims: The key neuropathological hallmarks of Alzheimer's disease (AD) is the deposition of Aβ peptides forming amyloid plaques and aggregation of Tau protein causing neurofibrillary tangles. Transgenic Thy1-hTau.P301S (tgP301S) mice express one human Tau isoform (383 aa, 0N/4R) containing a single P301S point mutation and recapitulate various molecular and cellular deficits associated with AD (Allen et al., 2002, J Neurosci, 22(21): 9340-51).
Methods: Multiple complementing OMICS data sets (transcriptomics, proteomics and lipidomics) were generated from the cortex of tgP301S mice collected at different disease stages: (a) 2-months (pre-disease onset), (b) 3.5-months (onset) and (c) 5-months (severe Tau aggregation).
Results: Increases in Tau aggregation in the cortex start around 3.5 months. Hierarchical clustering of significantly changed proteins (adjusted $p<0.05$, fold-change >1.2) led to identification of five clusters with 26 to 378 proteins that share a pattern of expression changes over time. Pathway enrichment indicated an upregulation of lysosomal clearance, detoxification, and metabolic pathways as well as cell lineage differentiation (glia / oligodendrocytes). Analysis of bulk RNAseq led to identification of six collectively changing clusters consisting of 61 to 407 significantly altered transcripts. To date, a limited overlap has been observed between the proteome and transcriptome enriched pathways, and comparing data with changes observed on lipidome level is challenging. Absolute quantification of 294 lipids indicated a general decrease in most lipid classes during disease progression.
Conclusions: In summary, these data provide valuable insights in the molecular mechanisms in this frequently used mouse model for AD and serve as a useful resource of baseline OMICS expression for future therapeutic studies.

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P0718 / #1431

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

HOME-CAGE BEHAVIOR DISCRIMINATES NEURODEGENERATION MODELS FROM HEALTHY AGING MICE

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Aims: Ageing is a common most important risk factor for these diseases. Longitudinal home-cage observations enable monitoring of undisturbed behavior and may be used for early detection of behavioral phenotypes in neurodegeneration models that are different from changes purely related to ageing.
Methods: To identify these early changes and compare this with healthy ageing we used an online publically available resource AHCODA-DB to analyze mouse models with pure motor function deficits and/or cognitive deficits, and compared their behavioral profiles with ageing C57BL/6J mice.
Results: Ageing C57BL/6J mice showed a profound decrease in general activity deterioration of their circadian pattern with increased age, whereas mouse models of neurodegeneration did not. Specifically, mouse models with cognitive function impairments in the Water Maze, including models of Aβ pathology (APP/PS1, ARTE10 and 5xFAD) showed hyperactivity at all ages tested. These Aβ pathology models showed specific changes in home cage behavior at ages when no pathology was present yet. Furthermore, mouse models that developed strong motor function deficits by 20 weeks, including the SOD1*G93A mouse model of amyotrophic lateral sclerosis (ALS) and models of Tau pathology, showed rather specific changes in home cage behavior when compared to age-matched wild-type controls. Similar to the Aβ pathology models, SOD1*G93A mutant mice displayed alterations in home-cage behavior at ages preceding pathology.
Conclusions: Different aspects of home-cage behavior are sensitive to different neurological conditions before emergence of classical pathology, and are clearly distinguishable from normal ageing.

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P0719 / #2077

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

INHIBITION OF ALPHA-4 BETA-2 NICOTINIC ACETYLCHOLINE RECEPTOR ATTENUATES SYSTEMIC INFLAMMATION AND NEUROINFLAMMATION TRIGGERED BY LAPAROTOMY

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Aims: Systemic inflammation in the body stimulates neuroinflammation is a risk factor leading to cognitive dysfunctions and may accelerate neurodegeneration. We have demonstrated sterile inflammation induced laparotomy, in which monocytes/macrophages play significant roles in transmitting systemic immune responses into neuroimmune responses. It has been shown that neurotransmitter receptor α4β2 nicotinic acetylcholine receptor (α4β2-nAChR) expresses on macrophages. The study aims to investigate if the roles of this receptor in systemic inflammation and neuroinflammation.
Methods: C57BL/6J mice were employed with the administration of α4β2-nAChR partial agonists for three days, and they were subjected to laparotomy or anesthesia group (2.5 % sevoflurane, 800 ml/min oxygen). Levels of cytokine in liver and hippocampus were examined 4 hours after surgery/anesthesia. In addition, LysMCre-$^{f/α4nAChR}$ mice were made by crossing our LysMCre mice with the α4-loxP mice to delete α4 subunit of nicotinic receptor on macrophages and microglia. They were subjected to laparotomy or anesthesia group, while C57BL/6J mice were used as background control. Levels of systemic and hippocampal cytokines were examined by real-time PCR 4 hours after surgery/anesthesia.
Results: Pro-inflammatory cytokines increased significantly in liver and hippocampus 4 hours after laparotomy, while the administration of agonist of α4β2nAChR, ABT594 reduced the levels of some pro-inflammatory cytokines. In addition, LysMCre-$^{f/α4nAChR}$ mice reversed the increase of some pro-inflammatory cytokines in liver and hippocampus 4 hours after laparotomy.
Conclusions: Taken together, specific knock-out of α4-nAChR in mice can attenuate the surgery induced systemic inflammation and neuroinflammation. These data suggest that cholinergic anti-inflammatory pathway have an anti-inflammatory effect in laparotomy model. The study is supported by General Research Fund from Research Grant Council GRF17120119.

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P0720 / #2027

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

EXPLORING THE BENEFICIAL EFFECTS OF RESISTANCE EXERCISE IN EXPERIMENTAL MODELS OF ALZHEIMER'S DISEASE

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Aims: Increased physical exercise improves cognition in human and animal studies associated with Alzheimer's Disease (AD). However, resistance-type regimes remain poorly investigated. The present study explored the effects of resistance exercise (RE) on the modulation of neuroinflammation, neuropathologies, and cognitive dysfunction.
Methods: To evaluate the role of RE in modulating pre-existing cognitive impairment, female 3xTg and 5xFAD mice underwent a five-week RE training protocol by climbing a 1-m ladder at an 85-degree incline with progressively heavier weights. A battery of behavior tests was used to probe for cognition and learning. The hippocampus, frontal cortex, and hindlimb muscles were harvested for western blot analysis, qPCR, or post-fixed in neutral-buffered formalin solution for immuno-histochemical exploration.
Results: Compared with sedentary counterparts, RE-trained mice showed improved cognitive function, reduced tau pathology in the hippocampus, and decreased ionized calcium-binding adapter molecule 1 (Iba-1) immunoreactivity. In addition, there was a decrease in interleukin-1β and phosphorylated JNK (Thr183/Tyr185) observed in both 3xTg and 5xFAD models.
Conclusions: RE may confer its neuroprotective effects via the inhibition of a shared inflammatory and signaling pathways and represent an alternative exercise strategy for ameliorating disease progression in AD.

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P0722 / #879

POSTERS: B07.C. ANIMAL MODELS: NON-MAMALIAN MODELS

LINKING MOLECULAR ABNORMALITIES TO BALANCE DEFICITS USING A ZEBRAFISH MODEL FOR TAUOPATHIES

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Aims: The ability to maintain balance is an evolutionarily-conserved behavior that is frequently disrupted in patients with neurodegenerative diseases. It remains unclear how molecular and cellular dysfunctions lead to behavioral deficits, especially during the early stages of pathogenesis. Here, we aim to develop a new zebrafish model for tauopathies that overcomes limitations of current models and allows us to link tau pathology to balance deficits.
Methods: We modeled progressive supranuclear palsy (PSP), a tauopathy where patients suffer frequent falls starting from the early stages. We generated tau fish by expressing human 0N/4R-tau in zebrafish balance neurons, which models early tau-overrepresentation in the brainstem balance neurons in PSP. Tau pathology is validated using immunohistochemistry staining with PHF-1 antibody. A unique apparatus developed in lab is used to examine balance behaivor of zebrafish larvae. To test function of balance neurons, we measured response of balance neurons to posture destabilization using 2-photon calcium imaging. We examined lysosomal dysfunction using Neutral Red dye staining and are currently developing new tools to study cellular mechanisms.
Results: Tau-expressing zebrafish exhibit balance deficits while maintaining normal locomotor ability. Interestingly, although human tau is abnormally phosphorylated in zebrafish balance neurons, we did not observe neuronal death. However, tau-positive balance neurons show impaired response to body tilt, which likely underlies balance deficits. In addition, we found ectopic accumulation of acidic organelles in cell bodies of tau-positive neurons, suggesting abnormal lysosomal function.
Conclusions: By modeling behavioral deficits, we have developed an unprecedented model for tauopathies that allows for dissecting disease mechanisms across molecular, circuit, and bahavioral levels. Importantly, neurons in our model remain functional behaviorally but show impaired activity, which allows investigation of disease mechanisms before cell death occurs and screen for potential drugs.

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P0723 / #504

POSTERS: B07.E. ANIMAL MODELS: OTHER

USING PRE-CLINICAL MODELS OF TRAUMATIC BRAIN INJURY TO INVESTIGATE ALZHEIMER'S DISEASE RELATED PATHOPHYSIOLOGY

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Aims: Traumatic brain injury (TBI) is a modifiable risk factor for Alzheimer's Disease (AD), although the mechanisms is not yet known. TBI may provide an ideal non-transgenic pre-clinical model with a clear instigating insult and long prodromal phase. In AD tau aggregates follow a stereotypical pattern of spread from the brainstem. There may be other early sites of tau accumulation. The olfactory system is known to be an early site of alpha-synculein spread in Parkinson's Disease, with AD similarly associated with early olfactory symptoms. This study aimed to confirm development of delayed cognitive deficits in a mild diffuse model of TBI in non-transgenic mice. Tissue was uniquely preserved so that the olfactory epithelium and its axonal brain connections remained intact for investigation of tau pathology within the brainstem and olfactory system.
Methods: Mice (n=14-16) were injured with a mild diffuse model of injury (CHIMERA) or allocated to sham groups, with separate cohorts undergoing a behavioural battery at one or six months post-injury.
Results: At six ($p<0.05$), but not one month post-injury ($p=0.63$), injured mice were significantly impaired in puzzle-box performance, where they escape through a passage with increasingly difficult obstacles. Similarly decreased recognition of a novel object was seen at 6 ($p<0.05$), but not 1 month ($p=0.55$) post-injury. No olfactory deficits were noted for preference towards a pleasant smelling peanut butter odour, nor to avoidance of the unpleasant 2-Methylbutyric Acid odour.
Conclusions: Surprisingly olfactory deficits did not develop prior to cognitive deficits in pre-clinial mTBI model. Nonetheless the delayed development of impaired cognition indicates ongoing neurodegenerative processes following TBI. Work is ongoing to analyse how TBI may promote accumulation of tau aggregates, their location and whether there is noticeable spread from one to six months post-injury prior to cognitive deficits emerging.

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P0724 / #995

POSTERS: B07.E. ANIMAL MODELS: OTHER

COMPARISON OF TAU PATHOLOGY IN THREE DIFFERENT MOUSE MODELS FOLLOWING INOCULATON WITH TISSUE FROM ALZHEIMER'S DISEASE PATIENTS

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Aims: Amyloid beta and tau are the two key proteins associated with Alzheimer's disease (AD), the leading cause of dementia worldwide, which are both thought to have prion-like properties with seeded propagation and spread of disease-related assemblies. We have investigated knock-in mouse models containing humanised versions of these proteins to further our understanding of how AD progresses, as well as deciphering the prion-like properties of both amyloid beta and tau, after the inoculation of amyloid beta/tau assemblies or seeds. These have included the *APP$^{NL-F/NL-F}$* model, containing both the Swedish and Iberian mutations (NL-F) in the amyloid precursor protein, expressing human amyloid beta 42, and the human (h)Tau$^{KI/KI}$ model, which contains all six human isoforms of human tau. A side-to-side comparison of both these models alongside the *App$^{NL-F/NL-F}$*/hTau$^{KI/KI}$ mouse line will provide an informative insight into the best model to study tau seeding after inoculation with AD cases.
Methods: Using transmission studies, we determined significant differences for tau seeding and aggregation within the *APP$^{NL-F/NL-F}$*, human (h)Tau$^{KI/KI}$ and *App$^{NL-F/NL-F}$*/hTau$^{KI/KI}$ mouse models. This was evident from histology and western blot analysis, alongside the use of Tau Biosensor Reporter Human Embryonic Kidney (HEK) cells to measure *in vitro* tau aggregation.
Results: Here we show that an *App$^{NL-F/NL-F}$*/hTau$^{KI/KI}$ mouse model shows earlier tau seeding of AD cases compared to its retrospective *APP$^{NL-F/NL-F}$* and hTau$^{KI/KI}$ mouse models *in vivo.*
Conclusions: Our results suggest that the *App$^{NL-F/NL-F}$*/hTau$^{KI/KI}$ mouse model may be a superior model for studying the role of prion-like behaviour of amyloid beta and tau assemblies in AD. We anticipate that this model will also prove useful in future characterisation of putative amyloid beta and tau strains which will require *in vivo* serial passages to characterise.

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P0725 / #2612

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

IN SITU STRUCTURAL STUDIES OF ALPHA-SYNUCLEIN FIBRILS

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Aims: Parkinson disease (PD) is the second-most common neurodegenerative disorder that affects 2-3% of the population 65 years of age and older. Neuropathological hallmarks are neuronal loss in the substantia nigra pars compacta and intracellular amyloid inclusions containing aggregated a-synuclein (a-syn), called Lewy bodies. The misfolded a-syn species may be especially harmful because of their suspected ability to spread as small fibrillar fragments – so-called seeds – from cell to cell, inducing the misfolding of the local a-syn population. This seeding process is the focal point of our research project, which we are trying to decipher using cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET).
Methods: In cryo-ET, thin lamellas of cells are produced in a cryogenic focused ion beam microscope (cryo-FIB), which are used in a transmission electron microscope (TEM) to generate tilt series of projection images. From these, the 3D cellular environment can be reconstructed, and the information contained within is used to localize proteins of interest. Multiple projections of a protein can be averaged to obtain a higher resolution protein structure (subtomogram averaging). With such information I hope to understand the seeding process. Does the structure change during incorporation? What does it tell us about the incorporation process? Is there structural variability from cell to cell?
Results: A single particle analysis pipeline was created that includes sample preparation, data collection and initial data processing to obtain and compare 2D class averages of different a-syn species in vitro.
Conclusions: Ultimately, the finished SPA pipeline serves as a stepping stone for the generation of a subtomogram averaging pipeline that allows the analysis of various a-syn species inside suitable cell models such as primary neurons or neurons differentiated from induced pluripotent stem cells.

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P0726 / #2642

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

THE RNA-BINDING PROTEIN TIA1 POTENTIATES SNCA PHOSPHORYLATION, AGGREGATION, AND TOXICITY

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Aims: T-cell intracellular antigen 1 (TIA1) is a broadly expressed DNA/RNA binding protein regulating multiple aspects of RNA metabolism. It is best known for its role in stress granule assembly during the cellular stress response. TIA1 colocalizes with neuropathology in brain tissue of subjects with Alzheimer's disease, frontotemporal dementia with Parkinsonism linked to chromosome 17, amyotrophic lateral sclerosis, and Huntington's disease. Herein, we examined whether TIA1 is implicated in the pathogenesis of Parkinson's disease (PD), characterized by the abnormal accumulation of alpha-synuclein (SNCA) in proteinaceous inclusions.
Methods: Transgenic Caenorhabditis elegans animals expressing human SNCA linked to GFP in either muscle or dopaminergic neurons were crossed with strains that either overexpress or are depleted of TIAR1 (the C. elegans ortholog of TIA1) in the same tissues. Imaging was used to evaluate the aggregation of SNCA-GFP and the survival of dopaminergic neurons. The expression of TIA1 was also assessed in the brains of PD patients. Following TIA1 overexpression, neuroblastoma SK-N-SH and differentiated SHSH-5Y cells were utilized to evaluate translation, mitochondrial, proteasomal, and autophagy functions, as well as differential proteome expression.
Results: We report that TIA1 induces SNCA phosphorylation, aggregation, and degeneration of dopaminergic neurons in vivo, whereas silencing TIA1 has the opposite effect. TIA1 is also weakly colocalized with SNCA pathology in PD patients' Lewy bodies. These effects were mediated by TIA1's interference with proteasomal and autophagy pathways, ATP/ADP ratio reduction, and induction of reactive oxygen species (ROS) production. TIA1 overexpression upregulated proteins involved in transcription, splicing, RNA-binding, actin depolymerization, and autophagy inhibition, whereas downregulated proteins were associated with translation and cell surface localization, as determined by proteomic analysis.
Conclusions: These findings suggest that TIA1 is potentially a crucial component of the pathogenetic mechanisms underlying alpha-synucleinopathies.

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P0727 / #2746

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

COMPARISON OF THE AGGREGATION KINETICS AND STABILITY BETWEEN HOMOLOGOUS AND HETEROLOGOUS AGGREGATED A-SYNUCLEIN FIBRILS

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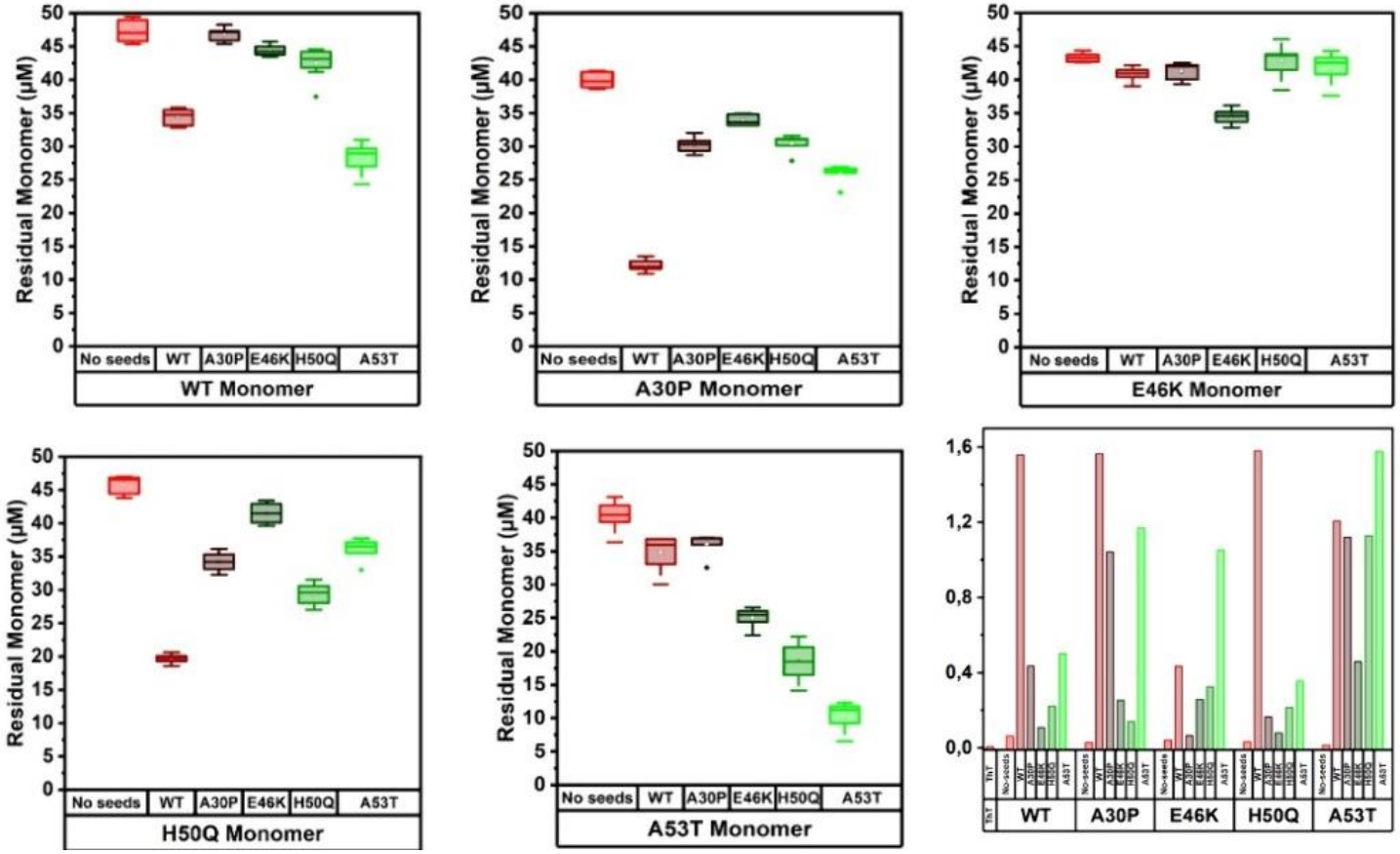
Aims: Significant research has focused on understanding the structure and assembly kinetics of α-synuclein amyloid fibrils, often with the assumption that the fibrils are terminally stable, i.e., that they do not degrade. However, our data suggest that a-synuclein fibrils are in fact rather unstable and prone to disassembly in many cases. Furthermore, previous research in the group has shown that small fibril fragments are more neurotoxic than full length fibrils. We therefore aim to better understand both the aggregation kinetics and stability of homologous as well as heterologous aggregated fibrils which are important for both sporadic and familial PD.
Methods: We set out to study the difference in aggregation kinetics and stability between homologous aggregated fibrils using monomers and seeds of the same type (WT-WT, A30P-A30P, E46K-E46K, H50Q-H50Q, A53T-A53T) and heterologous aggregated fibrils using WT monomers and different mutant seeds (WT-A30P, WT-E46K, WT-H50Q, WT-A53T). The seeds act as a template for new fibrils to form, propagating the morphology of the parent seed. Homologous aggregated fibrils were also subjected to several rounds of fragmentation and reaggregation to see if the equilibrium between monomer and fibril is shifted after fragmentation. A plate reader ThT-assay has been used for monitoring fibril aggregation kinetics and fluorescent decay was measured to compliment ThT-measurements. Secondary structure and morphology of the resulting fibrils was compared using CD and AFM. The residual monomer concentration was determined using UV-Vis Spectroscopy.
Results:



There are significant differences between the different a-syn variants and combinations for the residual monomer

concentration as well as for the fluorescence decay.

Conclusions: Results produced up until now have shown significant differences in aggregation kinetics and stability of the various α-synuclein amyloid fibrils, both for homologous and heterologous aggregated fibrils.

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P0728 / #509

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

A NEW POST-TRANSLATIONAL MODIFICATION OF A–SYNUCLEIN AT Q79 IN SYNUCLEINOPATHIES: JUST ANOTHER ONE?

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Aims: We present a recently discovered pyroglutamate (pGlu) modification at Q79 of α-synuclein (αSyn). The generation of pGlu79-αSyn requires two enzymatic activities: to form a truncated αSyn with Q79 at the N-terminus and to subsequently catalyze glutamine cyclization into pGlu. Candidate enzymes are matrix metalloproteinase-3 (MMP-3) and glutaminyl cyclase (QC), respectively.
Methods: The aggregation characteristics of pGlu79-αSyn compared to full-length αSyn were analyzed via Thioflavin T assay, electron microscopy and size exclusion chromatography. Further, the protein localization in brain tissue was determined by immunohistochemical single/triple stainings and confocal laser scanning microscopy.
Results: A specific antibody against the pGlu79-modified neo-epitope of αSyn was used to detect its colocalization with MMP-3 and QC in brains of two PD-like transgenic mouse models. Additionally, in human brain samples of PD and dementia with Lewy body subjects, pGlu79-αSyn was shown to be present in Substantia nigra neurons, in Lewy bodies and in dystrophic neurites. Importantly, there was a spatial co-occurrence of pGlu79-αSyn with QC in the human SN complex and a defined association of QC with neuropathological structures. Furthermore, an increased oligomerization propensity of pGlu79-αSyn, correlated with increased neurotoxicity, was observed.
Conclusions: Why should this novel post-translational modification of αSyn be so interesting among all those others that have been previously reported? Years ago, a similar pGlu-modification of Abeta was discovered, which is also catalyzed by QC and which plays an important role in the pathogenesis of Alzheimer´s disease (AD). As a result, there is an ongoing phase 2a/b clinical trial targeting QC for AD treatment (Vijverberg et al., 2021). We provide evidence that QC might have a similar pathogenic profile in synucleinopathies and, therefore, should be considered as a drug target for these clinical conditions as well.

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P0729 / #2123

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

INTERACTION OF ALPHA-SYNUCLEIN AGGREGATES AND GLIAL CELLS IN A HUMAN IPSC DERIVED CO-CULTURE MODEL

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Aims: Alpha-syunclein (aS) aggregation is the neuropathological hallmark of Parkinson's disease. In recent years, it has been shown that microglia and astrocytes directly interact with aS aggregates and can influence the pathology and disease progression. Several studies have been performed in rodent systems but since there are differences between human and murine glia, the objective of the present study was to investigate the interaction of aS aggregation and glia in a human 3D cell culture model.
Methods: We used previously published protocols (Yoon et al., 2019; Haenseler et al., 2017) to generate human iPSC derived cortical spheroids (hCS) and microglia and established a co-culture method to add microglia to hCS. Pre-formed fibrils (PFFs) derived from recombinant aS were used to induce seeded aggregation in the cortical spheroids before or after addition of microglia.
Results: Human cortical spheroids contained neurons, oligodendrocytes and astrocytes. Microglia precursor cells were added to the hCS and they readily migrated into the spheroids where they were stable for extended culturing periods. They showed microglial characteristics, including expression of relevant markers and ramified morphology. Seeding with PFFs induced aS-aggregates in hCS with different genetic backgrounds. Long maturation times of the hCS allowed the observation of aS aggregation over multiple months. Microglial as well as astrocytic interaction with aS aggregates as well as monomeric aS was observed.
Conclusions: The co-culture model described here is a powerful tool to investigate the molecular processes underlying the pathology in alpha-synucleinopathies in neuronal and glial cells. Due to its human origin, its 3D structure, and the presence of all relevant cell types, we hope that these co-cultures will allow to make discoveries easily transferrable to therapeutic development.

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P0730 / #2134

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

PREDICTIVE FACTORS OF PAIN IN PARKINSON'S DISEASE

Mariem El Fekih[1], Ines Bedoui[2], Bissene Douma[2], Jamel Zaouali[2], Ridha Mrissa[2]
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Aims: The aim of our study is to determinate predictive factors of pain in Parkinson's disease (PD).
Methods: A retrospective study including 136 patients diagnosed with PD was conducted in the department of neurology of the Military Hospital of Tunis from 2011 to 2022. Interrogation and examination of the patient made it possible to determine pain and their predictive factors in PD.
Results: Fifty-eight patients had a pain related to PD, including 24 women and 34 men. The mean age was 63 years old.Age less than 60 years old (p = 0.016), the absence of a personalmedical history (p= 0.014), a duration of disease progression more than 5 years (p= 0.0001), the age of onset of the disease less than 50 years (p = 0.024), a stage of Hoehen and Yahr more than 3 (p = 0.012), a UPDRS score more than 50 (p = 0.035), the presence of vegetative disorders (p = 0.0001), sebaceous sweating (p = 0.00001), hypersweating (p = 0.00001), the presence of cardio-vascular disorders (p = 0.021) and the presence of vesico-sphincteric disorders (p = 0.03) were statistically associated with the presence of pain during PD.
Conclusions: A good knowledge of the predictive factors of pain in PD makes it possible to reduce the handicap.

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P0731 / #2137

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

NEUROPATHIC PAIN IN PARKINSON'S DISEASE

Mariem El Fekih, Ines Bedoui, Bissene Douma, Jamel Zaouali, Ridha Mrissa
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Aims: The aim of our study is to is to assess the prevalence of neuropathic pain in patients with Parkinson's disease (PD).
Methods: A retrospective study including 136 patients diagnosed with PD was conducted in the department of neurology of the Military Hospital of Tunis from 2011 to 2022. Neuropathic Pain Scale 4 (DN4) was used to estimate the presence and severity of neuropathic pain.
Results: Fifty eight patients reported painful symptoms. Of these, 50 had neuropathic pain, which was central in 40 patients and peripheral in 45 patients. These were electric shocks (n=40), burns (n=35) and painful cold sensation (n=29). Central involvement differed in topography from peripheral involvement in the presence of comparable clinical semiology. Peripheral pain was radicular (n=35), trunk (n=14) and distal (n=10) damage. Central pain was axial (n=32), medullary (n=27), visceral (n=15), facial (n=5), anogenital (n=3). The course was paroxysmal in 41 cases and continued in 4 cases. The mean DN4 score was 4.7. The usual analgesics used by 15 patients did not improve. Adjustment of antiparkinsonian therapy was associated with a mean gain in DN4 score of 2 points (n=30).
Conclusions: Neuropathic pain is common in patients with PD and it cause disability and poor quality of life. More particular attention should be paid to reduce the functional handicap in such patients.

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P0732 / #1778

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

CHARACTERISING ALPHA SYNUCLEIN AGGREGATES FROM THE LINE 61 MOUSE MODEL OF PARKINSON'S DISEASE USING STORM

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Aims: The involvement of the loss of function and pathological aggregation of alpha synuclein (aSyn) protein has been long studied for Parkinson's disease (PD) and believed to underlie the cerebral atrophy. However, the toxicity mechanisms of aSyn and the relationship between the morphological and geometric structure of the aggregates and the damage they cause has not been understood. Here we studied how the methods used to harvest these aSyn aggregates from brain samples can yield different types of aggregates.
Methods: We first soaked and homogenised the brains of Line 61 and wild type control mice. Then the homogenised samples were further extracted with sarkosyl and triton-x. We characterised the aSyn aggregates in these samples using single-molecule pulldown (SiMPull) and stochastic optical reconstruction microscopy (STORM) with two commonly used antibodies, namely SC211, which is a sequence specific antibody and MJFR, which is a structure specific antibody.
Results: Our results show clear size and shape differences, as well as their numbers, between the wild type and Line 61 mice, at different ages. Moreover, the antibody used to study the aggregates, as well as the method of extraction also provides aggregates with statistically different sizes and shapes.
Conclusions: Since the geometric and structural characteristics of aggregates correlate witht heir toxicity and involement in different disease mechanisms, understanding how the method used to harvest these aggregates effects these properties is crucial. Here for the first time, we provide a super-resolution characterisation of aSyn aggreagtes from a well validated mouse model and show how using different methods of harvesting and imaging these aggregates can provide different results.

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P0733 / #1714

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

EFFECTS OF BRAIN-DERIVED NEUROTROPHIC FACTOR ON PRE-FORMED FIBRIL-INDUCED ALPHA-SYNUCLEIN AGGREGATION

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Aims: Parkinson's disease is the second most common progressive neurodegenerative disease characterized by loss of dopamine neurons in the substantia nigra and Lewy bodies - intraneuronal inclusions- as neuropathological hallmarks. The aim of this study is to investigate if brain-derived neurotrophic factor (BDNF) can reduce pre-formed fibril (PFF) induced Lewy body-like alpha-synuclein aggregation in mouse primary dopaminergic neurons.
Methods: Dopaminergic neurons isolated from the ventral midbrain floor of 13.5 mouse embryos were plated in 96-well plates and maintained in a culture medium without neurotrophic factors until the day *in vitro* (DIV)8. Glial cell line-derived neurotrophic factor (GDNF) was used as a positive control since it reduces the aggregation of alpha-synuclein in cultured dopaminergic neurons and the mouse brain. BDNF was added on a DIV8 1 hour after the PFF-treatment, or on DIV12. The cultures were fixed on DIV15 and stained with tyrosine hydroxylase (TH) and phosphoSer129-alpha-synuclein (pS129-alpha-syn) antibodies. Quantification of TH+ neurons and pS129-alpha-syn+ and TH+ neurons was performed with unbiased image analysis using CellProfiler™ software.
Results: Neither GDNF nor BDNF added at the late stages of culturing did not significantly affect the survival of TH+ neurons. Like GDNF, BDNF added either on DIV8 or DIV12 decreased pS129-alpha-syn positive aggregates in dopaminergic neurons. The effect of BDNF was slightly more pronounced when added earlier on DIV8 instead of on DIV12.
Conclusions: Research on neurotrophic factors' protective effects on multiple neuropathologies can help the development of new therapies against Parkinson's disease.

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P0734 / #1174

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

INTERPLAY BETWEEN ALPHA-SYNUCLEIN AGGREGATION AND DEGRADATION SYSTEMS IN PARKINSON'S DISEASE PATHOGENESIS

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Aims: Parkinson's Disease (PD) is the second most common neurodegenerative disease in the world. One of the major pathological hallmarks of the disease is the aggregation of a misfolded protein called alpha-synuclein (α-syn), which will lead to the formation of cellular inclusion known as Lewy bodies. However, how these aggregates disturb neuronal homeostasis leading to neurodegeneration remains elusive. Several studies showed a correlation between alterations of the degradation systems (autophagic or proteasomal), implicated in the protein quality control, and α-syn aggregation. Nevertheless, it is not clear yet how the degradation is impaired. Our aim is here to know precisely how an alteration of the degradation systems is involved in the pathogenesis of PD.
Methods: To study the effect of α-syn aggregation, the LIPA (Light-Inducible Protein Aggregation) system recently developed by our laboratory is used. This system nicely mimics key features of Lewy bodies and allows to optogenetically control and observe in real time the aggregation of α-syn.
Results: Using this model, we were able to observe for the first time the effect of LIPA-induced aggregates on the proteasome and autophagy systems by using specific markers. Moreover, we also get interested in the inhibition of these systems and the effect on aggregation. The results obtained show us the capacity of our LIPA system to mimic the potential effects of α-syn on the degradation systems.
Conclusions: Taken together our observations reveal the impact of autophagy and proteasome dysfunctions in PD pathogenesis. Interestingly, we found that both systems seem involved but in a different manner and with a different kinetic.

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P0735 / #902

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

GUT MICROBIOTA DYSBIOSIS: EVALUATION OF THE CAUSE AND THE ORIGIN OF DISEASE

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Aims: Our study aims to analyze the composition of gut microbiota of PD patients in the Indian population using stool samples from the patient. The study tends to investigate the origin of the disease and the involvement of gut microbiota in the progression of the disease.
Methods: The identification of the microbes will be done through phenotypic and genotypic processes i.e. by biochemical tests and by applying ERIC and RAPD-PCR respectively. Along with this, the 'Rotenone' induced mice model for Parkinson's will be developed and its gut microbiota will be analyzed relative to human samples. In the other group, a bacterial culture from the stool sample of PD patients was fed orally to the conventionally raised mice to observe the change in gut microbiota and to see if any symptoms of Parkinson's appeared in the mice.
Results: The study resulted into find a positive correlation between the gut flora and the disease onset and progression in the rotenone-induced mice which replicates with the Motor symptoms of the patient. We are looking forward to analyzing the effect of bacterial flora of PD Patients on the brain of mice. To see that brain sections of animals will be stained with suitable stain to analyze the occurrence of α-synuclein
Conclusions: The study concludes with the involvement of gut microbiota in the disease onset and progression. The results show, that the generation of Motor symptoms obviously originates from the brain but the source of the disease onset is indirectly related to the gut of the Patient. The comparison between the rotenone-induced mice model and the bacteria-induced mice model reflects the onset and the occurrence of disease.

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P0736 / #1356

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

RT-QUIC IN NEWLY DIAGNOSED PARKINSON'S DISEASE

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Aims: Real-time quaking induced conversion (RT-QuIC) is a novel, sensitive method to detect misfolded alpha-synuclein (α-syn) in cerebrospinal fluid (CSF) of patients with Parkinson's disease (PD), and detects PD in cohorts of advanced or pathologically confirmed cases with sensitivity and specificity close to 100%. We aimed to test the potential of RT-QuIC to detect early PD in a population-based cohort of PD patients at time of their clinical diagnosis.
Methods: CSF from 121 patients with PD, taken at time of clinical diagnosis, and from 55 controls without known neurodegenerative disease were analysed with our modified RT-QuIC assay. Patients were recruited from the population-based Norwegian ParkWest study with confirmed clinical PD diagnosis after follow-up for up to ten years. Controls were subjects undergoing elective lumbar puncture as part of their clinical workup. Patients underwent a comprehensive battery of motor and non-motor symptom tests and the association with RT-QuIC status was analysed using logistic regression analysis. The assay allows a fast determination within 48 hours on standard laboratory equipment.
Results: The assay had a sensitivity of 82.6% (95% CI: 74.7%-88.9%) and a specificity of 87.3% (95% CI: 75.5%-94.7%) with a positive predictive value (PPV) of 93.4% (95% CI: 87.7%-96.6%) and a negative predictive value (NPV) of 69.6% (95% CI: 60.5%-77.4%). No significant associations with PD symptoms at diagnosis and RT-QuIC status were identified.
Conclusions: This modified RT-QuIC detected the presence of misfolded α-syn in samples of patients with early PD with high sensitivity and specificity and can aid in early diagnosis of PD.

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P0737 / #814

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

HIGH-THROUGHPUT ARRAYED CRISPR ACTIVATION SCREENING FOR THE IDENTIFICATION OF POTENTIAL MODIFIERS OF ALPHA-SYNUCLEIN AGGREGATES.

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Aims: The progressive accumulation of misfolded α-synuclein proteins in the nervous system is the key histopathological hallmark of neurodegenerative diseases, including Parkinson's Disease, Multiple System Atrophy, and Dementia with Lewy body, which are collectively referred to as synucleinopathies. Under pathophysiological conditions, the native unfolded α-synuclein monomers assemble into the highly ordered β-sheet-rich structure. These amyloid fibrils give rise to the formation of intracellular inclusions known as Lewy bodies and cause the clogging of the endogenous protein degradation pathways, oxidative stress, synaptic dysfunction, and mitochondrial dysfunction eventually leading to neurodegeneration. We aim to understand the genetic players and molecular mechanisms underlying the α-synuclein aggregation.
Methods: Here, in our study by utilizing the robust CRISPR/Cas-9 arrayed activation library developed by our lab to activate protein-coding genes in HEK293 cells overexpressing the human SNCA followed by preformed fibrils treatments in an arrayed format. Utilizing the anti- Ser-P 129 antibodies, the newly formed aggregated were immunostained and followed by high-throughput imaging and analysis.
Results: We have optimized PFFs (Preformed Fibrils) assay in 384 well plates by treating the cells with different concentrations of PFFs and monomeric a-synuclein. We have successfully established the protocol to produce and sonicate the fibrils in a reproducible way. The development and validity of the assay pilot study were carried out using positive and negative controls. Activation RAB13 showed to decrease α-synuclein aggregates was used as a control in the study.
Conclusions: The identified hits will be further studied in neuronal models and in vivo models for the validation of the hits. Identifying novel key genetic players help in understanding the pathways underlying α-Synuclein aggregation, which would contribute in the development of new therapeutic strategies against synucleinopathies.

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P0738 / #1381

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

VALIDATION OF AN IN VITRO A-SYNUCLEIN AGGREGATION ASSAY IN PRIMARY CORTICAL CULTURES FOR HIGH THROUGHPUT RNA INTERFERENCE SCREENING

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Aims: In Parkinson's disease (PD), the formation and propagation of α-synuclein insoluble amyloid structures is a process hypothesized to drive the pathology of disease. However, there is currently a lack of understanding with regards to the pathways and proteins responsible for progression of α-syn aggregation, in particular in idiopathic PD, and in vitro genetic screens is one way to increase the knowledge about this.
Methods: We therefore developed a high-capacity *in vitro* model based on primary embryonic mouse cortical cultures in the 384-well format, where lentiviral shRNA was added at 3 days *in vitro* (DIV) to induce gene silencing, and endogenous α-synuclein aggregation was induced at 10 DIV using recombinant human α-syn pre-formed fibrils. Endogenous α-syn aggregation and cell health were then quantified at 17 DIV using immunocytochemistry and automated high content imaging and analysis.
Results: The outcome was a robust and sensitive α-synuclein aggregation assay for high throughput RNA interference screening. The throughput was more than sufficient for managing the library of 900 oligos targeting 300 genes with the required number of technical replicates and biological test occasions. Upon completion of the screen, the quality control metrics, e.g. signal to noise ratio, the variability in total cell count, no of neurons & SSMD all confirmed that the screen was a technical success. Furthermore, a number of genes decreasing as well as increasing α-synuclein aggregation were also identified.
Conclusions: We can conclude that the developed assay is well-suited for high throughput RNA interference for the discovery of new genes involved in α-syn aggregation.

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P0739 / #1711

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

CHARACTERIZING THE STRUCTURE AND RICH INCLUSIONS OF ALPHA-AYNUCLEIN IN PATIENTS WITH DEMENTIA WITH LEWY BODIES

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Aims: Dementia with Lewy bodies (DLB) accounts for 30% of dementia cases in patients over the age of 65. There is significant Lewy body formation in the paralimbic and neocortical regions of the brain in DLB. The ultrastructural analysis of phosphorylated alpha-synuclein and amyloid beta aggregates is necessary in order to gain a better understanding of the pathological mechanisms leading to DLB. We report the structural analysis of post-mortem brain tissue from donors with DLB disease, in order to gain insight into the pathologic mechanisms underlying Lewy body formation.
Methods: Fluorescent immunolabeling was performed on 60-micron thick free-floating, chemically fixed brain sections from DLB donors. We then processed the same sections for electron microscopy (EM) using heavy metal staining and resin-embedding. Using laser capture microdissection, we cut the regions of interest and thinned them with an ultramicrotome to 150 nm thickness. Images were recorded of the sections with light microscopy and EM, for correlative light and electron microscopy (CLEM) analysis.
Results: Several brain regions were examined, including the substantia nigra, hippocampus, cingulate gyrus, and entorhinal cortex. Phosphorylated alpha-synuclein pathology was present in the substantia nigra, entorhinal cortex and in the CA2, as expected. High resolution EM images showed abundant fibrils and densely aggregated membrane fragments in the Lewy bodies from these regions.
Conclusions: Lewy bodies in DLB bear a similar appearance as reported previously for Lewy bodies from Parkinson's disease (Shahmoradian *et al*., Nature Neuroscience 2019), typically being composed of densely aggregated membrane fragments and fibrils. Structural studies of Lewy bodies help understanding the mechanism and progression of DLB. The CLEM analysis can yield significant insight into alpha-synuclein and tau pathology in postmortem human brain with DLB.

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P0740 / #2036

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

IPD1 AS THERAPEUTICS AGAINST PARKINSON'S DISEASE

Deepak Sharma[1], Aamir Nazir[2], Arpit Gupta[1], Daniel Otzen[3], Bishwajit Kundu[4], Ashutosh Kumar[5], Gajendra Raghava[1], Priyanka Singh[1], Arpit Mehrotra[1], Ankur Gautam[1], Gagandeep Jaiswal[1], Krishna Upadhayay[1], K Srividya[2], Rajlaxmi Panigrahi[1], Shubham Vashishtha[4], Jasdeep Singh[4], Signe Frank[3], Janni Nielsen[3], Samir Nath[1]
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Aims: Parkinson's disease (PD) is the second most prevalent form of neurodegeneration. Once believed to be a rare disorder, the incidence of PD is on rise worldwide, including in India. Patients with Parkinson's disease share the presence of α-synuclein amyloid aggregates in dopaminergic neurons in the substantia nigra region of the brain. There have been various attempts to develop inhibitors of α-synuclein aggregation, but there is no clinical success yet and the disease remains incurable. Thus the primary focus of the present study is to identify potent inhibitors of α-synuclein aggregation for therapeutics against Parkinson's disease.
Methods: Methods: Various peptides were screened against α-synuclein aggregation using Thioflavin T based assay. The α-synuclein aggregation was further characterized in the presence and absence of identified peptide using circular dichroism, and Transmission Electron Microscopy. Molecular dynamics simulations were carried out to understand the mechanism of the peptide action. NMR studies provided binding region of α-synuclein with the peptide.
Results: In the current study, we screened for and isolated potent peptides that inhibit in vitro α-synuclein aggregation. In addition, we investigated the peptide's mechanism of action and its therapeutic efficacy in *C. elegans* and mouse models of Parkinson's disease. The peptide treatment ameliorated locomotor and histological abnormalities in transgenic PD mice, indicating its utility as a treatment for Parkinson's disease.
Conclusions: The present study shows that IPD1 is a potent inhibitor of α-synuclein fibrillation. The peptide inhibits α-synuclein aggregation in yeast and *C. elegans* model of PD. The NMR, Microscale thermophoresis and MD simulations studies show that the peptide and its cyclic derivative interact with α-synuclein. Peptide treatment ameliorated locomotor and histological abnormalities in transgenic PD mice, indicating its utility as a treatment for Parkinson's disease.

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P0741 / #669

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

A MULTICENTER, MATCHED CASE-CONTROL STUDY OF ALPHA-SYNUCLEIN ACCUMULATION IN THE GASTROINTESTINAL TRACT OF PARKINSON'S DISEASE

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Aims: This study aimed 1) to determine the possibility as a pathologic biomarker of alpha-synuclein (AS) accumulation in the gastrointestinal (GI) tract in Parkinson's disease (PD) and 2) to reveal pathological evidence of bi-directional progression of gut-brain axis in large-scale, multicenter, and matched case-control design.
Methods: Patients with PD who underwent radical GI surgery for cancer and matched controls were recruited from six tertiary hospitals. The serially stained slides with immunohistochemistry using phosphorylated AS (pAS) and neurofilament antibodies were evaluated by raters who were blinded to clinical information. pAS positivity and clinical characteristics were compared between patients and controls, and patients with pAS positive and negative results. The multivariate logistic regression analysis was conducted to determine the impact of clinical characteristics on pAS positive rate.
Results: Total 355 pathologic blocks from 97 patients with PD and 94 matched controls were evaluated. pAS positivity was significantly higher in patients (75.3%) than in controls (8.5%, p-value<0.001). Sensitivity and specificity of full-layer evaluation were 75.3% and 91.5%, respectively, while 46.9% and 94.7% when evaluation was confined to mucosa-submucosal layers. Rostrocaudal gradient of AS accumulation was found in patients. Duration of symptom onset to operation (DOO) was significantly longer in patients with AS accumulation than without (4.9±4.9 vs.1.8±4.1 years, p-value=0.005). In the regression analysis, both DOO and operation site remained significant contributors of pAS positivity in PD.
Conclusions: The results confirmed that the conventional immunohistochemistry of the GI tract did not have sufficient diagnostic accuracy for a pathologic biomarker of PD. The significant temporal relationship of AS accumulation in the GI tract at operation and symptom onset implies a consistent progression of Lewy pathology from brain to gut in the disease course of PD.

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P0742 / #938

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

THE ROLE OF THE N-TERMINUS IN A-SYNUCLEIN'S NUCLEATION PATHWAYS.

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Aims: Parkinson's disease is characterized by the accumulation of Lewy bodies, the main component of which is the protein α-synuclein. In neurodegeneration, intrinsically disordered α-synuclein monomers self-associate to form amyloid fibrils which are characterized by a β-sheet core. Several intrinsic factors (e.g., post-translational modifications) and extrinsic factors (e.g., solution pH) can change the protein's propensity to aggregate. One such post-translational modification of α-synuclein, N-terminal truncation, is of great interest as the N-terminus has been linked to both normal and toxic protein function. Recombinant production of physiologically relevant N-terminally truncated proteins faces many challenges, in particular achieving bacterial expression without the introduction of an initiating methionine or other non-native residues. Consequently, we aimed to express and characterize pathologically relevant N-terminally truncated α-synuclein.
Methods: We generated a fusion protein consisting of an N-terminally truncated fragment of α-synuclein placed at the C-terminus of an intein, which contained specific point mutations and a chitin binding domain. Column immobilization and thiol induced cleavage facilitated the isolation of truncated α-synuclein fragments. Varying aggregation conditions allowed us to monitor the different nucleation pathways to aggregation and the microscopic steps that compose them.
Results: We were able to successfully develop a method to generate highly pure, pathologically relevant N-terminally truncated variants of α-synuclein. Biophysical characterization by Thioflavin-T fluorescence, microscopy and TEM showed that these variants aggregated to different extents and formed morphologically distinct fibrils.
Conclusions: We were able to deliver a method to generate potentially any physiologically relevant N-terminally truncated α-synuclein fragment and determine that the N-terminus plays an important role in nucleation pathways linked to the protein's amyloid aggregation. This finding may provide insight into the mechanism of disease onset and toxicity.

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P0743 / #456

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

FEMALE-DRIVEN SEX EFFECTS IN MRI-DERIVED ALPHA-SYNUCLEIN-INDUCED WHOLE BRAIN ATROPHY PATTERNS PRECEDES FASTER DISEASE PROGRESSION AND LOWER SURVIVAL RATES IN MALES IN A MOUSE MODEL OF SYNUCLEINOPATHY

Stephanie Tullo[1,2], Daniel Gallino[1], Janice Park[1,2], Megan Park[1], Kristie Mar[1], Esther Del Cid-Pellitero[3], Edward Fon[4], M. Mallar Chakravarty[1,2]
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Aims: While sex-related differences in Parkinson's disease (PD) are well-described, with prevalence and onset higher and earlier in men compared to women, there is little information on sex differences in the patterns of neurodegeneration, and findings are mixed on sex differences related to disease progression.
Methods: Hemizygous M83 mice received an injection of alpha-synuclein preformed fibrils (PFF) or phosphate buffered saline in the right striatum (n=20 mice/group/sex). Spatial voxel-wise volumetric covariance patterns were derived using orthogonal projective non-negative matrix factorization (NMF) (k=6 components) (absolute Jacobians from T1-weighted images (100 µm3 isotropic voxels; Bruker 7T) acquired at 90 days post-injection). Group differences in subject-NMF-weights were assessed using general linear models and only components with a significant injection effect for each NMF run were examined. Three separate NMF runs were executed (all-subjects, female-only and male-only) and the spatial overlap between the all-subjects, male-only, and female-only injection-specific spatial patterns were examined using Dice-kappa overlap scores.
Results: Dice-kappa scores used to examine sex-specific spatial similarity of PFF-induced brain changes suggest a high degree of spatial similarity between the all-subjects and female-only spatial patterns (κ=0.62), thus suggesting that injection group-level findings are predominantly female driven. Conversely, when examining symptomatology and disease progression (survival rates), male PFF-injected mice succumbed to their symptoms at significantly higher rates than their female counterparts
(p=0.0015).

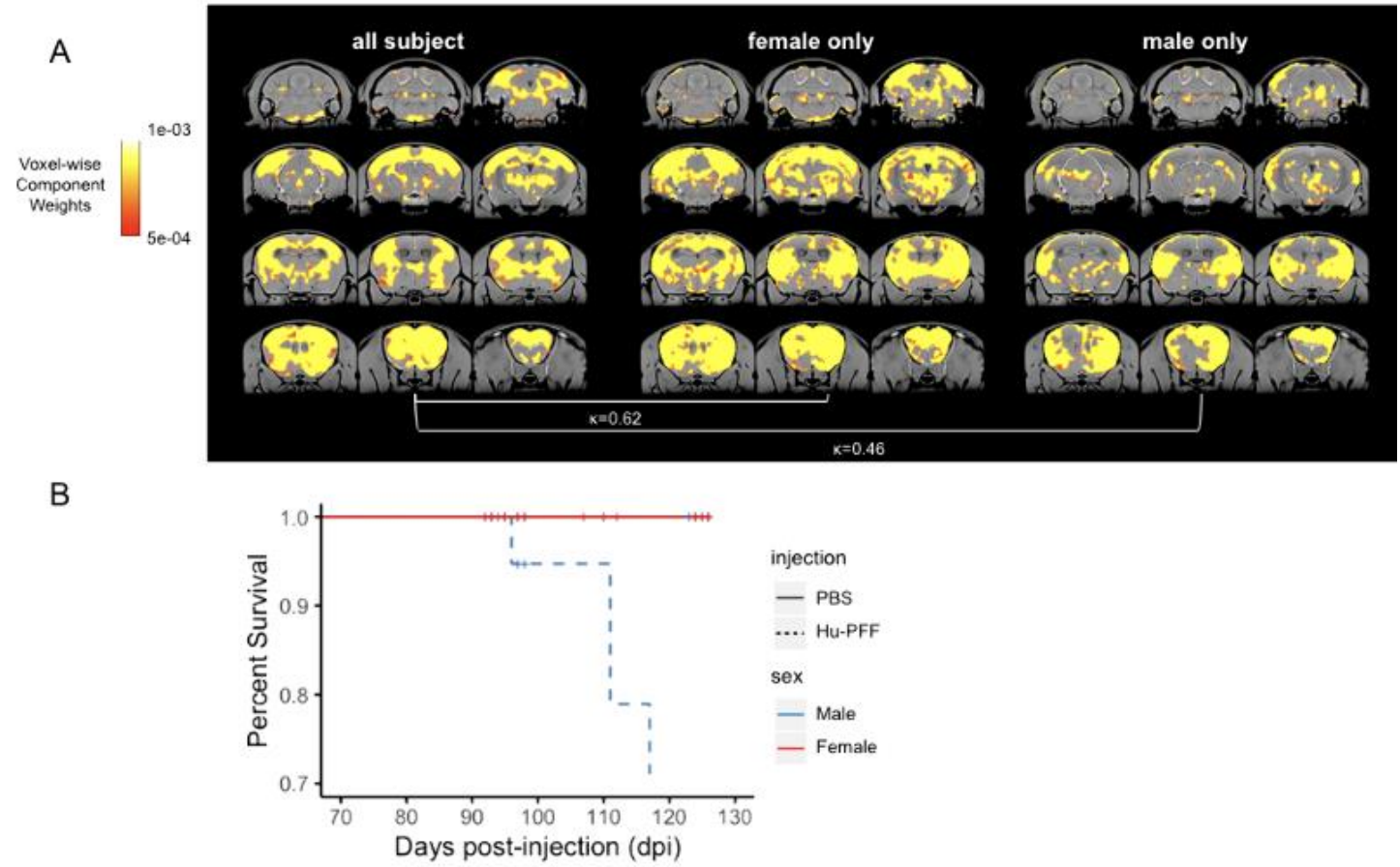

Figure. [A] NMF decomposition of voxel-based deformation in M83 aSyn^{A53T} transgenic mice for three separate NMF runs (all subjects versus females only versus males only); k=6 components. Significance for aSyn PFF-induced network level pathology assessed using a general linear model; significant group differences in subject component weights were observed for only one of six components for each of the three NMF runs (component 1, 1, and 5 respectively). The spatial pattern of voxel component weights (denoted by the colour map) plotted onto the mouse brain, depicting patterns of voxels sharing a similar variance pattern for each of the three NMF runs (left to right). Dice-kappa overlay score was used to examine the spatial similarity between the three spatial patterns, such that higher kappas denote greater overlap. The greatest overlap with the all subject NMF component is between it and the female-only spatial component (κ=0.62), thus suggesting that the all subject component is predominantly female driven, despite observing no statistical group by sex interaction significance of the subject weights for the all subject component 1. [B] Survival plot for M83 hemizygous mice; solid line for PBS-injected mice, dashed line for human PFF-injected mice, blue for male and red for female mice. Percent survival of the mice are plotted across the days post-injection (dpi) with the experimental endpoint being 130 dpi. Almost 30% of the male Hu-PFF-injected mice succumbed to their symptoms/disease progression a couple days prior to the 120 dpi time point. Group differences in survival rate were examined using general linear models, and a significant group by sex interaction was observed whereby male Hu-PFF-injected mice had lower survival rates (p=0.0015).

Conclusions: These findings suggest that sex may exert a differential impact on clinical features of synucleinopathy, with females showing a more benign phenotype while displaying greater and more accelerated neurodegeneration at early stages, prior to symptomatology. These findings support the idea that PD development may involve different mechanisms, yielding distinct prognosis between the sexes, which may have implications for research into neuroprotection and sex-specific analyses in pre-clinical drug trials.

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P0744 / #1112

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

UNDERSTANDING THE MECHANISMS OF A-SYNUCLEIN HETEROGENOUS AGGREGATION IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE FOR BETTER DIAGNOSIS

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Aims: Although traditionally, dementias are associated with the aggregation of one or two specific proteins, aggregates specific to one type of dementia have been found in patients diagnosed with another type of dementia. Examples of this are seen with the formation of amyloids by the intrinsically disordered amyloid-β peptide and α-synuclein which are traditionally considered hallmarks of Alzheimer's and Parkinson's diseases, respectively. Recently, it has been shown that 50% of Alzheimer's disease patients show aggregates of α-synuclein and 50% of Parkinson's disease patients show aggregate of amyloid-β. This further complicates both diagnosis and therapeutic intervention in these cases. Therefore, we investigated the heterogenous aggregation of these proteins with the view to identify potential biomarkers for diagnosis and possible therapeutic targets.
Methods: While it has been shown both proteins can co-aggregate, we have clarified this process using an array of biochemical and biophysical techniques including Thioflavin T aggregation assays, immunoblotting and immunogold labelling with negative stain transmission electron microscopy.
Results: We show that amyloid-β can trigger the aggregation of α-synuclein via heterogenous primary nucleation and that the aggregates formed in these conditions are formed solely of α-synuclein, with amyloid-β associated to but not present in the core of the resulting aggregates. This mechanism is a specific property of the soluble species of amyloid-β but not of the insoluble fibrillar aggregates. Additionally, our findings indicate that the aggregation of amyloid-β–α-synuclein co-incubation is a consequence of the property of amyloid-β to serve as nucleation interface for α-synuclein aggregation.
Conclusions: Our data provide a detailed mechanism of this disease related heterogenous aggregation which can now be developed towards diagnostic and therapeutic applications.

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P0745 / #2171

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

NOVAL NANOBODIES REDUCE ALPHA-SYNUCLEIN SEED INDUCED AGGREGATION AND TOXICITY

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Aims: Given the pathological role of α-syn aggregates, it serves as a promising target for therapeutic intervention in Pakinson's disease. Nanobodies derived from camels serves as an ideal candidate to target pathogenic α-syn due to its varied properties including its small size, stability, and binding properties.
Methods: We constructed a nanobody phage display library from RNA isolated from camels immunized with a-syn fibrils. After multiple rounds of panning and selection, two nanobodies, Nb-04 and Nb-40 were purified, and thoroughly characterized for their specificity and tested for their ability to inhibit α-syn seed induced aggregation and toxicity in vitro and in cells.
Results: Using filter retardation assay both Nb-04 and Nb-40 was found to specifically recognize α-syn aggregates and do not recognize aggregates and monomers of other amyloid proteins. Mapping of the epitope revealed that both Nb-04 and Nb-40 recognize the C-terminal region of a-syn. Nb-04 was found to be specific for human α-syn aggregates whereas, Nb-40 recognized both human and mouse α-syn aggregates. Interestingly, Nb-04 and Nb-40 also differ in their conformational specificity, with Nb-04 recognizing α-syn oligomers with beta-sheet structure whereas Nb-40 recognized oligomers with and without beta-sheet structure. Using an *in vitro* seeding assay both Nb-04 and Nb-40 was found to inhibit the aggregation of α-syn. Moreover, in an *in-vitro* cell model of α-syn expressing HEK cells, both Nb-04 and Nb-40 inhibited seed dependent aggregation and decreased the formation of insoluble phosphorylated α-syn at Ser 129 (pS129-α-syn). Finally, immunohistochemistry analysis of human post-mortem brain tissue demonstrated that both Nb-04 and Nb-40 was able to detect Lewy bodies pathology in PD cases.
Conclusions: Nb-04 and Nb-40 mentioned herein could serve as potential candidates for diagnostic and therapeutic intervention in PD and related disorders.

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P0746 / #1035

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

GENERATION OF ALPHA-SYNUCLEIN PREFORMED FIBRILS AND EVALUATION OF DIFFERENT QUALITY CONTROL METHODS

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Aims: In recent years, the use of alpha synuclein (aSyn) preformed fibrils (PFFs) to induce aggregation of endogenously expressed aSyn in cellular and animal models arose as a unique model to study the pathogenesis of Parkinson's disease. In this work, we describe the generation of different batches of PFFs, quality control methods for batch analysis, and evaluation of PFF seeding activity in a rat hippocampal primary neuron model.
Methods: Recombinant full length human aSyn A53T and S87N and mouse aSyn N87S monomers were used for fibril formation. To assess the best conditions for potent fibril formation, several parameters were tested such as reaction buffer, incubation time, protein concentration and purification method. Quality control was performed using Thioflavin-T (ThT) assay, sedimentation analysis, immunoassays, electron microscopy (EM), mass photometry and dynamic light scattering. The seeding capacity of the different PFF batches was evaluated in a rat hippocampal primary neuron cellular model. Cells were seeded at DIV9 and fixed for immunocytochemistry analysis at DIV20.
Results: When tested in the cellular seeding assay, different PFF batches had different seeding capacities and seeding capacity was not driven by the isoform of the monomer nor incubation conditions for PFF formation. Quality control with ThT, sedimentation analysis and immunoassays to detect aSyn aggregates could not predict seeding capacity in the cellular assay. Moreover, EM observations showed minor structural differences between PFF batches, in regard of length and appearance (flat or cylindrical) but could not distinguish potent from non-potent seeds.
Conclusions: Currently, the most reliable method to evaluate seeding capacity of PFFs is evaluation in a cellular model using rat hippocampal neurons. Seeding capacity in this cellular assay translates to *in vivo* seeding potency in wild type mice.

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P0747 / #513

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: _-SYNUCLEIN AGGREGATION

PATHOLOGICAL ALPHA-SYNUCLEIN PROFILING IN NASAL SPECIMENS OF PATIENTS WITH PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is an increasingly prevalent neurodegenerative disorder for which diagnosis is based on clinical criteria that can be difficult to interpret and distinguish from other parkinsonian syndromes. Biomarkers such as pathological alpha-synuclein (asyn) detection are established in cerebrospinal fluid (CSF). The underlying pathogenesis of PD is still unclear, but a peripheral origin is discussed. PD is thought to start in the olfactory bulb which is connected to the nose, rendering easily accessible nasal samples potent for biomarker development. We sought to identify whether asyn seed amplification assay developed to detect pathological asyn in CSF using samples from PD patients and healthy controls could detect pathological asyn in nasal lavage samples and olfactory mucosa to be used as a biomarker.
Methods: In this study, olfactory mucosa and nasal lavage samples were collected from PD patients recruited at the Paracelsus-Elena-Klinik, Kassel, Germany (DeNoPa Cohort) and from controls free of neurological disease. Samples were analysed using seed amplification assay and their seeding ability was compared to that of CSF samples.
Results: The asyn seed amplification assay activity in olfactory mucosa and nasal lavage samples from PD patients compared to the controls indicated the specificity and sensitivity of these samples. In addition, accuracy among results of asyn seed amplification assay activity for CSF, olfactory mucosa and nasal lavage from the same patient was estimated.
Conclusions: Our results suggest that asyn seed amplification assay analysis of nasal samples alone or combined with CSF testing are useful for increasing the diagnostic accuracy of PD. Finally, more research is necessary to establish the use of the assay in peripheral samples as a biomarker to detect the disease earlier and monitor progression and response to disease modifying approaches.

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P0748 / #2724

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

CERAMIDE AFFECTS THE ENDO-LYSOSOMAL PATHWAY IN PINK1-RELATED PARKINSON'S DISEASE

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Aims: Loss of Pink1 causes early-onset Parkinson's disease (PD), resulting in defective energy production and mitophagy. However, if and how these two processes are linked remains unknown. Interestingly, ceramide, the basic sphingolipid, plays a role in both processes suggesting ceramide can act as a link between both mechanisms. Previously, we showed increased ceramide levels in Pink1-deficient flies and patient-derived fibroblasts. Furthermore, inhibition of ceramide improves mitochondrial function and autophagy. Interestingly, ceramide affects the endo-lysosomal pathway in VPS35 and alpha-synuclein PD models. Hence, we aim to understand the effect of ceramide accumulation in *pink1*-mutant flies in the endo-lysosomal pathway.
Methods: Endo-lysosomal function was evaluated in control and *pink1*-mutant flies via immunolabeling and western blotting analyses. Furthermore, flies were treated with myriocin to assess the effect of decreased ceramide. In addition, mtkeima was used to analyze the level of mitophagy
Results: Inhibition of ceramide synthesis lowers autophagy and mitophagy in *pink1*-mutant flies. In addition, ceramide inhibition increases LAMP1 labeling as a measure for lysosomal function. The increased levels are similar as observed upon chloroquine treatment that blocks the fusion of the autophagosome with the lysosome. Finally, loss of Pink1 showed defects in the endo-lysosomal pathway.
Conclusions: Pink1 deficiency has a normal autophagic flux that is ceramide-dependent. Thus, Ceramide homeostasis is elevated in PINK1-related PD to maintain endo-lysosomal function and to overcome the lack of PINK1-dependent mitophagy.

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P0749 / #571

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

LRRK2-G2019S MUTATION ALTERS AUTOPHAGY AND MITOPHAGY DYNAMICS IN ASTROCYTES

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Aims: Astrocytes have been classically described as cells exerting mainly supporting functions toward neurons. In the aging brain, astrocytes undergo physiological changes and lose their trophic properties contributing to the onset of age-related neurodegenerative diseases such as Parkinson's disease (PD). Our hypothesis is that age-associated deficits in autophagy alter astrocyte functionality, and induce a senescent-like phenotype, which ultimately contributes to the neuronal degeneration observed in PD. The objectives of this study were 1) to identify autophagy and mitophagy dynamic defects in astrocytes carrying the PD-associated mutation LRRK2-G2019S; 2) to identify senescent-associated phenotypes in these cultures and try to establish a link between the two cellular processes.
Methods: Using induced pluripotent stem cell (iPSC) lines engineered with stable autophagy and mitophagy reporters. Developing a high-throughput phenotyping platform using automated high-content image analysis to assess autophagy and mitophagy pathway intermediates. Generation of 2D cultures of astrocytes derived from neural stem cells (NSC) differentiated from neuroepithelial stem cells (NESC). Using immunocytochemistry analysis to identify senescent markers.
Results: In 2D cultures, astrocyte differentiation from LRRK2-G2019S precursor cells was associated with early apoptosis, altered Wnt/βcatenin, and TGFβ signaling compared to LRRK2-WT cultures. The use of mitophagy and autophagy reporters allowed the identification of autophagy and mitophagy dynamics in astrocytes and showed alteration in cultures carrying the LRRK2-G2019S mutation. Moreover, the presence of the mutation predisposed to the acquisition of a senescent phenotype.
Conclusions: Our results suggest that there is a strong connection between senescence and autophagy in the context of the LRRK2-G2019S mutation.

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P0750 / #2000

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

DEVELOPING NOVEL THERAPEUTIC TREATMENT FOR PARKINSON'S DISEASE

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Aims: Gain-of-function mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are common in familial forms of Parkinson's disease (PD), which is characterized by progressive neurodegeneration that impairs motor and cognitive function. We previously demonstrated that LRRK2-mediated phosphorylation of beta-amyloid precursor protein (APP) triggers the production and nuclear translocation of the APP intracellular domain (AICD). Here, we aim to connect LRRK2 to AICD that AICD could enhance to LRRK2-mediated neurotoxicity.
Methods: We engaged the in vitro and in vivo model systems, including dopaminergic neurons derived from human patient carrying $LRRK2^{G2019S}$ mutation and $LRRK2^{G2019S}$ transgenic mice; $LRRK2^{G2019S}$ transgenic mice cross with APP knockout and AICD transgenic mice; as well as cell-based assay. In addition, pharmacological inhibition of AICD by itanapraced was applied in vitro and in vivo.
Results: We showed that in cooperation with the transcription factor FOXO3a, AICD promoted LRRK2 expression, thus increasing the abundance of LRRK2 that promotes AICD activation. APP deficiency in LRRK2G2019S mice suppressed LRRK2 expression, LRRK2-mediated mitochondrial dysfunction, alpha-synuclein accumulation, and tyrosine hydroxylase (TH) loss in the brain, phenotypes associated with toxicity and loss of dopaminergic neurons in PD. Conversely, AICD overexpression increased LRRK2 expression and LRRK2-mediated neurotoxicity in LRRK2G2019S mice. In LRRK2G2019S mice or cultured dopaminergic neurons from LRRK2G2019S patients, treatment with itanapraced reduced LRRK2 expression and was neuroprotective. Itanapraced showed similar effects in a neurotoxin-induced PD mouse model, suggesting that inhibiting the AICD may also have therapeutic benefits in idiopathic PD.
Conclusions: Our findings reveal a therapeutically targetable, feed-forward mechanism through which AICD promotes LRRK2-mediated
neurotoxicity in PD.

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P0751 / #2668

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

NEW C. ELEGANS MODELS OF 'GUT-TO-BRAIN' ALPHA-SYNUCLEIN TRANSMISSION AND TOXICITY IN PARKINSON'S DISEASE

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Aims: Objectives: Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by progressive motor decline and the aggregation of alpha-synuclein protein. Growing evidence suggests that alpha-synuclein aggregates may spread from neurons of the digestive tract to the central nervous system in a prion-like manner. While rodent models have recapitulated gut-to-brain alpha-synuclein transmission, animal models that are amenable to high-throughput investigations are needed to facilitate the discovery of disease mechanisms. To serve this need, we aimed to generate new models of 'gut-to-brain' alpha-synuclein toxicity using the highly genetically tractable *C. elegans* nematode.
Methods: Methods: Worms expressing human wild-type alpha-synuclein either in neurons or muscle were fed alpha-synuclein pre-formed fibrils (PFFs) or monomer in order to initiate pathology in the gut. At several time-points during aging, the worms were tested for motor function, aggregation of host alpha-synuclein, and dopaminergic neuron degeneration. Non-transgenic worms were treated in parallel as controls.
Results: Results: We have found that PFF feeding is able to promote the aggregation of host alpha-synuclein, and cause an overall reduction in movement. Specific motor deficits were also identified in terms of crawling wavelength, amplitude, center point speed, and straight line distance. PFF feeding resulted in accelerated dopamine neuron degeneration, whereas alpha-synuclein monomer was insufficient to produce these effects. Moreover, we identified the heparan sulfate proteoglycan (HSPG) pathway as playing an important role in the PFF-induced prion-like disease phenotypes.
Conclusions: Conclusions: This work offers new animal models by which to investigate gut-derived alpha-synuclein spreading and propagation of disease, and offers the first *in vivo* demonstration of HSPG regulation of alpha-synuclein PFF toxicity. Future studies utilizing these models can employ high-throughput approaches to further understand disease mechanisms and identify potential treatments for PD.

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P0752 / #2717

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

HOW OLIGODENDROCYTES PLAY DIFFERENT ROLES IN PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY

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Aims: Synucleinopathy is a spectrum of neurodegenerative disorders, which includes PD and MSA. Both diseases present motor-dysfunctions but with distinct pathologic α-synuclein features. PD presents dominant neuronal Lewy-pathology and minimal oligodendrocyte cytoplasmic inclusions. Opposite to PD, MSA brains contain a substantial amount of GCIs and relatively less significant neuronal Lewy pathology. This has indicated oligodendrocyte pathology is subsequent in PD but primary in MSA. It remains unknown what are the biological differences between oligodendrocytes in them and how these brain cells convey effects on neurons.
Methods: Using post-mortem human brains, we examined the oligodendrocyte lineage-changes in the subcortical white-matter of the motor-cortex. We found PD cases showed progressive disorientation of axons with segmental replacement of neurofilaments by deposited α-synuclein, enlargement of myelinating oligodendrocytes in the late disease stage, and increased density of oligodendrocyte precursors. This has captured an adaptive phenotype of oligodendrocyte lineage in PD, likely to compensate for the neural pathway changes during motor deficits.
Results: In MSA cases, only the parkinsonian-subtype but not the cerebellar-subtype has altered-expression of signature genes, although both subtypes have significantly enlarged oligodendrocytes with copious GCIs. These MSA cases have shown significant demyelination and giant deformed axons. We have further revealed the differently altered levels of oligodendrocyte DLG2, GRIA2, and ANKS1B in subtypes of MSA and these genes also showed dysregulated-methylation in MSA. It will be interesting to examine the expression of these genes in PD and their colocalisation with GCIs.
Conclusions: Our studies revealed oligodendrocyte-lineage in PD and MSA, indicating these cells play different roles and responses in the two diseases. This study highlights the importance to understand glia in synucleinopathies, which may imply novel insights to understand the disease mechanisms and reveal non-neuronal targets and biomarkers.

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P0753 / #1565

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

EFFECTS OF HEAT SHOCK PROTEINS IN INTRACELLULAR TRANSPORT OF FIBRILLAR ALPHA SYNUCLEIN

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Aims: Fibrillary a-synuclein (F-aSyn) can spread in a prion-like manner from neuron to neuron antero- and retrogradely. Kinesins and dyneins may mediate the transport of F-aSyn. Heat shock proteins (HSPs) can prevent the spread of F-aSyn in degradation and transport processes. In this study, we investigated the effects of F-aSyn on intracellular levels of 10 HSPs, and the roles of HSPs in the transport of F-aSyn.
Methods: 1 µM F-aSyn was administered to neuron-differentiated SH-SY5Y cells. Total cellular protein was isolated after 6 and 12 hours. Co-immunoprecipitation with kinesin-1 and alpha-synuclein antibodies was carried out after 12 hours. The samples were then analyzed by western blot and dot blot techniques. Then we determined the alterations in the intracellular levels of the HSPs. Finally, HSPs, which may bind to F-aSyn and kinesin-1 in its transport, were analyzed from immunoprecipitation samples.
Results: Intracellular levels of 7 HSPs decreased after 12 hours incubation with F-aSyn ($p<0,05$). On the other hand, all the HSPs immunoprecipitated with both aSyn and kinesin-1 in control and experimental groups. However, immunoprecipitation levels of HSPs decreased with F-aSyn administration ($p<0,05$), in exception with HSP40 and HSPA4 ($p>0,05$).
Conclusions: A decrease in the intracellular level of HSPs may cause cellular vulnerability. Such a condition may cause F-aSyn to overcome the cellular defense against itself, increasing its spread. Furthermore, immunoprecipitation results indicate that Hsp40 may accompany to F-aSyn during its intracellular transportation. However, whether its role as an adapter between kinesin-1 and F-aSyn is not known. Finally, chaperons can be biomarkers for the spreading of F-aSyn. Additionally, increasing the levels of HSPs may support the cells for their survival. This study was supported by Istanbul University-Cerrahpaşa BAP (Project ID:33479).

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P0754 / #1558

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

EXPLORING MODIFIERS THAT CAN REGULATE AGGREGATE PROPAGATION IN C. ELEGANS

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Aims: Accumulation of abnormal protein aggregates is the characteristic of neurodegenerative diseases. These pathological aggregates spread progressively from specific brain regions to larger areas as the diseases progress in the brain. On the basis that that cell-to-cell transmission of aggregates is associated with the pathogenic progression, understanding the mechanism of aggregates propagation would be a promising strategy to slow down the progression of disease.
Methods: We developed Caenorhabditis elegans (C. elegans) models that utilize bimolecular fluorescence complementation (BiFC) technique to exhibit fluorescence only when proteins are transferred transcellular and co-aggregation of the transferred proteins is formed in pharyngeal muscles and their associated neurons. Here, we investigated whether the transfer of aggregates can be regulated by the effects of genetic modulation and pharmacological treatment with in BiFC transgenic worms.
Results: We established in vivo model system capable of measuring the change in fluorescence intensity quantitatively in the C. elegans. Furthermore, we demonstrated in C. elegans BiFC model for transmission of proteinopathy that genetic factors and small molecules associated with aging/senescence, lysosomal function, and cellular trafficking can regulate transmission of aggregates and the associated disease phenotypes such as behavioral deficits, survival rate and mean life span.
Conclusions: These C.elegans BiFC models model would be useful not only for identification of pharmacological and genetic modifiers of aggregate transmission, but also for understanding the mechanism of pathogenesis of disease. And our current results can provide a basis for considering of general approaches as therapeutic strategies for slowing the progression of proteinopathies.

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P0755 / #2097

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

3D TRACING OF VTA TO CA2 NEURAL CIRCUIT BY COMBINATORIAL AAV TRACERS AND TISSUE CLEARING FOR PARKINSON'S DISEASE DEMENTIA STUDY

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Aims: In the late stage of Parkinson's disease (PD), most patients developed cognitive and executive decline, eventually leading to Parkinson's disease dementia (PDD). CA2 subregion in the hippocampus is one of the regions being affected in PDD, but rarely studied. Therefore, this study focuses on tracing the potential connection between CA2 and the midbrain. The first objective of this project is to establish a feasible 3D tracing protocol to trace the well-known nigrostriatal pathway. The second objective is to trace the 3D neural circuit connecting CA2 and ventral tegmental area (VTA) by the newly established protocol.
Methods: The combinatorial adeno-associated virus (AAV) tracing approach includes a set of two AAVs, anterograde AAV-DIO-EYFP and retrograde retro-AAV-Cre-mcherry. For tracing nigrostriatal pathway, AAV-DIO-EYFP was injected into substantia nigra, while retro-AAV-Cre-mcherry was injected into striatum. For tracing the VTA-CA2 neural circuit, AAV-DIO-EYFP was injected into VTA, while retro-AAV-Cre-mcherry was injected into CA2. After 3 weeks, the rats were euthanized by transcardial perfusion. The brains extracted were cleared with Accu-OPTIClearing for 5 days.
Results: EYFP-labeled axonal projections were observed from substantia nigra to striatum. Hence, it is feasible for this protocol to trace nigrostriatal pathway. In the connections between VTA and CA2, complete EYFP-labeled axonal projections from VTA to CA2 can be visualized in a 3D manner. Hence, the structural connection between VTA and CA2 is proved.
Conclusions: A novel 3D visualization protocol was established to map neuronal connections by using combinatorial AAV tracing approach with tissue clearing technique. With this protocol, the connection between VTA and CA2 was mapped, and it may explain the pathological spreading to CA2 in PDD. The study was supported by Innovative & Technology Fund ITS/381/15 and HKU Seed Funding for Applied Research (201910160016).

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POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

SELECTIVITY OF ALPHA-SYNUCLEIN PATHOLOGY TRANSMISSION IN SYNUCLEINOPATHIES : ROLE OF ALPHA-SYNUCLEIN STRAINS AND THEIR INTERACTOMES ?

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Aims: In synucleinopathies alpha-synuclein (asyn) aggregates and spreads in the brain in a prion-like manner, affecting different cells populations and brain regions depending on the disease, and leading to distinct histopathological and clinical features. However the mechanisms underlying the selective vulnerability and tropism for different cell populations remain unknown. We know that αsyn can misfold and acquire different conformations, generating polymorphs / strains that can propagate. These strains can be produced *in vitro* but also amplified from human brains with synucleinopathies. We have previously demonstrated that different strains (produced *in vitro* or amplified from post-mortem brain tissue) are able to propagate differently in cell culture and in rodents brains. We now hypothesize that the selectivity of pathological asyn for specific cellular populations relies notably on strain-specific interactions with intracellular and membrane proteins.
Methods: Using proteomic approaches, we investigate strain-specific interactomes in different cellular populations.
Results: We have identified specific interactomes for different asyn strains as well as common interactors for all strains.
Conclusions: Our aim is to determine which interactions play key roles in strain-specific and selective propagation of pathological αsyn, and to select potential interactors to target in order to prevent or limit the transmission/ amplification of αsyn strains.

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P0757 / #893

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

INTRAGASTRIC ADMINISTRATION OF LOW DOSE ROTENONE POST COLITIS EXACERBATES DAMAGE TO THE NIGROSTRIATAL DOPAMINERGIC SYSTEM IN PARKINSON'S DISEASE: THE PACE ACCELERATES EVEN MORE.

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Aims: Gastrointestinal inflammation and local neurotoxic exposure offer the most in-depth explanation of Parkinson's disease (PD) etiopathogenesis through aberrant aggregation and dissemination of alpha-synuclein (α-syn) aggregate from the gut to the brain. This study investigated the exacerbation of early intestinal inflammation in a progressive PD mouse model.
Methods: To induce chronic colitis, 10 month old C57BL/6 mice were treated with 1% Dextran Sodium Sulphate (DSS) for 3 cycles. After colitis-induction, animals received low dose of intragastric rotenone (which was undetectable in systemic blood or brain) for the next 8 weeks, followed by testing for Parkinsonian behavior and GI phenotypes of inflammation. During sacrifice, intestine, brain stem, and midbrain tissue were isolated and tested for misfolded α-syn, inflammatory markers, and dopaminergic neuronal loss. Gut microbial composition was assessed by 16S rRNA sequencing analysis.
Results: When compared to control, local rotenone exposure for 8 week had no effect on disease severity, barrier junction protein expression (ZO-1, Occludin, and Claudin-1), increase pro-inflammatory genes (TNF-α, IL-6, IL-1β, CCL2), as well as substantial buildup of α-syn in the colon. However, administration of rotenone post colitis exacerbated onset of animal's motor function impairment and rotenone-induced α-syn pathology in colon, which extended upward and resulted in severe dopaminergic neuron loss and astroglia activation in the locus coeruleus, substantia nigra as well as in striatum. In the case of rotenone alone, we found that α-syn induced ChAT+ neuronal death is restricted to the dorsal motor nucleus of the vagus. Colitis animals, on the other hand, demonstrated α-syn induced neuronal loss confined to the Locus coeruleus.
Conclusions: These results strongly suggest that long-term pesticide exposure in conjunction with early inflammatory intestinal milieu can exacerbate progression of PD.

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P0758 / #1276

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

GASTROINTESTINAL INJECTION OF ALPHA SYNUCLEIN PREFORMED FIBRILS INDUCES PARKINSON DISEASE PHENOTYPES IN LRRK2 G2385R ADULT MICE

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Aims: Leucine Rich Repeat Kinase 2 (LRRK2) has long been associated with familial Parkinson's disease (PD). A particular LRRK2 mutation known as LRRK2 G2385R has been shown to be linked with PD in Asian populations in China, Korea and Singapore. Therefore, it is known as an Asian risk variant of PD. Current models for LRRK2 G2385R exists but they lack robust phenotypes which limits them for downstream therapeutic studies. Recently, alpha synuclein preformed fibrils (PFF) have been used to accelerate phenotypes in PD rodent models by operating in a prion-like manner to convert endogenous alpha synuclein in the brain into pathologic PFF. The PFF eventually accumulates in the substantia nigra (SN) of the midbrain where it causes the classic symptoms of PD. Our study aims to establish a LRRK2 G2385R-PFF mouse model induced via gastrointestinal tract injection in order to unravel the mechanisms underlying cell-to-cell *in vivo* PFF propagation.
Methods: In this study, *in vitro* and *ex vivo* experiments were first conducted during which PFF was introduced to LRRK2 G2385R transfected Hela cells, LRRK2 G2385R stably expressed SH-SY5Y cells, and LRRK2 G2385R primary neurons. Subsequently, in the *in vivo* experiment, 3-month-old LRRK2 G2385R mice were injected with PFF in the pyloric stomach and upper duodenum in order to study the gut-brain propagation of PFF (gut-brain axis). Behaviour and biochemistry analyses were performed 9 months post-injection.
Results: Our results showed that PFF treatment induces accumulation of phosphoserine-129 aSN in *in vitro* and *ex vivo* studies. PFF treatment is also shown to increase motor impairment in the LRRK2 G2385 mouse study.
Conclusions: We establish a LRRK2 G2385R-PFF mouse model which would allow unravelling of the mechanisms that underly *in vivo* PFF propagation.

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P0759 / #2636

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

UNDERSTANDING BETA-GLUCOCEREBROSIDASE AND ALPHA-SYNUCLEIN-RELATED LYSOSOMAL DYSFUNCTION AND ITS RESCUE IN PARKINSON'S PATIENT-DERIVED IPSC MICROGLIA AND MACROPHAGES

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Aims: Emerging evidence from biology, genetics and GWAS studies suggest lysosomal disturbances and activation of the innate immune system, including microglia and macrophages, play critical roles in Parkinson's disease (PD) pathogenesis. The majority of PD patients bear a putative damaging variant in lysosomal storage disorder genes (56%) and, in about 10% of PD subjects, the disease associates with mutations in *GBA*, gene coding for the lysosomal hydrolase beta-glucocerebrosidase (GCase). Although alpha-Synuclein and GCase have been linked to PD, their roles in lysosomal dysfunction in microglia and macrophages is poorly understood. In this study, we aimed at investigating lysosomal dysfunction and its rescue in PD-patients iPSC-derived macrophages and microglia by whole-cell and lysosome-specific multi-omics.
Methods: We differentiated iPSC-derived microglia and macrophages from healthy control or PD cases with either *GBA-N370S* variant or *SNCA* triplication. We specifically modulated lysosomal GCase activity levels by treatment with a recombinant GCase-transferrin protein construct (GCase-Brain-Shuttle) and modulated alpha-Synuclein levels with an anti-*SNCA* locked nucleic acid (LNA). The cellular response to rescue of GCase activity and alpha-Synuclein levels was analyzed using LC-MS/MS proteomics and transcriptomics. Moreover, we investigated lysosomal-specific changes in this setup by lysosomal-immunoprecipitation (Lyso-IP) and proteomics
Results: Preliminary analysis of the proteomics results has identified numerous proteins strongly responding to variations in total GCase activity and alpha-Synuclein levels in iPSC-derived macrophages. We have identified alterations in organellar and endoplasmic reticulum membrane biology in response to modulation of GCase activity and alteration of the processing and presentation of endogenous peptides in response to modulation of aSynuclein levels.
Conclusions: Further analysis of the data and investigation of *post-mortem* PD brain tissue of donors bearing the same genetic background could aid the validation of the identified hits, potentially yielding disease-modifying targets.

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P0760 / #2767

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

INTERPLAY BETWEEN GBA AND LRRK2 AND ITS ROLE IN THE PATHOGENESIS OF PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is the first movement disorder in the world and affects about 1% of adults over 60 years of age, increasing with age. Recent studies on the aetiology of PD have identified mutations in the LRRK2 and GBA1 genes as the most important genetic risk factors for developing the disease. We proposed to investigate how LRRK2 kinase activity interacts with GBA and contributes to lysosomal dysfunctions associated with PD pathology.
Methods: We assessed lysosomal beta-glucocerebrosidase (GCase) activity in a model of human cell neuroglioma treated with two selective inhibitors of LRRK2 kinase activity (LRRK2-in-1 and MLi-2) and an irreversible inhibitor (condutirol-beta-epoxide, CBE), incubated 72 hours. Protein levels of GBA, phospho-Rab10, Rab 10 and alpha-synuclein were also quantified by Western blots and/or ELISA assays.
Results: We observed an increase in GCase activity and protein levels after treatment with LRRK2 inhibitors, in addition to a significant decrease in alpha-synuclein levels and in the ratio of phospho-Rab10/Rab10 protein. These results suggest a possible regulation of lysosomal function through the LRRK2 kinase domain.
Conclusions: Although it is not fully understood how LRRK2 and GBA interact, the enhancement of GCase activity appears to promote lysosome degradation of alpha-synuclein. It is also necessary to evaluate the participation of other molecules such as the Rab family or sphingolipid activator proteins as key intermediates in this lysosomal pathway.

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P0761 / #1598

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

A CELLULAR MODEL TO STUDY AGGREGATE MATURATION AND CLEARANCE

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Aims: Reducing alpha-synuclein aggregates may to prevent progression of Parkinson Disease. We have previously demonstrated that cultured cells can spontaneously clear aggregates that result from overexpression of alpha-synuclein. Yet, studying the cellular and molecular pathways that mediate aggregate clearance has remained difficult.
Methods: In order to facilitate the investigation of aggregate clearance we have established a paradigm where aggregates are formed by light-induced polymerization and subsequently followed by time-lapse fluorescence microscopy over 15 hours.
Results: Nearly all cells contained aggregates after 7 hours of light-induced polymerization. Aggregates subsequently resolved almost completely; 50% of cells were without aggregates after 1 hour. When autophagic clearance was blocked by bafilomycin, about 50% of cells remained with aggregates. When cells were illuminated for an extended amount of time, 35% of cells remained with aggregates even after 15 hours of follow-up. Moreover, aggregates obtained by extended light-induced polymerization showed a different immunocytochemical and biophysical profile.
Conclusions: This system allows investigation of aggregate clearance and maturation. Aggregates formed by short-term light-induced polymerization resolve by dissociation and autophagy. Maintaining aggregates for an extended amount of time entails a maturation process that makes aggregates more resistant to cellular degradation.

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P0762 / #1465

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

LYSOSOMAL AND ALPHA-SYNUCLEIN ALTERATIONS AS PREDICTIVE MARKERS OF PARKINSON'S DISEASE IN SUBJECTS WITH IDIOPATHIC REM SLEEP BEHAVIOR DISORDERS

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Aims: Idiopathic REM sleep behavior disorders (iRBD) is one of the most important prodromal markers for Parkinson's Disease (PD). Recent studies highlighted an increased incidence of RBD in subjects with lysosomal disorders, e.g. subjects carrying GBA mutations. We demonstrated that lysosomal-associated alterations in peripheral blood mononuclear cells (PBMCs) provide a unique profile distinguishing PD patient with GBA mutations from non-mutated PD and that GBA mutations, as well as sleep deprivation, are associated to an increased release of extracellular vesicles (EVs). Here we investigated the presence of lysosomal dysfunctions and we quantified intracellular, plasmatic and EV-associated levels of α-synuclein - which can accumulate as a consequence of lysosomal impairment - in subjects with RBD, to identify potential features defining the risk to develop PD.
Methods: We recruited 21 healthy controls, 19 iRBD subjects and 16 PD patients with RBD (PD-RBD). Plasma EVs were isolated by differential centrifugations. Lysosomal proteins' levels (glucocerebrosidase, saposin C, LIMP-2 and cathepsin D) and glucocerebrosidase activity were evaluated in PBMCs through western blot and fluorimetric tests, respectively. A-synuclein levels were quantified using ELISA assays.
Results: The results showed a significant reduction of LIMP-2 and Saposin C levels in PD-RBD patients, but not in subjects with iRBD. Lysosomal alterations in PD-RBD group are accompanied by a slight accumulation of intracellular α-synuclein. Compared to controls, both PD-RBD and iRBD subjects showed an increased plasma exosome concentration associated with higher content of exosomal α-synuclein. Interestingly, a significant increase of free circulating α-synuclein is observed in plasma of iRBD subjects.
Conclusions: This study provides preliminary evidence concerning lysosome alterations associated with RBD, paving the way to the identification of biomarkers predicting the risk of conversion to PD and new targets for possible neuroprotective strategies.

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P0763 / #235

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

LUHMES-DERIVED DOPAMINERGIC NEURONS AS CELL SYSTEM TO MONITOR LYSOSOMAL FUNCTION

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Aims: Differentiated LUHMES cells show many characteristics of dopaminergic neurons, the demise of which is a hallmark of Parkinson's disease (PD). Additionally, LUHMES cells are amenable to transduction, with expression of exogenous cDNAs persisting after differentiation, making them an attractive cell system to study PD-related pathophysiological processes. Dysregulation of the endo-lysosomal network is a major causal factor for development of PD. Proteins whose functions regulate endo-lysosomal pathways are, therefore, attractive candidates for therapeutic intervention. In this study, we aim to establish reporter cell lines based on LUHMES cells for high throughput monitoring of lysosomal parameters in drug discovery pipelines and target validation relevant to PD pathology.
Methods: Cells were transduced with lentivirus for expression of genetically encoded fluorescent reporters monitoring, for example, luminal lysosomal pH. After selection, cells were FACS sorted to obtain homogenous levels of reporter expression. After differentiation into dopaminergic neurons, cells were challenged with different treatments and reporter signal measured in a high-content imaging platform, after fixation. As an alternative to genetically encoded reporters, LUHMES cells were treated after differentiation with cell-permeable fluorescent indicator compounds to monitor different lysosomal parameters, for example activity of acidic hydrolases.
Results: Upon the differentiation protocol, LUHMES cells expressed several neuronal markers of dopaminergic lineage and showed spontaneous electrical activity of neuronal networks. Fluorescent readouts were robust enough to be monitored by high content imaging and changes in fluorescence intensity/distribution, and/or cell morphology were assessed.
Conclusions: Differentiated LUHMES cells have proven to be a valuable cell system for the study of endo-lysosomal function relevant to PD to facilitate target validation in early drug discovery pipelines.

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P0764 / #1775

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

AGGREGATES ARE TARGETED FOR DEGRADATION BY PHASE-SEPARATED PROTEASOME DROPLETS

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Aims: Increasing evidence suggest that αS aggregates and components of the UPS may undergo liquid-liquid phase separation (LLPS). We recently proposed that 'transient aggregate associated droplets' (TAADs) are formed by LLPS to concentrate proteasomes, chaperones and co-factors involved in disaggregation activities around aggregates to facilitate their clearance (Mee Hayes et al., 2022). However, unpublished results from our lab using advanced microscopy techniques show that disperse proteasomes assemble into foci that colocalise with aggregates in neurons in Parkinson's disease tissues but are absent in age-matched controls, suggesting that proteasome foci formation is associated with disease. Here we investigate the molecular properties of aggregate-induced proteasome foci (foci^{aggregate}).
Methods: We performed quantitative 2D and 3D single-molecule localisation microscopy on CRISPR-engineered HEK293 cells to demonstrate that eGFP-tagged proteasomes reorganise into distinct aggregate stress-induced foci following incubation with αS aggregates. Using imaging approaches developed in our lab, we demonstrated the assembly mechanism and physical states of these aggregate-induced foci.
Results: We show that proteasomes reorganise from disperse distribution to foci to target invading αS aggregates internalised by the host cell. Foci^{aggregate} are gel- or solid-like entities that only slowly disperse after 48 hrs incubation and are assembled in a cytoskeleton-dependent manner. Importantly, we demonstrate that foci^{aggregate} contain higher proteasome activity.
Conclusions: Together, our results lead to a model where diffuse proteasomes and redistribute into foci droplets at destinations where higher degradation activity is required for aggregate removal. We further speculate that these dense solid-like foci may not be reversible in disease states – resulting in disruption to cell proteostasis and potentially contributing to disease progression.

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P0765 / #2080

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

INVESTIGATING AUTOPHAGY IN DEMENTIA WITH LEWY BODIES WITH CONCOMITANT ALZHEIMER'S DISEASE RELATED PATHOLOGY

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Aims: Concomitant pathologies are frequently found in individuals with dementia with Lewy bodies (DLB), in particular Alzheimer's disease (AD) related pathologies. Clearance of both hyperphosphorylated tau (HP-*T*) and α-syn can be mediated through the autophagy-lysosomal pathway (ALP), which is impaired as the diseases progress. Therefore, increased HP-*T* in patients with DLB may further impair the ALP, and potentially alter the spread of α-syn pathology through the brain.
Methods: Human *post-mortem* tissue from DLB cases with high and low AD related concomitant pathology was immunohistochemically stained for antibodies against autophagy markers Beclin-1 and LC3 using Tissue Microarray (TMA) slides incorporating 15 anatomically distinct brain regions. Quantification of percentage area of immunopositivity of Beclin-1, LC3, HPT, Aβ, and α-synuclein phosphorylated at Serine 129 (pS129) was carried out using quantitative image analysis.
Results: With respect to Beclin-1, in DLB with low concomitant AD related pathology (up to Braak stage IV) burden of HP-*T* positively correlated with burden of Beclin-1 in cortical regions. This correlation is not observed when including DLB cases exhibiting high levels of AD related pathology (Braak stages V and VI). Interestingly, we observed a strong positive association between Beclin-1 and α-syn pS129 in brain regions involved in motor circuitry. No relationship was observed between Beclin-1 and amyloid beta, or LC3 with any pathology in this cohort. We are currently investigating p62 and co-localisations between autophagy markers and pathological protein aggregates.
Conclusions: Preliminary data suggests autophagy is increased in the early stages of tau deposition in DLB, however a critical point may be reached when autophagy is impaired, and potentially less effective in degrading pathological protein aggregates. Therapies targeting the upregulation of autophagy warrant investigation.

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P0766 / #2464

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

CELL TYPE DIFFERENCES IN FATTY ACID METABOLISM AND STORAGE IN PARKINSON'S DISEASE

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Aims: While commonly believed to be a proteinopathy, recent studies have suggested a role for lipids in Parkinson's disease (PD) pathogenesis. Previously, cell type specific lipid storage changes have been shown in PD patient brains and lipid droplet binding may play a role in the oligomerization of alpha synuclein, the protein present in the disease's hallmark Lewy bodies. The aim of this study was to assess the role of fatty acid metabolism and storage across cell types.
Methods: FABP (Fatty Acid Binding Protein) expression was assessed in PD and control human tissue by immunohistochemistry and western blot to understand fatty acid processing over the course of disease. Wild type SHSY5Ys, alpha synuclein over-expressing SHSY5Ys and H4 cell lines were treated with fatty acids and stained for lipid droplet and lipid droplet associated proteins in both live and fixed cells to assess cell type specific differences in fatty acid processing and better understand this mechanism across cell types.
Results: show that FABP expression is higher in PD human tissue than in age matched controls. SHSY5Y and H4 cell lines show differing fatty acid metabolism and differing levels of resiliency to fatty acid treatment and a fundamental role for alpha synuclein in fatty acid metabolism based on the differences in fatty acid metabolism in WT and alpha synuclein over-expressing SHSY5Y cells lines.
Conclusions: Investigating changes in lipid storage provides powerful insights into disease progression and possible disease modifying treatments. Observing differences in FABP expression in PD human tissue relative to controls, we can understand the role of lipid dysregulation in PD. Furthermore, investigating fatty acid metabolism across cell types may provide further insights into cell type specific changes in lipid metabolism and storage in PD.

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P0767 / #1643

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

AN IN-SILICO STUDY OF PATHOGENIC VARIANTS OF PLA2G6

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Aims: Mutations in the Phospholipase A2 Group 6 (PLA2G6) gene cause neurodegenerative disorders, possibly due to their effects on membrane homeostasis. In-silico prediction methods and molecular docking analyses were performed to investigate the pathogenicity of PLA2G6 mutations.
Methods: We employed PolyPhen 2, MUpro etc and did molecular docking analysis of antipsychotic drugs on the predicted AlphaFold structure of the protein using Schrodinger Maestro software package.
Results: We detected a homozygous Arg741Gln variant in two individuals with AREP, a p.Arg741Trp variant in an individual with INAD, a heterozygous deleterious variant p. Asp377Tyr in three siblings diagnosed with schizophrenia with Parkinsonian features, a p.His117Arg variant in another person diagnosed to have schizophrenia and a p.Ile256Val in a healthy individual. All five mutations were predicted to be damaging and affected conserved aminoacid positions and protein stability.
Conclusions: The in-silico analysis of the pathogenic/deleterious variants of the human PLA2G6 gene shows that these mutations may impact the protein structure and function. The two individuals with AREP developed severe Parkinsonian side effects when treated with antipsychotics for their psychological symptoms. In the patients who had a diagnosis of schizophrenia, the PLA2G6 mutations were predicted to affect protein structure and possibly drug binding. Prolonged treatment with antipsychotics in these patients might have precipitated symptoms of PD and extrapyramidal symptoms in later life. Modelling the links between genetic variation, protein structure, and the impact on cell biology can thus help understand the risk of disease, and its progression, as well as drug response and side effects.

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P0768 / #2169

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

ALTERED APOLIPOPROTEINS AND LIPOPROTEIN-BOUND ALPHA-SYNUCLEIN LEVELS IN CEREBROSPINAL FLUID FROM PARKINSON'S DISEASE PATIENTS – VALIDATION STUDY

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Aims: The aggregation, progressive accumulation and spread of alpha-synuclein are common hallmarks of Parkinson's disease pathology. Also, the genotype of apolipoprotein E, although mostly implicated in Alzheimer's disease, influences Parkinson's disease progression. Previously we described alpha-synuclein interaction with lipoprotein vesicles in human cerebrospinal fluid. We also reported an increased level of ApoE, ApoJ and lipoprotein-bound alpha-synuclein in cerebrospinal fluid from early Parkinson's disease patients compared to matched controls. Additionally, we detected reduced plasma ApoAI in Parkinson's disease patients. The aim of this study was to validate our previous results in the BioFind cohort and to extend the studies to examine correlations with ApoE genotype, demographic variables, clinical symptoms and other biochemical findings available for the Biofind cohort.
Methods: For measuring apolipoproteins levels in cerebrospinal fluid and plasma samples from Parkinson's disease patients and healthy controls we used the Western-Blot technique. Further, for the measurement of alpha-synuclein bound to lipoproteins, we combined the immunodepletion method with the enzyme-linked immunosorbent assay. Statistical analysis was performed using the multiple linear regression method with age, sex and blood contamination as covariates for cerebrospinal fluid, and age and sex for plasma data analysis.
Results: We confirmed increased levels of ApoE, ApoJ and lipoprotein-bound alpha-synuclein in cerebrospinal fluid from Parkinson's disease patients compared to controls. Conversely, we were unable to validate decreased levels of ApoAI in plasma from Parkinson's disease patients. We also observed a correlation between plasma ApoE level and its allelic variants.
Conclusions: Concluding, the obtained data validate our previous findings. Lipoproteins appear to be important in early Parkinson's disease pathology and may be involved in mechanisms behind alpha-synuclein cell-to-cell transfer in the nervous system. Apolipoproteins alteration can be also deployed in algorithms for early disease diagnosis.

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P0769 / #1587

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

PATHOMECHANISMS OF MEMBRANE VERSUS CYTOSOL A-SYNUCLEIN EXCESS CONVERGE ON FATTY ACID METABOLISM

Arati Tripathi[1], Heba Alnakhala[2], Elizabeth Kantor[2], Thibaut Imberdis[2], Lei Liu[2], Saranna Fanning[2], Silke Nuber[2], Ulf Dettmer[2], Nagendran Ramalingam[2], Dennis Selkoe[2]
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Aims: α-synuclein (αS) plays a key role in Parkinson's disease (PD). Although PD is typically 'sporadic', inherited αS missense mutations provide crucial insights into molecular mechanisms. My research focuses on two biochemically divergent αS clinical mutants, E46K and G51D. E46K increases while G51D decreases αS-membrane interactions. I took advantage of a protein-engineering method to amplify G51D (V40D+G51D+V66D = "3D") and systematically compared E46K/3K vs. G51D/3D.
Methods: Cell culture and Neurons using cellular and biochemical assays
Results: My work shows that G51D increased cytosolic αS in neural cells and 3D aggravates this. Both amplified variants 3D and 3K, caused cellular stress in rat primary neurons and reduced growth in human neural cells. Importantly, both 3K- and 3D-induced stress were ameliorated by pharmacologically inhibiting stearoyl-CoA desaturase (SCD) or by conditioning the cells in palmitic (16:0) or myristic (14:0) acid. SCD inhibition lowered lipid-droplet accumulation in both 3D- and 3K-expressing cells and benefitted G51D by normalizing multimer:monomer ratio, as reported previously for E46K. My findings suggest that despite divergent cytosol/membrane partitioning, both G51D and E46K neurotoxicity can be prevented by decreasing fatty-acid unsaturation as a common therapeutic approach.
Conclusions: My findings suggest that despite divergent cytosol/membrane partitioning, both G51D and E46K neurotoxicity can be prevented by decreasing fatty-acid unsaturation as a common therapeutic approach.

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P0770 / #2660

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

A ROLE FOR LRRK2 IN MODULATING THE COURSE OF INFLAMMATION IN INFECTIONS DUE TO RNA VIRUSES

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Aims: We have demonstrated that LRRK2 plays a role in host defences against infection and that the kinase-linked LRRK2 mutant, p.G2019S, confers a heightened immune response. We sought to investigate whether mutations in Lrrk2 combined with pathogenic infections in mice can promote Parkinson disease (PD)-linked pathology in the adult brain of surviving animals.
Methods: We nasally inoculated Lrrk2 p.G2019S (knock-in) mice using established LD50s for two distinct RNA viruses: influenza A virus, subtype H1N1, leading to a pulmonary infection; and vesicular stomatitis virus (VSV), causing encephalitis. Readouts were performed in both the acute stage (6 days post-inoculation) and following resolution (6 weeks post-inoculation) in survivors. Levels of oxidative stress, alpha-synuclein, cytokines/chemokines, and viral burden in the brain were quantified. Further, disease outcomes during acute illness (weight, survival to humane endpoint) were measured. Transcriptomic analysis of infected olfactory bulbs at 2 days post-inoculation are underway.
Results: Following nasal inoculation, both non-neurotropic H1N1 and neurotropic VSV led to heightened oxidative stress and altered alpha-synuclein levels in infected brains compared to mock-treated controls at six weeks post-inoculation; in both male and female mice. We observed no difference in acute outcomes following H1N1 infection between genotypes. However, following VSV infection, Lrrk2 p.G2019S female mice showed increased mortality compared to wild-type mice.
Conclusions: The Lrrk2 p.G2019S mutation modulates the course of illness in a pathogen- and sex-dependent manner. Viral infections, even those that are not neurotropic, can cause changes in the levels of oxidative stress and total alpha-synuclein in the brain as late as six weeks after the acute illness. Our findings identify complex interactions in adult mice between nasally acquired infections due to an RNA virus, sex, and the *Lrrk2* genotype in the development of PD-associated pathological outcomes.

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P0770A / #820

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

ASTROCYTES HAVE THE CAPACITY TO ACT AS ANTIGEN-PRESENTING CELLS IN THE PARKINSON'S DISEASE BRAIN

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Aims: Objectives: Many lines of evidence suggest that accumulation of aggregated alpha-synuclein (αSYN) in the Parkinson's disease (PD) brain causes infiltration of T cells. However, in which ways the stationary brain cells interact with the T cells remain elusive. Astrocytes, the most numerous glial cell type in the brain, become reactive and enter an inflammatory state in neurodegenerative disorders. The aim with this investigation was to clarify the role of astrocytes in antigen presentation and T-cell activation in PD.
Methods: To investigate the role of astrocytes in antigen presentation and T-cell activation in the PD brain, we analyzed post mortem brain tissue from PD patients and controls. Moreover, we studied the capacity of cultured human astrocytes and adult human microglia to act as antigen-presenting cells following exposure to preformed αSYN fibrils.
Results: Our analysis demonstrated that post mortem brain sections from PD patients express high levels of MHC-II, which correlated with the load of pathological, phosphorylated αSYN. Interestingly, a very high proportion of the MHC-II co-localized with astrocytic markers. Importantly, we found both perivascular and infiltrated CD4+ T cells to be surrounded by MHC-II expressing astrocytes, confirming an astrocyte T cell cross-talk in the PD brain. Moreover, we showed that αSYN accumulation in cultured human astrocytes triggered surface expression of co-stimulatory molecules critical for T-cell activation, while cultured human adult microglia displayed very poor antigen presentation capacity.
Conclusions: In conclusion, our data from histology and cell culture studies suggest an important role for astrocytes in antigen presentation and T-cell activation in the PD brain, highlighting astrocytes as a promising therapeutic target in the context of chronic inflammation.

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P0771 / #2001

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

PAIN IN PARKINSON'S DISEASE LINKED TO MICROGLIOSIS AND ALPHA-SYNUCLEIN OLIGOMERISATION IN THE SPINAL CORD

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Aims: Parkinson's disease (PD) is the second most common neurodegenerative disease. It is characterised by motor disabilities due to dopaminergic loss in the substantia nigra. However, non-motor symptoms appear long before diagnosis of PD, with pain being one of the most debilitating symptoms. The aetiology of PD-related pain remains elusive and conventional treatments are ineffective. A-synuclein oligomerisation and aggregation are the key pathological hallmarks of PD and their accumulation has been linked to increased neuroinflammation. Many studies focus on forebrain and midbrain regions; however, the spinal cord is often overlooked. Further histopathological examination of the spinal cord in PD may explain why pain develops in some but not others.
Methods: We used PD-diagnosed and age-matched control human *post-mortem* samples from the spinal cord. PD sample groups were further stratified into those that reported pain (SPPD) and those that did not (No SPPD), using clinical notes. Immunohistochemistry and the proximity ligation assay (PLA) were performed to investigate synucleinopathies and inflammation in the dorsal horn of the spinal cords.
Results: PD cases exhibited no evidence of formic acid-resistant α-synuclein in the dorsal horn. However, α-synuclein PLA positive cell detections were increased five-fold in SPPD compared to the No SPPD cases. Furthermore, SPPD cases exhibited increased $Iba1^+$ and $CD68^+$ staining in the dorsal horns when compared with the No SPPD and control.
Conclusions: Spinal cord samples from PD patients that exhibit pain show no Lewy pathology but do have an increase in pre-aggregate, α-synuclein oligomers. This is coupled with increased activated microglia, indicative of a pro-inflammatory environment in the dorsal horns of PD patients exhibiting pain. Reversal of proinflammatory signals in the spinal cord of PD patients exhibiting pain may be a novel therapeutic strategy.

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P0772 / #2028

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

SYSTEMIC INFLAMMATION TRIGGERED BY LPS ENHANCES THE CLEARANCE OF THE NEUROTOXIC A-SYNUCLEIN BURDEN INDUCED BY A-SYNUCLEIN PREFORMED FIBRILS

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Aims: Preformed fibrils (mPFFs) of α-synuclein (aSyn) can seed and transmit endogenous aSyn to phosphorylate and accumulate into Lewy Body-like structures, which can impair neuronal functions. Progression of Lewy Body-like structures initiated by aSyn mPFFs is slow, therefore our study aims to investigate if systemic immune responses triggered by lipopolysaccharide (LPS) could accelerate the spread of aSyn pathology in mice
Methods: PBS/aSyn mPFFs (3µg) were stereotactically injected into the medial forebrain bundle of C57BL/6 mice, which later was challenged by one single intraperitoneal injection of PBS/LPS (5mg/kg). The behavioral phenotype was examined 90 days after the administration of PBS/mPFFs into the brain, and immunohistochemical techniques were used to detect aSyn pathology and other molecular effects. Additionally, cultured microglia were exposed to PBS/aSyn mPFFs (1µg/mL) and later to PBS/LPS (10ng/mL) to evaluate their functional properties i.e., migration and phagocytosis.
Results: aSyn mPFFs *per se* led to an increased aSyn burden in hippocampal subregions concurrent with a substantial loss of dopaminergic neurons in substantia nigra. Additionally, mice stereotactically injected with aSyn mPFFs displayed impaired fine locomotor functions and spatial hippocampal working memory. Inflammation triggered by LPS attenuated the neurotoxic burden of aSyn in hippocampal subregions while restoring the number of dopaminergic neurons in substantia nigra. This in turn led to restored fine locomotor functions and spatial working memory. In cultured microglia, aSyn mPFFs had little effects on microglial migration and phagocytosis, however aSyn mPFFs and LPS together increased migration and phagocytosis.
Conclusions: While aSyn mPFFs injected into the brain mildly increase the neuropathological burden of aSyn but affecting the behavioral phenotype, non-sterile systemic inflammation enhanced pathological clearance, which is likely driven by enhanced microglial phagocytosis. The study was supported by Health and Medical Research Fund (HMRF 15163051).

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P0773 / #1040

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

UNMASKING MIRNA 486-5P ROLE IN PARKINSON'S DISEASE: INFLAMMATION IN THE SPOTLIGHT

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Aims: Parkinson's disease (PD) has traditionally been characterized by motor impairment but is now considered a multisystemic disorder displaying a plethora of non-motor symptoms, such as, gastrointestinal complaints including constipation, that appear years before PD clinical diagnosis. Remarkably, a direct correlation between gut microbiota and disease progression was found in PD patients. More recently, a novel and interesting link between gut microbiota and microRNAs (miRNAs) was demonstrated. In fact, a recent study showed an enrichment of submucosal miRNA-486–5p in routine colonic biopsies from PD patients as compared to age-matched healthy individuals supporting this miRNA gene targets involvement in PD onset and progression. We aimed to investigate *in vitro* effects of miRNA-486-5p that was shown to be altered in PD patients on mitochondrial-mediated innate immunity activation.
Methods: To do so we overexpressed miRNA-486-5p in Caco-2 cells to model the intestine and SHSY-5Y cells to model neurons and evaluated mitochondrial function and the inflammatory pathway.
Results: We observed that in Caco-2 cells overexpressing miRNA-486-5p mitochondrial membrane potential and ROS levels remained unaltered whereas in SHSY-5Y cells we detected an increase in ROS production. Interestingly in both cell lines, pro-inflammatory IL6 and IL1β levels were found to be increased. Moreover, we found a decrease in ZO-1 levels and occludin disarrangement in Caco-2 cells transfected with miRNA 486-5p indicating a loss of tight junction function. Finally, we observed an increase in alpha-synuclein oligomerization in SHSY-5Y cells overexpressing miRNA-486-5p.
Conclusions: Overall, miRNA-486-5p seems to have a role in the activation of the inflammatory response in both neuronal and intestinal cells. **Funding:** FCT—EXPL/MED-NEU/1515/2021

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P0774 / #2246

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

INFLUENCE OF PERIPHERAL INFLAMMATION IN PARKINSON'S DISEASE USING A RECOMBINANT ALPHA-SYNUCLEIN PRE-FORMED FIBRIL BRAIN-INJECTION MODEL

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Aims: Over the past decades, increasing evidence points towards the interplay of peripheral inflammatory triggers and neurodegenerative diseases. However, the underlying mechanisms of how peripheral inflammation or gut dysfunction adds to Parkinson's Disease (PD) brain pathology remain vastly unknown. Therefore, this project investigates the influence of peripheral or gastrointestinal inflammation on the onset and progression of PD-like symptoms and the involvement of neuroinflammation in these pathological processes.
Methods: We make use of an injection model in which murine recombinant α-synuclein pre-formed fibrils (PFFs) are injected in the striatum of wildtype mice where they seed the misfolding, aggregation and fibrillar deposition of endogenous monomeric α-synuclein. Next, a specific trigger was administered to induce peripheral or gastrointestinal inflammation. Motor function tests were performed on different timepoints following the PFF injection to assess onset of motor dysfunction. The presence of α-synuclein aggregates was confirmed by phospho-S129-α-synuclein staining and Western Blot analysis of brain tissue. Neuroinflammation was assessed by microglia characterization and the loss of dopaminergic neurons was quantified.
Results: This model allows us to study if a peripheral trigger, such as gut inflammation or systemic inflammation, has an effect on the progressive spreading of aggregated a-syn and the development of PD-like phenotypes, as brain inflammation and motor dysfunction. By performing vagotomy we will subsequently establish the specific role of the gut-brain axis in PD.
Conclusions: These data will shed a light on the mechanistic role peripheral inflammation has on the onset and progression of α-synuclein driven pathology in a PFF-injection based PD mouse model, with a focus on gut-brain axis driven neuroinflammation.

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P0775 / #2183

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

PROGNOSTIC SIGNIFICANCE OF PERIPHERAL NEUTROPHILS AND LYMPHOCYTES IN EARLY PARKINSON'S DISEASE

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Aims: To explore whether peripheral blood neutrophils and lymphocytes are associated with longitudinal motor and cognitive decline in patients with early Parkinson's disease (PD) and, to uncover the disease-specific mechanisms underlying these associations.
Methods: In this cohort study, 376 patients with recently diagnosed, drug-naïve PD and 178 matched healthy controls were included. The patients underwent annual assessments, which included the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDSUPDRS) part 3 test to measure motor function and the Montreal Cognitive Assessment (MoCA) to measure cognitive function, for up to 8 years of follow-up. Dopamine transporter (DAT) imaging was performed at baseline and at the 1-, 2-, and 4-year follow-up visits.
Results: At baseline, patients with PD showed higher neutrophil counts and lower lymphocyte counts, resulting in a higher neutrophil-to-lymphocyte ratio (NLR) than that in healthy controls. Higher neutrophil counts were associated with a greater increase in MDS-UPDRS part 3 scores in patients with PD (estimate: 0.25, 95% confidence interval [CI]: 0.12 to 0.37, $p<0.001$). Correspondingly, higher neutrophil levels were related to a greater reduction in DAT activity in the caudate (estimate: −0.007, 95% CI: −0.014 to −0.001, $p=0.046$) and putamen (estimate: −0.0039, 95% CI: −0.0077 to −0.0002, $p=0.042$). However, there were no significant effects of lymphocyte count and NLR on changes in MDS-UPDRS part 3 and MoCA scores and striatal DAT uptake over time.
Conclusions: Among the blood biomarkers, only a higher neutrophil count was associated with faster motor progression along with accelerated nigrostriatal dopaminergic degeneration in patients with PD. The impact of neutrophils and lymphocytes on longitudinal cognitive changes remains unclear.

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P0776 / #685

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

INVESTIGATING THERAPEUTIC EFFECTS OF INDOLE DERIVATIVES TARGETING INFLAMMATION AND OXIDATIVE STRESS IN NEUROTOXIN-INDUCED CELL AND MOUSE MODELS OF PARKINSON'S DISEASE

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Aims: Objectives: Neuroinflammation and oxidative stress have been emerging as important pathways contributing to Parkinson's disease (PD) pathogenesis. Microglia when activated release inflammatory mediators such as interleukin (IL)-β, IL-6, tumor necrosis factor (TNF)-α, nitric oxide (NO), that are toxic to neurons. Inflammation and oxidative stress interact synergistically to augment cytotoxicity. Indole derivative NC009-1 has been indicated to produce neuroprotection in BE(2)-M17 cells expressing fibrils-seeded A53T α-synuclein aggregates.
Methods: Methods: In this study, we further investigated the neuroprotective potential of NC009-1 using 1-methyl-4-phenylpyridinium (MPP^+)-activated human microglial HMC3 cells and sub-chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD.
Results: Results: *In vitro,* NC009-1 alleviated MPP^+-induced cytotoxicity, reduced NO, IL-1β, IL-6 and TNF-α production, and suppressed NLR family pyrin domain containing 3 (NLRP3) inflammasome activation in MPP^+-activated HMC3 cells. *In vivo*, NC009-1 ameliorated behavioral impairments, increased dopamine and dopamine transporter levels in the striatum, and reduced oxidative stress as well as microglia and astrocyte reactivity in the ventral midbrain in MPTP-induced mice. These protective effects were mediated by downregulating NLRP3, IL-1β and IL-6, and their downstream nuclear factor (NF)-κB inhibitor alpha (IκBα)/NF-κB P65 subunit (P65), c-Jun N-terminal kinase (JNK)/proto-oncogene c-Jun (JUN), mitogen-activated protein kinase (MAPK) 14 (P38)/signal transducer and activator of transcription 1 (STAT1), and Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathways.
Conclusions: Conclusions: The study results strengthen the involvement of neuroinflammation and oxidative stress in PD pathogenic mechanism, and indicate NC009-1 as a potential drug candidate for PD treatment.

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POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

PERIPHERAL BLOOD INFLAMMATORY MARKERS IN PARKINSON'S DISEASE

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Aims: The aim of the study was to study the concentration of proinflammatory cytokines interleukin 6 and neurospecific neuroprotein s100 in the blood serum of patients with Parkinson's disease.
Methods: The study included 56 patients with PD, mean age 69.7 ± 3.16 without dementia. The control group included 19 healthy individuals comparable in sex and age with the main group. In patients and the control group, the concentration of pro-inflammatory cytokines IL-6 and neuropeptide s100 were determined by ELISA
Results: The average duration of disease was 4 (3-8 years). The duration of the disease significantly differed in patients with different severity of the disease. In 60% of patients, an increase in IL-6 was observed, and in 10% an increase in the s100 index, which indicates a long-term inflammatory reaction in the development of the immune response. The mean concentration of IL 6 was 10.2±4.09 pg/ml and s100 was 0.087±0.053 ng/ml. The median concentration of IL-6 in patients of the main group was 5.9±1.39, which was significantly lower $p<0.05$, and the concentration of s100 did not differ $p>0.05$.
Conclusions: Patients with PD have significantly higher levels of IL-6 in the blood serum compared to the control group, which may indirectly indicate the involvement of inflammation in the mechanisms of the development of the disease.

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POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

NEUROINFLAMMATION OF THE ENS AS AN INITIAL EVENT IN THE PATHOGENESIS OF PARKINSON'S DISEASE – A MOUSE-BASED STUDY

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Aims: Parkinson's disease (PD) is pathologically characterized by a progressive midbrain neurodegeneration and by intraneuronal alpha-synuclein aggregates. PD patients suffer from non-motor symptoms such as gastrointestinal dysfunction, which can precede classic motor disturbances by many years. Moreover, alpha-synuclein deposits have also been found in the intestinal wall and in the enteric nervous system (ENS), which brings the gut and the ENS in the focus of PD pathogenesis. Increasing evidence suggests that PD may begin in the gut, where inflammatory processes are triggered by a dysbiosis and can initiate alpha-synuclein aggregation in the ENS. From there, pathology may spread to the brain via the vagus nerve. Macrophages are present in the intestinal muscle layer and the ENS and possess a variety of pattern recognition receptors, including toll-like receptors (TLRs), through which they can be activated. Investigation of early intestinal neuroinflammation provides insights into the pathogenesis of PD.
Methods: Distribution of macrophages and the expression of TLRs in the intestinal wall and the ENS of Parkinson mice was investigated by immunostainings and qPCR. TLR expression was also analysed in the mesenteric lymph nodes (MLNs) and the midbrain. Furthermore, the expression of selected inflammatory markers related to antigen presentation and T cell co-stimulation was investigated in MLNs using flow cytometry.
Results: We detected a significantly altered expression of several TLRs and inflammatory markers in both, gastrointestinal and lymphatic compartments, suggesting an enhanced intestinal inflammatory process. Moreover, PD mice showed significantly increased numbers of macrophages within the ENS and the intestinal muscle layer. Furthermore, antigen presentation and co-stimulation was altered in PD mice.
Conclusions: These data substantiate the idea that PD originates in the gut and that Parkinson pathogenesis is triggered by an initial intestinal inflammation.

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P0779 / #337

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

THE MER TYROSINE KINASE MEDIATES THE INTERNALIZATION OF ALPHA-SYNUCLEIN FIBRILS BY HUMAN MICROGLIA

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Aims: TAM receptors (TYRO3, AXL and MerTK) are a family of receptor tyrosine kinases that mediate the immunologically silent phagocytic uptake of cellular debris including apoptotic cells and myelin. Therefore, AXL and MerTK on microglia are receiving increasing attention as potential therapeutic targets in neurodegenerative diseases characterized by aberrant accumulation of cellular debris and aggregated proteins. Involvement of TAM receptors in the clearance of protein aggregates, such as alpha-synuclein fibrils that accumulate in Parkinson's disease (PD), has yet to be demonstrated. The current study aims to investigate the role of AXL/MerTK in the phagocytosis of alpha-synuclein fibrils by human microglia.
Methods: Human induced pluripotent stem cell-derived and primary microglia were employed to study the involvement of AXL/MerTK in the internalization of pre-formed alpha-synuclein fibrils (PFF).
Results: Using knock-down experiments, PFF uptake by human microglia was observed to be dependent on MerTK but not AXL. Accordingly, interaction between PFF and MerTK but not AXL was evidenced by proximity ligation assay. Furthermore, the expression of protein S1 (PROS1), an activating ligand of MerTK, was observed to be significantly lower in microglia from PD patients as compared to healthy control microglia in a single-nuclei RNA-sequencing dataset of substantia nigra.
Conclusions: Our study suggests dysregulation of MerTK activation state in PD substantia nigra, potentially resulting in diminished clearance of alpha-synuclein fibrils by microglia.

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P0780 / #382

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

NEURONAL CONTROL OF MICROGLIA TROUGH THE MITOCHONDRIA

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Aims: Microglia represents the major component of the innate immune system in the brain, responsible for neuronal integrity maintenance. In neurodegenerative diseases as Parkinson Disease(PD), aberrant microglia function is an early event involved in disease progression. Besides microglia, neurons are also capable of activate innate immunity in response to pathogen infection or to danger associated molecular patterns(DAMPs), contributing to the neuroinflammation process by recruiting/activating microglia. Microbial toxins derived from dietary sources or produced by gut microbiota may target neuronal mitochondria, an "ancestral bacteria", that will expose DAMPs leading to neuronal innate immunity activation and neuroinflammation. β-N-methylamino-L-alanine(BMAA), a microbial neurotoxin produced by cyanobacteria, has shown to induce gut-first PD in wild-type mice. Therefore, BMAA showed to be an an environmental trigger for the onset of neurodegeneration.
Methods: To understand the role of microglia in the neuronal innate immunity activation by microbial toxins, N9 microglial cell line was BMAA-treated for 6/24hours.
Results: Contrary to BMAA-treated cortical neurons, in BMAA-treated N9 cells there has no changes in proteins levels associated to NLRP3 pro-inflammatory pathway, nor in the cytokines production/release (TNFα, IL-1β or IL-6), indicating that BMAA by itself is not able to activate microglia inflammation pathways. Seahorse analysis showed that mitochondrial function remains intact in N9 cells after BMAA treatment. Interestingly, when cortical neurons were treated with BMAA for 24hours and co-cultured with N9 cells for additional 24hours, N9 cells show increased levels of NLRP3 pro-inflammatory pathway proteins and impaired mitochondrial function. These results demonstrate that, in the presence of a bacterial toxins, the activation of microglia is dependent on the neuron inflammation signaling.
Conclusions: This work challenges the understanding of neuroinflammation by giving to neurons the principal role in neuroinflammation and microglial activation through mitochondria signaling.

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P0781 / #1314

POSTERS: C01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

IS VIMENTIN AN OVERSHADOWED CLUE FOR UNDERSTANDING PARKINSON'S DISEASE PATHOLOGY?

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Aims: Elevated expression of the cytoskeletal protein Vimentin is a major hallmark of reactive astrocytes. However, in the neurodegenerative brain, vimentin can also be detected in neurons and amyloid plaques. These findings, along with numerous studies from outside the brain, indicate that vimentin is much more than a mere intermediate filament. Despite its clear upregulation in the PD brain, surprisingly little is known about vimentin's role in disease progression. The aim of this study is to clarify the involvement of vimentin in PD pathology.
Methods: Human iPSC-derived astrocytes were exposed to sonicated α-syn fibrils for 3 days and then cultured for 4 additional days without α-syn. Immunocytochemistry was used to follow vimentin expression and study the presence of phosphorylated subunits. Moreover, Western blot analysis of the supernatant and pellet fraction from cell lysates was used to study the "soluble" and "insoluble" astrocytic vimentin species, respectively.
Results: Our results show that human astrocytes express vimentin and also have the capacity to modulate its function via phosphorylation, as confirmed by the presence of Ser39-phosphorylated vimentin (p-vim) positive cells. Interestingly, p-vim was only detected in the insoluble fraction of the cell lysates, suggesting a role besides filament disassembly. Our preliminary results indicate that there is an increase in p-vim in α-syn treated cultures, compared to controls. In addition, western blot analysis showed SDS resistant forms of multimeric insoluble vimentin and differences in the soluble/insoluble ratio between the treatment conditions.
Conclusions: Taken together, our data indicate that not only the levels of astrocytic vimentin can be affected by the presence of intracellular α-syn deposits. Also, its phosphorylation and assembly dynamics are changed, suggesting a role of vimentin in PD pathology.

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P0782 / #2085

POSTERS: C01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

PERIPHERAL IMMUNE CELLS INDUCE A REACTIVE PHENOTYPE IN HUMAN IPSC-DERIVED MIDBRAIN ASTROCYTES

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Aims: Parkinson's disease (PD) is characterised by accumulation of misfolded alpha-synuclein protein and loss of dopaminergic neurons in the *substantia nigra pars compacta*. Involvement of astrogliosis and microgliosis in PD is well established. Recently infiltration of $CD4^+$ T cells, facilitated by a disrupted blood brain barrier was demonstrated in post-mortem brain tissue of PD patients and linked to neurodegeneration. However, the implications of this infiltration on astrocytes remains to be elucidated.
Methods: iPSC-Astros were differentiated from a healthy control individual. $CD4^+$ T cell conditioned media (CD4CM) was collected following stimulation with anti-CD3 and anti-CD28. iPSC-Astros were then stimulated with the CD4CM and their reactivity profile was assessed.
Increasing evidence supports the role of the $CD4^+$ T cell subtype, Th17 in PD. IL-17, their main secreted cytokine is demonstrated to synergise with TNFα, commonly secreted by activated microglia and known to induce reactive astrocytes. We therefore stimulated the iPSC-Astros with IL-17, TNFα or a combination of the two.
Results: Following evidence that CD4CM induced reactivity in the iPSC-Astros we aimed to determine the probable origin of this response. Although IL-17 had a negligible effect, a synergistic relationship between IL-17 and TNFα was observed with regards to astrocytic IL-6 secretion. In order to investigate the potential implications of chronic cytokine exposure on astrocyte reactivity and viability, responses at 72 hrs and 7 days were also assessed. Results suggest that duration of time has no effect on astrocyte reactivity however, cellular integrity may be comprised.
Conclusions: Together this data provides a novel insight into the effect of peripheral immune cell infiltration on astrocyte reactivity in PD.

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P0783 / #229

POSTERS: C01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

HOW ALPHA SYNUCLEIN AGGREGATION IS RELATED TO MITOCHONDRIAL DYSFUNCTION.

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Aims: The aim of the research is to link the dysfunctional state of the mitochondria in neurons to the overexpression of alpha synuclein, aggregation and synucleinopathies and also, on the flip side, elucidate the role alpha synuclein aggregates play in the alteration of mitochondrial morphology, reduced respiratory chain complex activities and impairment of mitochondrial functions, which, further, accelerates aggregation of alpha synuclein.
Methods: The biology of mitochondria, the power house of the cell, which produces ATP, the energy currency of the cell, is intensively studied. Additionally, the several molecular mechanisms responsible for alpha synuclein conformation and aggregation were taken into account and one of the major links to alpha synuclein, a simple protein, becoming aggregated is the dysfunctional state of the mitochondria. Other biological cellular processes studied and documented, in arriving at the conclusion of the research, also include the ubiquitin pathway, proteasomal degradation and several genetics linking alpha synuclein being overexpressed and unable to be degraded, eventually leading to formation of toxic protofibrils and synucleinopathies.
Results: Alpha synuclein overexpression and mitochondrial dysfunction are linked to mutations of genes, and such are implicated in the formation of misfolded alpha synuclein, which later become toxic protofibrils. The misfolded alpha synuclein interfere with dopamine metabolism at the synaptic bud terminal of presynaptic neurons by preventing dopamine repacking to the vesicles, leading to increase metabolism of dopamine into toxic metabolites posing oxidative stress burden on the neurons. Moreover, aggregated alpha synuclein also causes dramatic effects on mitochondrial morphology.
Conclusions: Understanding the complex mechanisms involved in alpha synuclein aggregation, depletion of dopamine and mitochondrial dysfunction give a clearer picture of the underlying mechanisms involved in the pathophysiology of the Parkinson's disease.

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P0784 / #2198

POSTERS: C01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

PROTECTIVE EFFECT OF WHEAT ARABINOXYLAN AGAINST 6-HYDROXYDOPAMINE-INDUCED PARKINSON'S MODEL CELL DEATH IN SH-SY5Y CELLS

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Aims: Wheat Arabinoxylan (WAX) is the main ingredient of the cell walls of wheat with a linear backbone of (1→4)-linked β-d-xylopyranose units with a variety of protective effect; neuroprotective, antioxidant, antiexcitotoxic, bioenergetic. This experiment was performed to investigate the protective effects of WAX against 6-hydroxydopamine (6-OHDA)-induced cell death in neuroblastoma SH-SY5Y cells and the possible molecular mechanisms involved in certain effect. 150 μM of 6-OHDA exposure to SH-SY5Y cells for 24 h caused an effective concentration-dependent cell death observed as a diminution of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) reduction and as an annex the DNA fragmentation formed by apoptotic signaling cascade and altered cells morphology. SH-SY5Y cells incubated for 24h with WAX alone (0.5–10 mg/mL) was not cytotoxic. Though, pre and co- treatment with 6-OHDA (150 μM) for 24 h reduced 6-OHDA-induced toxicity. Transcription factor controlling antioxidant protein Nuclear factor erythroid 2-related factor 2 (Nrf2) augmented by WAX treatment.

Methods: Materials and Methods Drugs and chemicals Cell culture Cell treatments MTT measurement Bright field analysis Detection of cellular Reactive Oxygen Species Western blot Statistical analysis
Results: Nuclear factor erythroid 2- related factor 2 (Nrf2) augmented by WAX treatment. WAX increase the expression of anti-apoptotic B-cell lymphoma 2 (Bcl-2) and antioxidant enzymes heme oxygenase-1(HO-1) and superoxide dismutases(CuZnSOD and MnSOD) to which regulated by Nrf2. WAX treatment may have protective effects against oxidative cell death in Parkinson's Disease (PD) through the feasible cellular adaptive survival responses via fortifying of Nrf2 and upregulation of HO-1, leading to increasing cellular defense potency.
Conclusions: WAX suppressed 6-OHDA-initiated apoptotic cell death in SH-SY5Y neuroblastoma cells by upregulating anti-apoptotic enzyme Bcl-2,
downregulating pro-apoptotic enzymes such as BAX, Cleaved caspase-3 and increasing Nrf-2 activation which further activates Ho-1 and SOD.

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P0785 / #1482

POSTERS: C01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

MITOCHONDRIAL ALTERATIONS IN SUBJECTS WITH IDIOPATHIC REM SLEEP BEHAVIOUR DISORDERS AND THEIR POSSIBLE IMPLICATIONS IN PARKINSON'S DISEASE CONVERSION

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Aims: Idiopathic REM sleep disorders (iRBD) are the most important prodromal marker of Parkinson's disease (PD). Nevertheless, only few studies investigated the mechanisms involved in the development of PD in iRBD subjects. Since the presence of mitochondrial dysfunctions have been linked to sleep disturbances in PD (Smith et al., 2018; Milanese et al., 2019), we explored mitochondrial alterations in fibroblasts of iRBD subjects, in order to characterize a biochemical profile that could predict the onset of PD in this condition.
Methods: The project involved 36 subjects divided in four groups: healthy subjects, subjects with iRBD, iRBD subjects subsequently converted to PD (RBD-PD) and patients who developed RBD after the diagnosis of PD (PD-RBD). Expression levels of mitochondrial proteins were evaluated by western blotting. The rate of mitochondrial respiration was evaluated using an XFe24 Seahorse Analyzer.
Results: The evaluation of the mitochondrial metabolism revealed a reduction in maximal and spare respiration in all groups with RBD, with and without PD. Furthermore, the RBD-PD subjects showed a decrease of ATP production. The impairment of mitochondrial function in RBD-PD and PD-RBD groups was associated with a decrease in the expression levels of mitochondrial complex I, for PD-RBD subjects, and III and V for RBD-PD. These alterations were associated with mitochondrial fragmentation. iRBD subjects showed similar but less severe alterations.
Conclusions: These findings suggest that mitochondrial alterations observed in the fibroblasts of iRBD subjects may predispose to the worsening of the bioenergetic profile observed in RBD-PDs, indicating a potential mechanism underlying the progression of PD in iRBD patients.

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P0786 / #2640

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

TOWARDS STRUCTURAL CHARACTERIZATION OF SYNAPSES IN HEALTH AND DISEASE.

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Aims: Cryo-electron tomography (cryo-ET) of neurons and their synapses has revolutionized our understanding of synaptic (ultra)structure, neuronal transmission, and protein aggregation in neurodegeneration. Achieving molecular resolution, cryo-ET enables deciphering the correlation between disease-associated pathologies and cellular dysfunction. However, methodological challenges concerning sample thinness and synapse targeting still limit applications of cryo-ET for synapse imaging. Here, we aim to improve synapse imaging by cryo-ET to study mechanisms of synaptic function as well as pathological dysfunction in neurodegeneration.
Methods: Cryo-ET enables visualizing synapses at unprecedented, molecular resolution. In contrast to conventional EM, samples are fixed by vitrification – a process in which immobilization of water molecules by rapid freezing precedes ice crystal formation and samples are preserved in a fully hydrated (frozen) and close-to-native state. This allows direct 3D imaging of vitrified synapses without the need for chemical fixation, dehydration or staining and eventually enables structural characterization of macromolecules in their native environment.
Results: To improve synapse imaging by cryo-ET, we developed a workflow of cryo-correlative light and electron microscopy (cryo-CLEM). We combine precise targeting by cryo-CLEM with cryo-focused ion beam milling to achieve unrestricted accessibility to synapses of intact neuronal cultures as well as sample thinness sufficient to accomplish molecular resolution *in situ*. Within our workflow, we introduce different labelling strategies to allow targeting and correlation of synapses in cryo-light microscopy as well as cryo-ET.
Conclusions: Our workflow combines fluorescence-based synapse targeting in intact and extensively interconnected neurons with thinning of synapses prior to cryo-ET to provide sufficient resolution and throughput for functional analysis. Thereby, our work lays the foundations for characterizing the molecular correlates of synaptic function as well as dysfunction in the context of neurodegenerative diseases.

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P0787 / #1248

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

EFFECTS OF ANTISEIZURE DRUGS ON EPILEPTIC ACTIVITY IN TRANSGENIC MICE EXPRESSING A53T HUMAN A-SYNUCLEIN

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Aims: The goal of this study was to evaluate the effectiveness of anti-seizure drugs (ASDs) in attenuating α-synuclein-dependent epileptic activity. New evidence shows network hyperexcitability can accelerate synaptic and cognitive deficits in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). While 90% of epileptic activity is detected during sleep in patients with Alzheimer's disease, epileptic activity during different vigilance states in PDD or DLB is poorly understood.
Methods: Transgenic mice expressing the A53T mutant human α-synuclein (TgA53T) were used as a model of motor and cognitive decline in PDD and DLB. Using cortical electroencephalography with electromyography, epileptic events 24 hours before and after intraperitoneal injection of ASDs were measured and evaluated over all vigilance states. Pathological high frequency oscillations (HFOs), a biomarker of epileptogenesis, are being quantified before and after drug administration using RIPPLELAB. We tested the following ASDs: vigabatrin (n=7), lacosamide (n=6), brivaracetam (n=6), gabapentin (n=6), valproic acid (n=4), carbamazepine (n=4), phenobarbital (n=3), lamotrigine (n=3), and phenytoin (n=3).
Results: Preliminary studies indicate vigabatrin (300mg/kg) and lacosamide (30mg/kg) are most effective in acutely reducing interictal epileptiform events by 77% (p=0.03, paired t-test) & 42% (p=0.06, paired t-test) respectively. The number of HFOs (80–200Hz) was higher in TgA53T mice than in wild-type mice and HFO number correlated with number of epileptic events (Pearson r=0.6, p=0.007).
Conclusions: Vigabatrin and lacosamide suppress epileptiform activity in the TgA53T model suggesting these ASDs as a novel treatment for cognitive dysfunction in DLB and PDD through a GABA and/or sodium channel mechanisms. HFOs could be useful biomarkers of epileptic activity in this model. ASD-induced reversal of synaptic and cognitive deficits would provide evidence that epileptic activity plays a causal role in αS-dependent pathology.

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P0788 / #2044

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

PROTEOMIC ANALYSIS OF THE HUMAN HIPPOCAMPUS IDENTIFIES NEURONAL PENTRAXIN 1 AS A SYNAPTO-AXONAL TARGET IN LATE-STAGE PARKINSON'S DISEASE

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Aims: While symptomatic treatment is available for motor symptoms of Parkinson's Disease (PD), non-motor complications - such as dementia - result in diminished life quality for patients, and are far more difficult to treat. In this study we analyzed PD-associated alterations in the hippocampus of PD patients, a brain region strongly affected by PD dementia.
Methods: We focused on synapses, analyzing the proteome of postmortem hippocampal tissue (16 PD/14 control cases) by mass spectrometry. Whole tissue lysates (WTL) and synaptosomal fractions (SF) were analyzed in parallel. Proteomic analysis was conducted via DIA-MS/DDA-MS (for WTL and SF respectively). To assess/validate the expression of NPTX1 in human brain tissue, we used immunohistochemistry (on paraffin embedded postmortem hippocampal tissue) and western blotting (fresh frozen postmortem tissue). To mimic increased levels of NPTX1 observed in PD samples, recombinant NPTX1 protein was added to primary mouse hippocampal neuron cultures
Results: Differential analysis combined with bioinformatic network analyses identified 55 significantly differentially expressed proteins between PD and controls, while analysis of SF yielded 194 DE proteins. Neuronal pentraxin 1 (NPTX1) was found significantly up-regulated in PD samples. Network analyses revealed its interaction with proteins present in the synaptic compartment. Modulation of NPTX1 protein levels in primary hippocampal neuron cultures validated its role for synapse morphology. Our analysis suggests that NPTX1 contributes to synaptic pathology in late-stage PD and represents a putative target for novel therapeutic strategies.
Conclusions: Our results describe alterations in PD hippocampal proteome, identifying NPTX1 as a novel target for disease-modifying treatment approaches. We suggest a new role for NPTX1 in the synaptic pathology in PD/PD dementia. Our data speak for additional investigation of the mechanism of extracellular NPTX1 elevation and suggest further studies analyzing whether inhibition of NPTX1 has beneficial disease-modifying effects in PD.

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P0789 / #2745

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

AUF1 IS A MULTIFACETED REGULATOR OF ALPHA-SYNUCLEIN EXPRESSION

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Aims: Genetic and biochemical studies have established a central role for alpha-synuclein (SNCA) accumulation in the pathogenesis of Parkinson's disease. Delineating and interfering with the physiological mechanisms that control SNCA expression is one strategy for limiting disease progression. To this end, the 2550-nt-long, AU-rich 3'UTR of SNCA mRNA was investigated as a potential regulatory target of the AU-Rich Element RNA-Binding Protein 1 (AUF1). AUF1 expression has been linked to mRNA instability and decay by facilitating microRNA-mediated silencing and potentially recruiting the CCR4/NOT deadenylase complex.
Methods: We pulled down AUF1 from murine brain extracts using biotinylated SNCA 3'UTR RNA as bait. Then, we analyzed the effect of AUF1 overexpression and silencing on SNCA mRNA stability, levels and localization and pinpointed the underlying mechanisms.
Results: AUF1 binds to the 3'UTR region of SNCA mRNA but not the 5'UTR or CDS. AUF1 overexpression reduced SNCA mRNA levels by destabilizing its mRNA, while AUF1 silencing showed the opposite effect. This consequence occurs independently of the SNCA inhibition mediated by miR-7 or miR-153. The destabilized mRNA displayed a shorter poly(A) tail due to CCR4/NOT deadenylase complex engagement upon excess AUF1. AUF1 overexpression also decreased SNCA mRNA association with ribosomes and decreased SNCA protein synthesis. In the case of shRNA-mediated AUF1 silencing, the increased SNCA mRNA levels did not coincide with poly(A) tail extension but rather with nuclear SNCA mRNA retention, resulting in decreased SNCA protein output.
Conclusions: These results indicate a multimodal mechanism by which AUF1 regulates SNCA mRNA expression and confirm the long-hypothesized link between AUF1 with the CCR4/NOT deadenylase complex on target mRNAs.

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P0790 / #1382

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

NON-CODING RNA DYSREGULATION UNDER GUT MICROBIOTA DYSBIOSIS IN RAT MODEL OF PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a chronic neurodegenerative disease associated with aggregation of α-synuclein that can be induced at various levels including the enteric nervous system (ENS). Non-motor symptoms (NMS) in PD are various and affect Parkinson's patient's life but are underestimated. Recently, a link between gutmicrobiota dysbiosis and PD has been established, suggesting its involvement in the appearance and propagation of α-synuclein aggregates in the ENS through the gut-brain axis. Thus, leading to PD pathogenesis. Although, the molecular pathways underlying the progression of PD from the ENS are unclear. The present project aims to study the disruption of the intestinal microbiota and the aggregation of α-syn proteins in the ENS with a particular interest in the expression of the enteric neuron's lncRNA in rat model of PD.
Methods: Our methods consist of analysing existing RNA-seq databases to select differentially expressed lncRNAs in brain samples of PD patients and control individuals. Then, these centrally identified lncRNAs will be explored in the rat models of PD to confirm the presence and dysregulation of these lncRNAs in the ENS.
Results: Our analysis showed dysregulation of several types of RNAs including some lncRNAs . The overlappe of differentially expressed genes revealed 10 lncRNAs that are communly dysregulated in the analysed datasets. From this lncRNAs MIR9-1HG, DNMBP-AS1, DOCK9-AS2, LINC01497, OTX2-AS1, LINC00645, CTB-131B5.5, RMST, and HNRNPD-1 show low level of expression and RP11-6O2.3 with high level of expression. This centrally dysregulated lncRNAs will be validated in a rat model of PD.

Conclusions: Our study should illustrate the alteration of lncRNA in the ENS of PD that may lead to progression of the disease and should lead to additional strategies for RNA therapy in PD

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P0791 / #448

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

SINGLE NUCLEI RNA-SEQ REVEALS OLIGODENDROCYTES AND THEIR PROGENITORS AS VULNERABLE CELL TYPES IN THE PARKINSONIAN BRAINS WITH GBA AND LRRK2 RISK MUTATIONS

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Aims: Among the approximately 95% of patients with Parkinson's disease (PD) that are known to be idiopathic, there are individuals carrying certain genetic variants that significantly increase their likelihood of developing PD, including LRRK2 (G2019S) and GBA (N370S; L444P). Although much research has been conducted on PD, no study has yet explored the differences between these two risk mutations in terms of investigating gene expression signature and disease trajectory at the cellular level and also to come up with the brain cells which are likely to be more vulnerable to PD. In addition, several recent studies have shed light on the role of glial cells in the brain, which has been underestimated in PD research.In our study, we aimed to make an analogy between LRRK2-PDs and GBA-PDs at the unprecedented resolution of single-cell transcriptomics and investigate the contribution of glial cells to PD outside of midbrain.
Methods: We used parallel single-nuclei RNA sequencing and bulk RNA sequencing to investigate the transcriptional signatures in the mesocortex and neocortex of parkinsonian post-mortem brains at Braak 5-6 stage compared with healthy controls.
Results: As our primary results, we identified Oligodendrocytes (ODC) and their progenitor cells which are known as Oligodendrocyte Precursor Cells (OPC) as vulnerable cells since they highly express the PD risk loci discovered by GWAS. We further looked into these cells and found up- and downregulation of certain genes and also of genes predicted to be associated with the pseudotime, put differently, dynamically expressed genes. At the moment, our results are pending validation of curated genes within these pathways by immunohistochemistry.
Conclusions: As we have found so far, there are specific transcriptional signatures that show a relatively distinct involvement of PD-implicated pathways in GBA-PD compared to LRRK2-PD.

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P0792 / #559

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

TARGETED LONG-READ RNA-SEQUENCING REVEALS COMPLEX SNCA TRANSCRIPT USAGE

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Aims: Parkinson's disease is the most common neurodegenerative movement disorder and the fastest growing neurological disease. Overwhelming evidence suggests that the abnormal aggregation of the protein α-synuclein, encoded by the SNCA gene, is the causative agent of Parkinson's, driving the neuronal death and cellular dysfunction characteristic of the disorder. However, the mechanisms by which α-synuclein aggregates and causes cellular toxicity, and the role in which specific SNCA transcript isoforms play in this process, are yet to be fully elucidated.
Methods: Here, we use targeted long-read RNA-sequencing to dissect SNCA transcript usage in both highly enriched iPSC-derived midbrain dopaminergic (mDA) neurons, the vulnerable cell type in Parkinson's disease, and across multiple brain regions.
Results: Using this approach, we have identified a high number of transcripts in both iPSC-derived mDA neurons and post-mortem brain. Novel transcripts identified include those with alternative 5' start sites, variable 3' UTR lengths, novel exon skipping events, and novel exon inclusions. Interestingly, we reveal that novel protein coding transcripts are some of the most abundantly expressed transcripts. We further demonstrate that *SNCA*transcript usage is altered in iPSC-derived midbrain neurons carrying *SNCA* mutations compared with controls.
Conclusions: Overall, we provide new insight into the transcriptional landscape of *SNCA* and demonstrate that the genetic risk may impact on transcript usage, and not only through expression levels and aggregation propensity.

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POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

MUTANT TMEM230 IMPAIRS MITOCHONDRIA TRANSPORT AND INDUCES NEURODEGENERATION

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Aims: Recent studies have identified a new Parkinson's disease (PD) PD associated gene, *TMEM230* (transmembrane protein 230). However, the pathological roles of TMEM230 and its variants are not fully understood. We are interested in studying the PD-linked mutant *TMEM230* variants in neurodegeneration and exploring the underlying molecular mechanisms.
Methods: *TMEM230* gene encodes two protein isoforms. Isoform2 is the major protein form (~95%) in human. In this study, we used TMEM230 isoform II constructs including wild-type (WT) and four reported PD-linked mutation constructs (Y92C, R141L, 184Wext*5, and 184PGext*5). We employed in vitro cell cultures including HEK293 cells and mouse primary neurons to study the effects of TMEM230 up or down expression using genetic tools and living cell imaging technology.
Results: In cultured HEK293 cells, ectopic expression of WT and PD-linked mutant TMEM230 variants dramatically induced apoptotic cell death. Mutant TMEM230 caused cell toxicity at an increased severity than WT TMEM230. Expression of TMEM230 increased mitochondrial reactive oxygen species (ROS) levels, decreased cellular ATP, activated caspase 3/7, and increased poly(ADP-ribose) polymerase-1 (PARP1) cleavage. Treatment with *N*-acetylcysteine (NAC; an ROS scavenger) or Z-VAD-FMK (a caspase inhibitor) significantly attenuated TMEM230-induced apoptosis. In primary culture neurons, overexpression of WT and mutant TMEM230 or knockdown of endogenous TMEM230 induced neurodegeneration and impaired mitochondria transport at the retrograde direction in axons. Mutant TMEM230 caused more severe neurotoxicity and mitochondrial transport impairment than WT-TMEM230 did.
Conclusions: These findings provide novel insight into the molecular mechanisms of mutant TMEM230-induced neurodegeneration underlying PD pathogenesis.

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P0795 / #2581

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

KARYOPHERIN ABNORMALITIES IN ALPHA-SYNUCLEIN MEDIATED NEURODEGENERATIVE DISEASE

Daulet Sharipov[1], Erika Bereczki[2], Richard Killick[3], Tibor Hortobagyi[4], Claire Troakes[5], Dag Aarsland[6], Frank Hirth[7]
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Aims: Alpha-synuclein (ASYN) is an intrinsically disordered protein prone to phase separation from soluble monomers to irreversible aggregates found in the cytoplasm and nucleus of Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and Parkinson's Disease Dementia (PDD). While nuclear accumulation of ASYN has long been controversial and overlooked, phase separation is associated with nuclear transport receptors called karyopherins that can also act as disaggregases against misfolding proteins. Thus, karyopherin abnormalities and nuclear ASYN have been implicated in synucleinopathies, but their role in disease formation remains enigmatic.
Methods: Here, using a multi-disciplinary approach, we characterised levels and localisation of karyopherin and ASYN in human post-mortem brain tissue areas BA9, BA24 and B40 of Healthy Controls (HC), PD, DLB and PDD. We also used differentiated human SH-SY5Y cells and *Drosophila* to accumulate wildtype and mutant ASYN and established the levels, localisation and effect on karyopherin.
Results: We found nuclear accumulation of monomeric and aggregated forms of ASYN in BA9 of PD, PDD and DLB vs HC. Further analysis revealed karyopherin alpha 3 (KPNA3) colocalised with ASYN in the nucleus of synucleinopathies but not in HC, which was accompanied by cytoplasmic depletion and nuclear accumulation of KPNA3. Proteomics analysis and qWB of BA9 identified karyopherin alterations in PD, DLB and PDD. *Drosophila* and SH-SY5Y cell experiments further revealed that accumulating ASYN caused downregulation and mislocalisation of KPNA3 and progressive motor impairment in *Drosophila* , which was exacerbated by A30P mutant ASYN.
Conclusions: These findings establish nuclear accumulation of ASYN together with altered levels and localisation of KPNA3 in PD, PDD and DLB that can be induced in *Drosophila* and SH-SY5Y cells, suggesting a direct role of karyopherin abnormalities in the onset and progression of neurodegenerative synucleinopathies.

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P0796 / #2250

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

THE LEVELS OF CHAPERONE GRP78 INCREASE WITH RESPECT TO LEWY PATHOLOGY PROGRESSION IN THE AMYGDALA OF PATIENTS WITH PARKINSON'S DISEASE.

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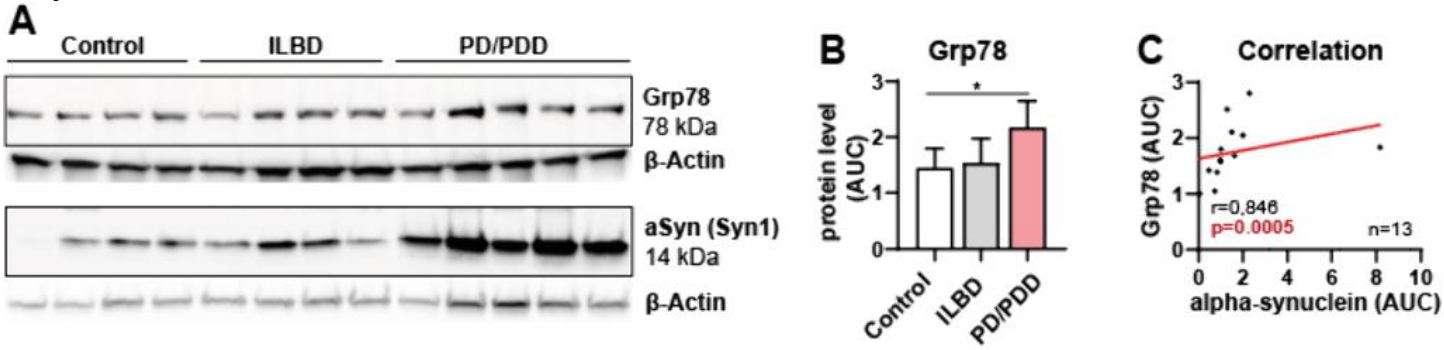
Aims: The unfolded protein response, its role in the pathogenesis of Lewy body diseases, and its extent in the brain during disease progression have not yet been fully understood. In a recent study, we systematically analyzed its potential activation through changes in Grp78 and eIF2alpha levels in the human brain by focusing on a variety of brain areas in different stages of the disease.
Methods: In the study, we used postmortem brain tissue from 40 subjects in total - symptomatic Parkinson's disease/Parkinson's disease with dementia/Dementia with Lewy bodies patients (Braak stage 5-6, n=12), patients with incidental Lewy body disease (Braak stage 1-4, n=16) and healthy controls (n=12). Frozen tissue and formalin-fixed paraffin-embedded sections were used for western blot and immunohistochemistry/immunofluorescence analysis. The areas analysed included the oblongata, pons, amygdala, striatum, temporal, entorhinal, occipital, and frontal cortex.
Results: Grp78 levels were increased in the amygdala of the patients (P<0.05) and positively correlated with alpha-synuclein levels (r= 0.866, P=0.0005). Similarly, levels of total eIF2alpha were increased in the striatum of the patients (P<0.01), and positively correlated with alpha-synuclein levels (r=0.721, P<0.0001). Further, Grp78 was downregulated in the frontal cortex (P<0.05) of the patients. Additionally, Grp78 was upregulated in substantia nigra of the patients (immunohistochemistry). Interestingly, Grp78 rarely colocalised with mature Lewy bodies and Lewy neurites in confocal microscope
analysis.



Conclusions: The levels of Grp78, the regulator of unfolded protein response, increase with the progression of the Lewy pathology in the amygdala and positively correlate with alpha-synuclein levels. Similar results could be observed when analyzing eIF2alpha levels in the striatum. The study suggests an uneven distribution of ER stress in the human brain, thus helping to focus future studies towards analyzing specific areas of the brain.

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P0797 / #174

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

PROTECTIVE EFFECTS OF NOVEL 4-PBA DERIVATIVES ON THE ROTENONE-INDUCED NEUROTOXICITY IN SHSY5Y NEUROBLASTOMA CELLS

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Aims: Aggregation of α-synuclein (α-Syn) in the Substantia nigra region marks a major pathological hallmark of Parkinson's disease (PD). So, α-Syn aggregates represent an attractive target for drug development. Chemical chaperones are small moieties known to prevent the aggregates pointing towards amelioration of such diseases. 4-Phenyl butyric acid (4-PBA), is one such chemical chaperone with well-documented neuroprotective potential, however, a higher dosage is required to obtain noticeable effects, calling for further optimization. The current study aims to design, develop, and validate novel 4-PBA derivatives to come up with compounds having better chaperone ability.
Methods: Herein, we designed a library of over 10,000 novel derivatives of 4-PBA and studied their binding potential with mutated α-Syn protein (PDB ID: 6UFR) using Schrödinger software. Top-identified lead compounds filtered on the basis of high-dock scores and good ADME profiles were synthesized in the laboratory. The compounds were examined for their anti-aggregation capabilities using the Dithiothreitol (DTT) assay and the Thermal aggregation assay. The new compounds' ability to prevent rotenone-induced neurotoxicity in SHSY5Y neuroblastoma cells was examined using the MTT cytotoxicity assay for additional validation.
Results: Out of a total of 10,000 derivatives, the top 4 compounds 3P1, 3P2, 5P1, and IP1 showed potent inhibitory activity against α-Syn, with dock scores in the range of -7.4 to -7.9 in comparison to the reference 4-PBA (-6.152). The compounds demonstrated good anti-aggregation ability under *in vitro* settings. Further validation using MTT assay revealed that IP1 significantly suppressed rotenone-induced toxicity in SHSY5Y neuroblastoma cells to around 40% when compared to the toxicity induced in the rotenone alone exposed cells.
Conclusions: Novel compounds 3P1, 3P2, 5P1, and IP1 demonstrated significant neuroprotective ability thus making them potential candidates for the development of anti-PD medications.

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P0798 / #1731

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

CRYO-ELECTRON MICROSCOPY STRUCTURE OF ALPHA-SYNUCLEIN FIBRILS OF DEMENTIA WITH LEWY BODIES: PMCA-AMPLIFIED AND MUTATED NAC DOMAINS (E83Q)

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Aims: Synucleinopathies are neurodegenerative diseases characterized by the accumulation of misfolded alpha-synuclein (aSyn) within neurons and glia.The similarities and differences between synucleinopathies might be correlated with the atomic structure of aSyn fibrils in each disease. There is evidence that multiplication of the SNCA gene coding for aSyn is sufficient to cause PD and DLB. Understanding the structure of fibrils formed bySNCA mutations leads to a better understanding of the intracellular processes influenced by specific fibrillar assemblies. Here we present the high-resolution structure aSyn fibrils amplified by protein misfolding cyclic amplification (PMCA) from DLB patient brain and aSyn recombinant fibril ofE83Q mutation obtained by using cryo-electron microscopy.
Methods: The amplified fibrils were prepared according to Burger *et al.*[1], and the E83Q mutation fibrils according to Kumar *et al*. [2]. A Titan Krios microscope was used to acquire the cryo-EM data sets, which were processed with the RELION software. aSyn filaments were manually picked from the micrographs. To select suitable segments for further processing, reference-free 2D classification was performed with all data sets. Based on filament cross-over distances observed in micrographs, a 3D reference model was built, using 2D class averages and a rise estimate of 4.75°A.
Results: PMCA-amplified aSyn fibrils from DLB brain showed a similar appearance as previously reported for PMCA-amplified aSyn fibrils from PD and Multiple System Atrophy (MSA) brain, resembling polymorph 6b [1]. In contrast, the fibrils generated from E83Q aSyn monomers indicate the presence of at least two different fibril polymorphs.
Conclusions: High-resolution structural information of fibrillar aSyn in DLB is essential to characterize the disease and correlate it with a specific aSyn fibril strain. 1. D. Burger,et al., BioRxiv, 2021 2. S. T. Kumar,et al., Scienceadvances, 2022.

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P0799 / #1458

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

NEW INSIGHTS FROM MULTIMODAL MASS SPECTROMETRY: COMPARING THE IMPACT OF METAL IONS ON THE AGGREGATION OF ALPHA-SYNUCLEIN AND HIAPP

Francesca Bellingeri[1], Meng Li[2], Yuko Lam[2], Mark Barrow[2], Peter O'Connor[2], Joanna Collingwood[1]
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Aims: Strong evidence suggests there is an interplay between protein aggregation and metal ions, and localised alterations in metal levels are observed in neurodegenerative diseases. Aggregation of alpha-synuclein and human islet amyloid polypeptide (hIAPP) are hallmarks of Parkinson's and type-2 diabetes (a risk factor for Alzheimer's) respectively and associated with cognitive decline. This study monitored the effect on alpha-synuclein and hIAPP aggregation of bioavailable metals, including physiologically essential elements and those associated with environmental exposure.
Methods: Trapped-Ion-Mobility (TIMS) Mass Spectrometry (MS) was implemented to monitor protein conformational shifts during incubation with metal ions. Time-Of-Flight (TOF) MS was used to track changes in relative quantitation between different oligomer species during aggregation, and Fourier-Transform-Ion-Cyclotron-Resonance (FTICR) MS was combined with several fragmentation methods [1] to gain further information on protein structure.
Results: Mass spectrometry methods enabled analysis of micromolar protein concentrations. TIMS-MS revealed distinct conformational profiles for oligomer species, including the presence of multiple possible conformations for hIAPP dimer, and allowed us to observe oligomer signals which were too low intensity to be detected using other MS methods. TOF-MS of alpha-synuclein and hIAPP incubated with metal ions revealed varying binding profiles across samples, including aggregation inhibition and secondary solution effects. FTICR-MS fragmentation methods allowed for high protein sequence fragment coverage which will aid in future metal binding site determination.
Conclusions: Complementary MS techniques enabled precise monitoring of aggregation of alpha-synuclein and hIAPP in the presence of physiologically relevant metals, including conformational shifts observed and tracked during initial aggregation. Protocols developed through this work provide a multi-modal approach for gathering information about peptide aggregation and the impact of metals on this process. [1] Lermyte, Everett, Brooks, Bellingeri et al, 2019, Cells DOI: 10.3390/cells8101231

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P0800 / #2620

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

ASSESSMENT OF ROTENONE FACILITATED A-SYNUCLEIN SPREADING AND NEUROTOXICITY IN MURINE A-SYNUCLEIN PFF MODEL OF PARKINSON'S DISEASE.

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Aims: To investigate whether rotenone administration can enhance α-synuclein spreading in the dopaminergic neurons. To investigate whether rotenone administration can enhance dopaminergic neuronal loss in the substantia nigra. To investigate whether rotenone administration can enhance neuro-inflammation.
Methods: Human α-synuclein PFF seeds are injected into mouse (C57BL6) striatum by stereotactic surgery, after which 2.5mg/kg.body-weight rotenone is administered intraperitoneal once daily for four consecutive weeks. Animals are sacrificed twenty-four hours after the last injection for immunohistochemical analysis.
Results: Our preliminary immunofluorescence analysis suggests that 2.5mg/kg. body weight rotenone enhances the spreading of endogenous synuclein in the cortex and SNc area. We observed a decrease in the staining intensity for Dopamine transporter in striatal brain sections and a decrease in the number of TH neurons in the SNc of the experimental group (PFF + Rotenone) as opposed to the control (PFF + Vehicle). We also observed an increased activation of microglia in the SNc in mice treated with rotenone and inoculated with PFF as compared to the control group.
Conclusions: Our results indicate that administration of above-mentioned dose of rotenone causes enhancement of α-synuclein spreading, neurotoxicity, and neuro-inflammation; thereby laying a foundation for the development of a strong PD animal model that can replicate key pathological processes underlying PD. Such a model system would be useful in identifying therapeutic targets that respond to α-synuclein pathology which would be useful in the development of effective treatment strategies for PD patients.

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P0801 / #377

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

THE GUT-IMMUNE-BRAIN AXIS IN PARKINSON DISEASE

Emanuel Candeias[1], Inês Melo-Marques[1], Mario Munoz[1,2], A Raquel Esteves[1,2], João Magalhães[1,3], Diogo Carneiro[1,4], Nuno Empadinhas[1,2], Sandra Cardoso[1,5]
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Aims: Parkinson disease (PD) patients may report non-motor symptoms decades before clinical diagnosis, exhibiting features such as constipation and intestinal dysbiosis in the prodromal period. Moreover, arising evidence suggest that intestinal homeostasis is regulated by gut microbiota that may modulate gut-derived inflammation, impacting the central nervous system (CNS) with implications in the development of neurodegeneration. Herein, we hypothesized that PD patients gut microbiota-mediated intestinal immune alterations triggers PD-related neurodegeneration.
Methods: For this purpose, we challenged the gut-immune-brain axis of wild-type mice (WT) through colonization with human fecal material from a healthy-control (HC) and a PD patient. To complement, human substantia nigra and human blood from controls and PD patients were also evaluated.
Results: We observed a clear increase in gut inflammation (TNF-α, IL-1β, IL-8 and IL-17 levels) that may be correlated with an accumulation of α-synuclein aggregates in PD transplanted mice. In addition, we demonstrated an increase in pro-inflammatory cytokines in the blood, compatible with systemic inflammation, and again an accumulation of α-synuclein oligomers in PD fecal material treated mice. Consequently, PD gut microbiome induced a significant decrease in the levels of striatal dopamine, together with symptoms of motor dysfunction (Open field, hindlimb clasping and inverted grip tests). Accordingly, subtantia nigra and blood of PD patients showed an increase in neuroinflammatory markers, systemic innate immune responses and α-synuclein aggregation. Interestingly, mitochondrial fragmentation occurred in enteric neurons and in mesencephalic neurons in PD microbiome transplanted mice, which implicates mitochondrial dysfunction in the activation of neuronal innate immunity and neuroinflammation.
Conclusions: Altogether, our results suggest that a PD dysbiotic gut may be the trigger of PD-like pathogenesis in WT mice, which supports the gut-to-brain hypothesis for sporadic PD.

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P0802 / #408

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

TRANSCRIPTOMIC ANALYSIS OF CLINICAL MILESTONES IN PATIENTS WITH PARKINSON'S DISEASE

Raphael Gerraty, Magali Haas, Lee Lancashire
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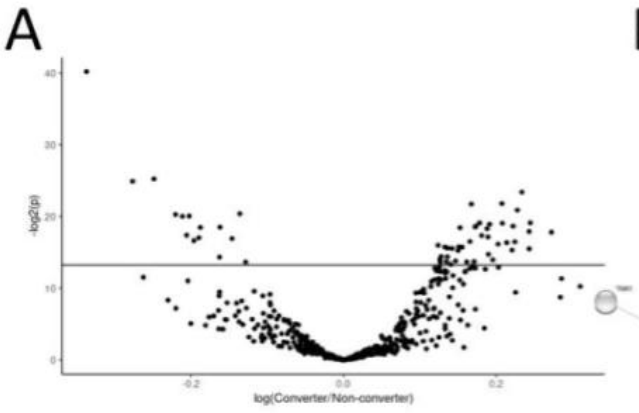
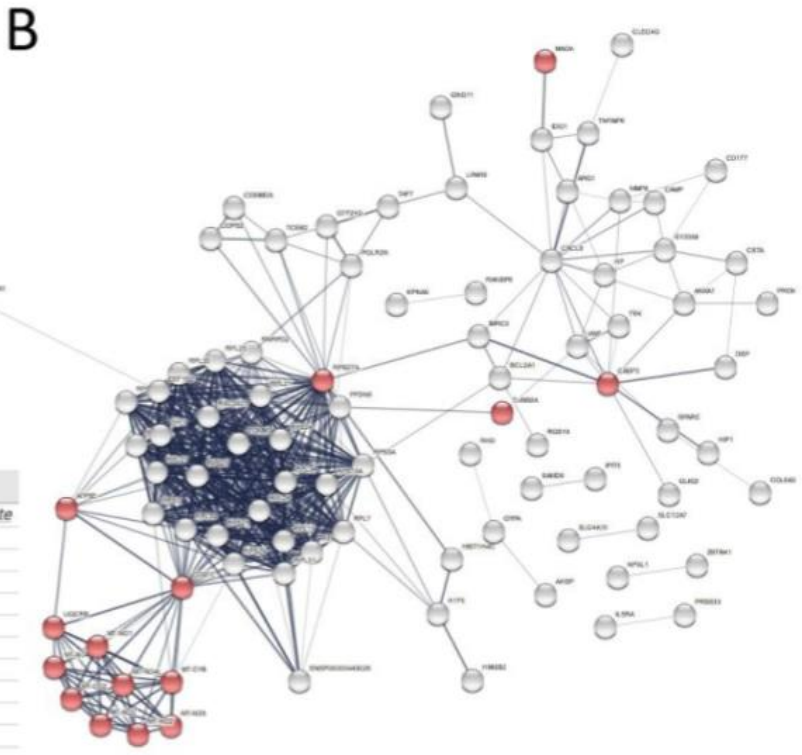
Aims: Parkinson's disease (PD) patients vary widely in symptom trajectories, and the mechanisms underlying this heterogeneity remain largely unknown. Here we tested whether RNA expression patterns distinguish patients reaching clinical milestones in domains such as walking, cognition, and daily activities from those who do not.
Methods: We used RNAseq data collected from the PPMI study, available from the Laboratory for Neuroimaging (LONI), as well as UPDRS and MoCA scales. Patients were divided into "converters" and "non-converters" based on clinically relevant thresholds for 25 symptom milestones, which were then aggregated into 6 clinical domains, as well as a binary overall milestone converter index. After preprocessing RNA seq data and selecting genes with highly variable expression, we ran univariate mixed-effects models predicting expression of each gene from overall milestone status. Significant genes were enriched using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. In subsequent exploratory analyses, we integrated genes into Causal Reasoning sub-networks and repeated the differential expression analyses on aggregate scores for each sub-network.
Results: A number of genes were differentially expressed in converters and non-converters, including a network of MT-ND genes previously associated with PD, MAOA, and a large group of ribosomal protein genes. KEGG pathways enriched in the network of differentially expressed genes (Fig 1B) included PD, ribosome, oxidative phosphorylation, and prion disease (Fig 1C). **Figure 1. Differential RNA expression in PD milestone converters and enrichment of network of significant genes**





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KEGG Pathways

description	strength	false discovery rate
Ribosome	1.41	5.03e-21
Parkinson disease	0.97	2.41e-08
Huntington disease	0.91	3.15e-08
Oxidative phosphorylation	1.11	2.02e-07
Prion disease	0.87	2.69e-06
Amyotrophic lateral sclerosis	0.78	7.97e-06
Thermogenesis	0.86	2.73e-05
Alzheimer disease	0.74	4.20e-05
Retrograde endocannabinoid signaling	0.86	0.0025
Non-alcoholic fatty liver disease	0.79	0.0187

Conclusions: While previous reports have used RNA expression to differentiate PD patients from controls, these results suggest that there may be transcriptomic patterns which predict clinical outcomes within patients.

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P0803 / #1573

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

INVESTIGATION OF THE EFFECTS OF A-SYNUCLEIN OVEREXPRESSION ON JUN, RELA, HMGA1, TP53 AND SMAD3 MRNA EXPRESSION LEVELS IN HEK293T CULTURE

Ebru Keskin[1], Merve Alaylıoglu[2], Zuhal Yurttaş[2], Tugay Çamoğlu[2], Büşra Şengül[1], Pelin Sordu[2], Duygu Gezen Ak[2], Erdinç Dursun[2]
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Aims: Alpha-synuclein(α-syn), is a cytosolic protein, involved in functions such as synaptic function, neuronal plasticity, learning, phosphorylation and regulation of dopamine uptake.α-syn toxicity affects synaptic vesicles, ER, Golgi, lysosomes and nucleus. Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of α syn protein in Lewy bodies. Recent studies have shown that α-syn can be localized in the nucleus of various cell types, that its presence in the nucleus is regulated by oxidative stress and posttranslational modifications of the protein, and that it can bind to nuclear DNA, regulate histone modification, and affect the expression of many genes.These results suggest that α-syn as a transcription factor(TF) can directly regulate the expression of some genes. Based on this information we aimed to investigate whether α-syn pathology affects the expression of genes encoding general transcription factors rather than directly regulating gene expression.
Methods: In our study, PD-like pathology was established with overexpression of α-syn in the HEK293T cell line.TFs potentially associated with α-syn were determined using the TRRUST v2 database, and the effect of α-syn on the mRNA expression levels of selected transcription factors (JUN,RELA,HMGA1,TP53,SMAD3) was investigated using the qRT-PCR technique.
Results: According to our results, the mRNA expression of JUN,HMGA1 significantly decreased in SNCA group (the group with α-syn overexpression) compared to control, while the RELA expression increased. Our findings also show alteration of the expression of TP53 and SMAD3.
Conclusions: As a result of this study, our data suggest that α-syn can interact with DNA in the nucleus and affect the expression of general transcription factors.The present work was supported by the Research Fund of Istanbul University-Cerrahpaşa(Project No: 34211).

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P0804 / #378

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

EVIDENCE FOR ALPHA-SYNUCLEIN INVOLVEMENT IN INNATE IMMUNE RESPONSE AFTER BACTERIAL INFECTION: IMPLICATIONS TO PD

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Aims: Parkinson's disease (PD) patients develop a multitude of non-motor symptoms at the prodromal stage, such as hyposmia, sleep disturbances and most importantly, constipation. This finding led to the "Gut-first PD" hypothesis, which assumes that, at least, some idiopathic PD cases may start in the gut. Our goal is to depict the pathways involved in PD pathology propagation from the gut into the brain.
Methods: *Listeria monocytogenes* was administrated by oral gavage to C57BL/6 mice. Gut inflammation, mitochondrial fragmentation and α-synuclein (aSyn) expression were assessed by immunofluorescence and ELISA kits. Primary mesencephalic neurons isolated from E16 C57BL/6 embryos and NT2 cells (with a functional mitochondria – Rho^{+} or without a functional mitochondria – Rho^{0}) were infected with *Listeria monocytogenes* at a 1:10 MOI. Mitochondrial membrane potential, fragmentation and inflammatory parameters were measured by TMRM, immunofluorescence and ELISA kits, respectively. Metabolic parameters were determined by using a Seahorse XF Analyzer.
Results: We have found that bacteria administration to mice induces gut inflammation exerting enteric neuronal mitochondria dysfunction and, consequently, a strong pro-inflammatory response and aSyn aggregation. AAlso, mice displayed a loss of intestinal barrier integrity accompanied by systemic inflammation with consequences for the brain. Mice infected with *Listeria monocytogenes* show mitochondrial fragmentation in TH^{+} neurons, which allows the activation of neuroinflammation with aSyn accumulation. Moreover, we demonstrated for the first time that functional mitochondria are essential for the proinflammatory response induced by *Listeria monocytogenes.*
Conclusions: Mitochondrial dysfunction triggers PD neurodegenerative process and is required for bacterial-induced inflammation. Our results demonstrate that gut inflammation triggered by bacterial infection impacts the brain through systemic inflammation. This work provides a more comprehensive proof of concept that an invasive pathogen can trigger PD.

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March 28 - April 1, 2023 | Gothenburg, Sweden

P0805 / #624

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

EFFECTS OF LENTIVIRAL SHRNA-MEDIATED TARGETING OF SELECTED GENES ON ALPHA-SYNUCLEIN AGGREGATION IN CORTICAL NEURONS

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Aims: Insoluble aggregates (Lewy bodies) consisting of the misfolded protein alpha-synuclein (αSyn) progressively accumulate in the nervous system of most Parkinson's disease (PD) patients. In the current study, the aim was to identify targets involved in modulation of αSyn aggregation using an in vitro model.
Methods: Based on literature, 20 targets were chosen for their potential role in modulating αSyn aggregation. Lentiviral shRNAs were added to primary mouse (E18) cortical cultures and mouse pre-formed αSyn fibrils (PFFs) were added 6 days later. An unbiased, automated image analysis workflow was used to assess the effect of selected mRNAs on αSyn aggregation in NeuN-positive neurons and MAP2-positive neurites one and two weeks after addition of PFFs.
Results: Lentiviral shRNA-mediated downregulation of some targets caused effects on neuronal survival. However, one week after PFF addition, targeting Zscan21, Vps35 and Fyn resulted in an increase, whereas targeting Ppp1r15a, USP14 and Bach1 resulted in a decrease in αSyn aggregation without effects on neuronal health. Two weeks after PFF addition, targeting Atp13a2, Fyn and Aimp2 resulted in an increase, and targeting Ppp1r15a, Rhot1, Ttbk1 and Bach1 resulted in a decrease in αSyn aggregation without effects on neuronal health. For some of the targets, the effect on αSyn aggregation was thus time-dependent.
Conclusions: Our in vitro model is useful to test potential targets affecting the αSyn aggregation process over time. We provide a list of potential targets for modulation of αSyn aggregation, which should next be tested in αSyn aggregation models in human neurons and in vivo aiming to develop disease-modifying therapies for PD.

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P0806 / #1459

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

IMAGE BASED CHARACTERIZATION OF IPSC DERIVED CO-CULTURES OF NEURONAL AND GLIAL CELLS

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Aims: Cellular differentiation of human induced pluripotent stem cells to specific neuronal and glial cell subtypes represents an efficient tool for *in vitro* modelling of human brain diseases and provides an innovative opportunity in the development of new therapeutic drugs. So far, the more defined mono-cultures of especially neuronal cells have been the preferred choice of studying, for example, disease linked genes and their effects on specific cellular phenotypes and functionalities. However, it is becoming more and more evident that the presence of additional cell types, such as astrocyte and microglia, influences the function and response of neuronal cells. Thus, co-cultures of these cell types represent a more pathophysiological relevant *in vitro* system. We have recently reported on the use of iPSC derived cortical neurons as a Parkinson's disease model to study alpha-synuclein seeding (Vajhøj *et al*. 2021). We are now interested in extending this model to a co-culture model consisting of both neurons and glial cell types to study the seeding and turnover of alpha-synuclein.
Methods: So far, the use of co-cultures for brain disease modelling has been limited, which may partly be due to the technical difficulty in maintaining their simultaneous growth and correct development. Thus, a better cellular characterization and comparison of mono-cultures and co-cultures can aid in defining the preferred protocols.
Results: We use high content imaging to compare the presence and absence of markers specific for these cellular subtypes. In addition, we evaluate their neuronal cellular phenotype by various readouts such as neurite outgrowth.
Conclusions: In this present study, we report the characterization of a iPSC derived neuronal and glial cell type co-culture system and compare it to individual mono-cultures at early and late stages during differentiation.

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POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

PATHOLOGICAL MANIFESTATION OF HUMAN ENDOGENOUS RETROVIRUS-K IN PARKINSON'S DISEASE

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Aims: An emerging aspect of neurodegenerative diseases is the contribution of human endogenous retroviruses (HERVs) to their pathogenesis. HERVs have infiltrated the human genome millions of years ago. The significance of HERVs in humans is underscored by the fact that HERV genes constitute ~8% of the genome. Increasing evidence indicates that HERVs contribute to the pathogenesis of neurodegenerative and neurological diseases, including amyotrophic lateral sclerosis (ALS) and multiple sclerosis. Importantly, antiretroviral drugs have been shown to reduce HERV-K levels and symptoms in ALS patients. Despite this, very little is known about the role of HERV-K in Parkinson's disease (PD). We therefore hypothesize that HERV-K contribute to PD pathology. Our study objective is to determine whether HERV-K levels are altered in PD serum and brain, and define how HERV-K contributes to PD pathology.
Methods: We measured the HERV-K *env* gene in sporadic PD (N=25) and healthy control (N=25) serum by ddPCR. We measured HERV-K *env* in the disease-affected cerebellum and disease-unaffected visual cortex of sporadic PD (N=8) and controls (N=10) by qPCR. We also analyzed HERV-K Env protein in PD brain tissues by immunohistochemistry and microscopy.
Results: We show that HERV-K *env* levels are significantly decreased ($P<0.001$) in PD compared to control serum. HERV-K *env* levels are specifically and significantly elevated ($P<0.005$) in the cerebellum of PD compared to controls. HERV-K env levels are correlated strongly with glial fibrillary acidic protein. Finally, we reveal that HERV-K Env is largely localized in astrocytes.
Conclusions: These results suggest that manifestation of HERV-K is possibly associated with PD pathology. Analysis of HERV-K in PD may provide insight into an unrecognized but targetable perturbed pathology in PD.

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P0808 / #2170

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

THE ROLE OF APOE4 IN PRODROMAL AND MILD DEMENTIA WITH LEWY BODIES: A STUDY OF THE STRASBOURG COHORT

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Aims: We want to determine the role of ApoE4 in prodromal and mild dementia with Lewy bodies (DLB) using a cohort of patients from Strasbourg.
Methods: ApoE genotyping was performed on the AlphaLewyMA cohort. In this cohort, 197 patients were genotyped. Among them 105 DLB patients, 37 Alzheimer's disease (AD), 29 comorbidity AD/DLB and also 26 control subjects (CS). These groups are also classified according to the stage of evolution of the disease: MCI or demented. We also analyzed other parameters in relation to ApoE4, such as socio-educational levels (SEL) and Alzheimer CSF biomarkers.
Results: There were significantly more ApoE4 carriers in the AD (51%) and AD/DLB (72%) groups compared to the DLB (26%) and CS (11.5%) groups. Despite a higher percentage of ApoE4 carriers in the DLB group than in the CS group, no significant difference was found between the two groups. Concerning the SEL in AD group, we find a correlation between the age of onset of the disease and the SEL. However, the association does not reach significance in DLB. Interestingly, in this latter group, taking the median of SEL (Education=11 years), the group of patients with high SEL (≥ 11) has significantly more patients with ApoE4 than the group of patients with low SEL (<11). The AD biomarkers do not seem to be impacted by the presence of ApoE4, except for Ab42. Ab42 is decreased in ApoE4 demented DLB patients compared to ApoE4 prodromal DLB patients.
Conclusions: ApoE4 does not appear to be a risk factor for DLB patients with the possible exception of patients with high SEL. In the DLB group, ApoE4 would be responsible for the Ab42 decrease between the MCI and demented group.

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P0809 / #621

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

DIFFERENTIAL MRNA EXPRESSION IN LEWY BODY DISEASE AND ALZHEIMER DISEASE

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Aims: The pathophysiology of Lewy body disease (LBD) is not well understood. One problem in both clinical and pathological studies is that in LBD there commonly is Alzheimer's disease (AD) co-pathology. Here we use a carefully curated collection of brain tissues with LB and AD pathologies to determine Lewy body-specific differences in gene expression in brain regions more and less affected in LBD.
Methods: We studied tissue of two different brain regions (frontal[BA9] and posterior cingulate[BA23]) each in 200 individuals with pathological LBD and AD, pure AD, pure LBD, or no degenerative disease (controls). RNASeq was used to identify differentially expressed genes.
Results: Controlling for concomitant disease (i.e. LBDAD vs AD) resulted in more limited, specific set of expressed genes expression differences. For cingulate cortex, brains with LB showed 10% of genes were differentially expressed. In contrast, in frontal cortex, LB gene differences were only significant in 0.2% of genes. For AD itself, 18% and 13% of all genes were differentially expressed, in frontal and cingulate regions respectively. We further refined associations using expression of NEUN, GRAP, RBFOX and S100B as surrogates for cell-type constitution. Amongst candidate AD and PD loci, VPS35 (p=0.01) and SPR (p=0.01) were associated with LB pathology.
Conclusions: LBD pathology shows larger expression differences in posterior cingulate(BA23) than frontal(BA9) regions. Differentially expressed genes can relate in part to differing neuronal and astrocytic constitutions; using regression adjustments for tisuse cell type constitution can improve analytic processes. Use of additional methylation analysis, and GWAS (for QTL analysis) may still increase power, and potentially allow development of differentially expressed brain proteins as CSF or plasma biomarkers. Furthermore, pathway analysie to identify biological mechanisms amongst differentially expressed of genes in LBD degeneration are underway.

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P0810 / #214

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

PREVALENCE OF HELICOBACTER PYLORI IN PATIENTS WITH PARKINSON'S DISEASE.

Nargiza Mansurova
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Aims: Introduction: Helicobacter pylori (HP) is a bacterium associated with gastrointestinal diseases and It was stated that HP might lead to the pathogenesis of PD by causing direct damage to the dopaminergic neurons or acting as neurotoxins via increasing the level of cholesterol glucosides. In addition, HP can increase the level of proinflammatory mediators induced by peripheral inflammatory, which can cross blood brain barriers and subsequently trigger neurodegeneration. Our aim is to determine frequency of helicobacter pylori among Parkinson's disease patients.
Methods: We prospectively recruited 39 PD patients from November 2020 to December 2021. All patients underwent a detailed neurological evaluation and urea breath test for H. pylori infection. Positive and negative patients were considered to be the cases and controls, respectively.
Results: We have found that 38.5% of 39 PD patients were infected with HP. These infected PD patients were older (age, 67.4±4.98 years). Compared to HP-negative patients, HP-positive patients had a statistically significantly worse score according to the UPDRS (34.0±13.0 vs. 27.3±10.0, p=0.04); That study revealed important effects of HP infection on UPDRS-III of PD patients; it was found that HP status and its relationship with these motor results varied according to age.
Conclusions: The prevalence of HP infection among PD patients is significantly higher and is more common in patients over 60 years of age. The relationship between HP and PD should be further clarified by more-comprehensive studies in the future.

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P0811 / #2277

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

ALTERED BRAIN STRESS SYSTEM CIRCUITRY AND IMPAIRED NEUROGENESIS IN A RAT MODEL OF PARKINSON'S DISEASE

Katerina Karali[1], Modestos Nakos-Bimpos[1], Christina Antoniou[1], Leonidas Stefanis[1], Yassemi Koutmani[1], Alexia Polissidis[1,2]
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Aims: Preclinical studies point to a crucial role of α-synuclein in the regulation of hippocampal neurogenesis. Our work aims to study the interplay between the brain stress system, alpha-synuclein overexpression and adult hippocampal neurogenesis by examining hippocampal stress circuitry at baseline and following chronic unpredictable stress in BAC transgenic rats that overexpress human alpha-synuclein.
Methods: 9 month-old male human alpha-synuclein BAC transgenic rats underwent a 14-day chronic unpredictable stress procedure followed by assessment of transcription levels of glucocorticoid receptors (GR, MR) and corticotropin releasing hormone (CRH) in the hippocampus using RT-PCR. These levels were compared to hippocampal tissue from Parkinson's Disease patients and healthy controls. Adult hippocampal neurogenesis was then assessed with RT-PCR to measure cell proliferation (Sox2) and immunofluoresence labeled and quantified for radial glia-like cells (RGLs; GFAP+) and neural progenitors (Doublecortin (DCX+)).
Results: Our data indicate an impairment in the transcription of glucocorticoid receptors (GR, MR) and corticotropin releasing hormone (CRH) in the hippocampus, demonstrating a deficit in coping with stress in both Parkinson's disease patients (PD) and in human α-synuclein BAC animals. BAC animals also demonstrate impaired adult neurogenesis, but chronic stress neither worsens the stress system imbalance observed nor the neurogenesis deficit.
Conclusions: This study provides a link between alpha-synuclein overexpression, neurogenesis deficits in the dentate gyrus, levels of CRH and dysregulation of the GR:MR ratio in the hippocampus. Aberrant α-synuclein expression/accumulation potentially creates a vicious cycle between stress system dysregulation and impaired adult neurogenesis. An enhanced α-synuclein burden leads to stress homeostatic deficits and over time, as the disease progresses, could potentially enhance stress susceptibility.

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P0812 / #1545

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

NOVEL UPSIDE-DOWN CULTURING APPROACH AS A NEW MODEL TO STUDY NEURODEGENERATIVE DISEASES OF THE ENTERIC NERVOUS SYSTEM IN VITRO

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Aims: The enteric nervous system (ENS) comprises millions of neurons and glial cells embedded in the wall of the gastrointestinal tract. It controls important functions of the gut including motility, secretion and blood flow. Extensive research over the last decades also revealed interactions of the ENS with the immune system, gut microbiota and the gut-brain-axis. It thus might be involved in the pathophysiology of various disorders, including neurodegenerative diseases like Parkinson's disease. However, studying direct effects of pathogens onto isolated cells of the ENS can be a challenging task, considering the limited time that these cells can be kept vital under *in vitro* conditions.
Methods: To overcome this limitation, we developed an alternative approach in cultivating cells on glass samples with photolithographically fabricated distance holders, allowing to grow them upside-down in a spatially confined environment. This increases the concentration of supporting molecules, released by the ENS cells, thus providing an in-vivo like microenvironment. To evaluate the use of this approach in the study of neurodegenerative disorders, we compared isolated cells of myenteric plexus from wildtype mice and an A30P-Synuclein overexpressing Parkinson model.
Results: Culturing cells of the ENS upside-down lead to several intriguing effects, especially regarding geometry and lifespan of the cultures. The number of dead cells was significantly decreased, the architecture of upside-down cultures showed higher resemblance to the structure of the myenteric plexus *in vivo* while revealing intrinsic differences in growth and behavior of wildtype and A30P model derived cells.
Conclusions: Our results indicate that the upside-down approach may be regarded as a new model for studying the ENS in longterm cultures, as they are needed for realistic studies of chronic impact of pathological peptides, such as alpha-synuclein.

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P0813 / #1461

POSTERS: C01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

ACETYLCHOLINESTERASE ACTIVITY CHANGES IN CD9-POSITIVE EXTRACELLULAR VESICLES FROM THE PLASMA OF PATIENTS WITH PARKINSON'S DISEASE

Sumin Jeong[1], Kyu Hwan Shim[1], Heewon Bae[2], Danyeong Kim[1], Seunghwan Shin[1], Yunseo Gong[1], Da-Eun Jeong[2], Min Ju Kang[2], Seong Soo A An[1]
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Aims: Exosomes are small extracellular vesicles from all cell types with intercellular roles, implicated in health and disease. They contain and transport proteins, nucleic acids, and other components for both paracrine and endocrine effects. Recent studies reported that exosomes were closely associated with the occurrencse and progressions of various types of diseases, various cancers, Alzheimer's disease (AD), Parkinson's disease (PD) and other neurodegenerative diseases. Interestingly, exosomal α-synuclein levels in blood were significantly increased in PD, indicating its critical roles in the pathophysiology.
Methods: Previously, the decreased acetylcholinesterase activity in peripheral organs of PD patients was reported, Here, changes of exosome acetylcholinesterase (AChE) activity were investigated to see their correlations. Plasma exosomes were isolated with conjugated magnetic beads with antibodies targeting exosomal markers (CD9, CD63, and L1CAM). AChE activities and the quantities of proteins were measured from the isolated exosome samples from healthy control and PD patients.
Results: As a result, AChE activities from isolated exosomes with CD9 antibody had a statistical significance between two groups. However, no significant difference in AchE activities was observed from isolated exosome samples with antibodies of CD63- and L1CAM.
Conclusions: Since the isolated exosome with CD9 antibody would be generally secreted from various cells rather than from a specific organ, exosomal AChE might be closely associated isolated exosomes from the peripheral system than the brain in PD, which should be verified in a further study with a large cohort.

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P0814 / #2674

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

ALPHA-SYNUCLEIN PROTAC DEGRADERS FOR THE TREATMENT OF PARKINSON'S DISEASE AND RELATED SYNUCLEINOPATHIES

Lili Zhang[1], Haou-Tzong Ma[2], Yih-Shyan Lin[3], Xujin Zhan[2], Xia Wu[2], Jie Hong[2], Chenhua Zhang[2], Yen-Ting Lai[4], Ming-Kuei Jang[1], Paul Tempest[5]
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Aims: Misfolded alpha-synuclein (aSyn) is a pathologic hallmark of Parkinson's disease (PD) and related synucleinopathies. Aberrant accumulation of aSyn in neurons leads to synaptic dysfunction and neuronal death. Growing evidence implicates oligomeric aSyn as a major toxic specie in early stage of disease. APRINOIA degradation projects aim to develop PROTAC degraders to selectively reduce pathologic aSyn as a novel treatment for PD and related neurodegenerative synucleinopathies.
Methods: aSyn PROTAC library is generated by combining proprietary aSyn warheads and ligands of E3 ubiquitin ligase using a variety of linker classes. The resulting degraders engage the cellular proteasome system to selectively degrade oligomeric aSyn. A dopaminergic neuron model is developed for degrader screening and oligomer aSyn is detected using a high content imaging assay with antibody MJFR14. Lead degrader compounds are further evaluated in Line 61 mouse model that overexpresses wild type aSyn.
Results: Compound A is identified as a lead degrader molecule from our screening effort. In our cellular assay, Compound A eliminates 67% of oligomeric aSyn with half-maximal degradation concentration (DC_{50}) at 20 nM. Addition of excess E3 ligand or proteasome inhibitor abolishes the degrader-mediated aSyn degradation, confirming the mechanism of of aSyn clearence by Compound A is proteasome-dependent. Preliminary results from in vivo studies show reduction of aSyn in brain tissue of line 61 mice.
Conclusions: APRINOIA degraders developed based on proprietary aSyn binders drive selective degradation of pathological aSyn. PROTAC is a promising approach to the next generation therapy of PD and related synucleinopathies.

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P0815 / #1654

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

PROTEOMIC ANALYSES OF PATHOLOGICAL ALPHA-SYNUCLEIN IN SYNUCLEINOPATHIES IN SEARCH FOR NEW BIOMARKERS AND THERAPEUTIC TARGETS

Belén Garcia Sintes[1,2], Michal Lubas[1], Helle Bogetofte Barnkob[2], Thomas Jørgensen[2], Karina Fog[1], Martin Larsen[2]
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Aims: Synucleinopathies are one of the most common group of neurodegenerative diseases, including Parkinson's disease, multiple system atrophy and dementia with lewy bodies, and are characterized by a pathological aggregation of alpha-Synuclein (α-Syn) protein in neurons. The intracellular α-Syn fibrillary aggregates are widely linked to neurotoxic pathways such as mitochondrial impairment, autophagic- and synaptic dysfunction, and are thought to be eventually released and spread to neighboring cells, causing aggregation in different brain areas. Changes of post-translational modifications (PTMs) of α-Syn have been observed in α-Syn inclusions and may contribute to pathology development, regulating aggregation, clearance, uptake and secretion of α-Syn. However, a systematic analysis of α-Syn modifications across synucleinopathies and mechanistic links to the pathology development are lacking.
Methods: Quantitative analysis of α-Syn PTMs from human brain disease material will be performed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), to compare multiple system atrophy, Parkinson's disease, and control groups.
Results: Mass spectrometry–based analyses aim to generate a comprehensive map of α-Syn PTMs across synucleinopathies, using human disease material. The identified PTMs will be used to identify novel disease-relevant biomarkers for the differentiation of synucleinopathies, and to find new intracellular therapeutic entry points using data on the protein interactome and PTMome of pathological a-Syn species.
Conclusions: The goal of the project is to enable new entries into drug discovery within synucleinopathies. A successful outcome of the project will identify potential biomarkers for the differentiation of synucleinopathies and strengthen the scientific rationale for new intracellular therapeutic entry points.

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P0816 / #2428

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

INHIBITION OF ALPHA-SYNUCLEIN SEEDING DEPENDENT AGGREGATION BY SSDNA APTAMERS SPECIFIC TO C-TERMINALLY TRUNCATED A-SYNUCLEIN FIBRILS.

Issam Hmila[1], Indulekha Sudhakaran[1], Simona Ghanem[1], Nishant Vaikath[1], Omar El-Agnaf[2]
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Aims: Our aim is to identify aptamers against fibrillar forms of C-terminally truncated α-syn as an important target in PD. The characterization of the identified aptamers for their specificity and the effect of these aptamers on the seeding-dependent aggregation will also be checked.
Methods: Full-length recombinant human α-syn (α-syn 140) and Truncated α-syn (α-syn α-syn 130, α-syn 122, α-syn 115, and α-syn107) were expressed in Escherichia coli BL21 (DE3). Aptamers were selected from a single-stranded DNA aptamer library using SELEX protocol followed by High-Throughput Sequencing Technology. The specificity of the aptamers was checked using slot blot. The secondary structure changes were checked by circular dichroism (CD). The inhibition of aggregation was checked using the α-syn seeded aggregation assay in vitro, in cells, and using the RT-QuIC assay by adding samples from patients containing pathogenic α-syn as seeds and the recombinant α-syn monomers.
Results: We report *in-vitro* selection of aptamers targeting the fibrillar forms of C-terminally truncated α-syn. We identified a panel of aptamers that bound with high specificity to different truncated forms of α-syn fibrils. Interestingly, two of the aptamers (named Apt11 and Apt15) showed an evident inhibition of α-syn seeded aggregation *in vitro*. Moreover, Apt11 was also found to reduce the insoluble α-syn in cell model, and also can inhibit α-syn aggregation seeded with brain homogenates extracted from patients affected by PD.
Conclusions: The aptamers discovered in this study demonstrate potential useful tools for research as well as diagnostic or therapy towards PD and DLB.

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P0817 / #2432

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

SYNTHETIC PROTEIN MIMETIC-BASED THERAPEUTIC AND MECHANISTIC INSIGHTS INTO SYNUCLEIN AGGREGATION MEDIATED PARKINSON'S DISEASE

Sunil Kumar
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Aims: Alpha-Synuclein (αS) is a neuronal protein expressed at high levels in dopaminergic neurons in the brain. The aggregation of αS is a pathological hallmark of Parkinson's disease (PD). The process of the aggregation of αS impairs the release of dopamine in the dopaminergic neurons and it is considered to be one of the main sources of PD pathology. Modulation of this pathological process is a promising and innovative therapeutic approach to slow or stop the progression of PD. One big challenge is the lack of ligand-based approaches to specifically target these αS sequences to modulate the aggregation and rescue PD phenotypes. Aims: 1. Identification of synthetic protein mimetics-based potent inhibitors of αS aggregation. 2. Testing the potent inhibitors in rescuing PD phenotypes in cellular and *C. elegans* PD models.
Methods: ThT aggregation assay, 2D-NMR, Cellular toxicity assays, confocal imaging, flow cytometry, C elegans based PD models.
Results: 1. We have identified potent inhibitors of αS aggregation. 2. The potent inhibitors were able to rescue αS aggregation mediated degeneration of dopaminergic neurons in *C. elegans* PD models. 3. The ligands were also able to rescue PD phenotypes in novel early and late-stage *C. elegans* PD models.
Conclusions: The study will lead to the identification of potential lead therapeutics for the treatment of PD.

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P0818 / #1339

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

METFORMIN NANOFORMULATION MEDIATED EPIGENETIC REGULATION RETARD PARKINSON'S DISEASE

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Aims: Parkinsonism (PD) is the second most neurodegenerative disease predicted to be doubled by 2030 around the globe. In the PD etiology, post-translational modification, synuclein agglomeration, protein misfolding; genetic and epigenetic changes have been highlighted as the causative factors. Recently, the role of epigenetic modification and regulation in the interrogation of PD progression has been getting more attention. The existing therapy has side effects and that is also not curative. Therefore, a new neurotherapeutic candidate has been warranted to overcome the limitation in PD prevention. Recently, the wonder molecule metformin has been repurposed for neurodegenerative diseases. However, metformin has a rapid absorption kinetic with renal acidosis. Thus, a newer strategy like nano-drug delivery has been employed to overcome it. The nature-inspired polydopamine-based metformin (Met)nanoformulation has been demonstrated to endow metformin efficacy *in vitro*, *ex vivo,* and *in vivo* PD models.
Methods: The nanoformulation has shown complete clearance from the body system without accumulation in any vital organ. The behavioral study also reflected the anti-anxiety, anti-PD, and anti-cognitive effects of nanoformulation. The neuroprotective potential was arbitrated by the downregulation of phospho-serine 129 (pSer129) α- Syn, with a reduction in oxidative stress, prevention of apoptosis, and anti-inflammatory activities.
Results: In the exploration of epigenetic assisted neuroprotective mechanism, epigenetic regulator EZH2 mediated ubiquitination and proteasomal degradation of aggregated pSer129 α-Syn has been revealed. Indeed, the epigenetic modulation of synuclein expression through transcription regulation has also been noted in which nanoformulation induced SIRT1 mediated SNCA histone deacetylation.
Conclusions: In summary, this study divulges the neuroprotective role of Met-loaded polydopamine nanoformulation in reversing the neurochemical deficits by confirming an epigenetic-mediated nanotherapeutic approach for PD prevention.

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P0819 / #1377

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

REDUCING TOXIC ALPHA-SYNUCLEIN OLIGOMERS IN PD THROUGH PRECISE TARGETING OF THE MOLECULAR MECHANISMS OF OLIGOMER FORMATION WITH SMALL MOLECULE INHIBITORS

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Aims: Oligomeric forms of alpha-synuclein have been shown to have wide-ranging neurotoxicity and underlie the onset and progression of Parkinson's Disease (PD). These oligomers bind to membranes, receptors and organelles, disrupt metabolic and neuronal functional pathways and ultimately cause neuronal death, but are challenging to target with conventional drug discovery approaches. Here, we present a platform for the discovery and development of inhibitors of the key processes generating toxic alpha-synuclein oligomers.
Methods: In vitro protein aggregation assays starting from monomeric recombinant human alpha-synuclein were used to screen and characterise compounds. Following refinement of compound potency, oral pharmacokinetics and brain penetration, the effect of probe compounds was explored in wild type and A53T mutant iPSC-derived cortical and dopaminergic neurons and the Line-61 transgenic mouse model.
Results: Small molecule compounds demonstrated efficacy by inhibiting the key processes generating alpha-synuclein oligomers by >96% in vitro, with comparable potency when the aggregation was seeded using alpha-synuclein fibrils from PD patient tissue. Efficacy was also demonstrated in iPSC derived cells treated with compound, reducing oligomers and pS129 aggregates and improving functional markers. In the Line 61 mouse model, the same compound substantially reduced pS129 aggregate levels (-44% vs vehicle) with on-target reduction of oligomers (-25% vs. vehicle) after dosing at 15 mg/kg for 10 weeks.
Conclusions: We have demonstrated a robust technology platform for the discovery and development of specific, potent small molecule inhibitors of alpha-synuclein oligomer generation and have shown target engagement and functional benefit in a range of translational models.

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P0820 / #1074

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: _-SYNUCLEIN

RESTORATION OF LYSOSOMAL FUNCTION WITH PH-RESPONSIVE ACIDIC NANOPARTICLES RESCUE CELL DEATH IN A30P A-SYNUCLEIN NEURONAL MODEL OF PARKINSON'S DISEASE

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Aims: Parkinson disease (PD) is the second most common neurodegenerative disease in the world. While the etiology of PD is multifactorial, it has been linked to the abnormal accumulation of alpha-synuclein (α-syn) in Lewy bodies (LBs), leading to progressive loss of dopaminergic neurons. Recently, studies have shown that in α-syn overexpression and preformed fibrils (PFF) induced cellular and rodent models of PD, endolysosomal autophagy pathway is compromised, contributing to the accumulation of α-syn and hence PD pathogenesis. While strategies to promote lysosomal function has been used, such as improving lysosomal enzyme activity, the direct modulation of lysosomal pH has not been widely explored. In this study, we used a novel pH-responsive acidic nanoparticles (acNPs) as an agent to induce lysosomal acidification in SH-SY5Y cells with A30P a-syn overexpression and PFF.
Methods: Human neuroblastoma cell line (SH-SY5Y) were transfected with A30P a-syn, and the lysosomal pH is measured with LysoSensor Yellow Blue dye. Mitochondria function is determined using MitoSox™ red superoxide indicator assay and TMRE dye to determine mitochondrial membrane potential. Autophagic function is determined via immunoblotting and the cell viability of SH-SY5Y cells is measured using MTT assay.
Results: We showed that upon restoration of lysosomal acidification in SH-SY5Y cells, autophagic function is rescued, leading to reduction in α-syn accumulation and secretion to surrounding media. Moreover, lysosomal reacidification restored mitochondria function and mitophagy, and rescued cell death. We further showed that in A30P α-syn PFF treated human primary dopaminergic neurons, the restoration of lysosomal acidification with acNPs rescued cell death.
Conclusions: In sum, acNPs can serve as a tool to study the mechanism of lysosomal acidification and can be applied as a potential therapeutic for PD.

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P0821 / #1162

POSTERS: C02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

REDUCTION OF BRAIN PATHOLOGY AND EARLY COGNITIVE SYMPTOMS IN TRANSGENIC MICE TREATED WITH A MONOCLONAL ANTIBODY AGAINST ALPHA-SYNUCLEIN OLIGOMERS/PROTOFIBRILS

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Aims: Immunotherapy against alpha-synuclein (α-syn) holds promise for the treatment of Parkinson's disease. We have previously shown that systemic treatment with the monoclonal α-syn oligomer/protofibril-selective antibody mAb47 can reduce the levels of such species in the central nervous system and possibly also reduce late-stage symptoms in aged (Thy-1)-h[A30P] α-syn transgenic mice. In the current study we wanted to evaluate brain pathology and behavioral outcomes following long-term treatment in the same mouse model.
Methods: From six weeks of age, the mice (n=22) received weekly intraperitoneal injections with 20 mg/kg of mAb47 or the corresponding volume of sterile PBS (n=23). At 2, 6 and 11 months of age the mice were assessed behaviorally, by using the novel object recognition and multivariate concentric square field tests. After 9.5 months the mice were sacrificed, followed by immunohistochemistry of brain sections against α-syn pathology and neuroinflammatory markers.
Results: Compared to the placebo group, a preserved recognition memory and risk assessment behavior could be seen in mice which received immunotherapy. In addition, treated mice displayed a strongly reduced aggregation of phosphorylated α-syn (pS129) in the upper brain stem. No signs of neither microgliosis nor astrocytosis were seen in the brain tissue of treated mice.
Conclusions: This study supports the strategy of targeting α-syn oligomers/protofibrils with monoclonal antibodies to counteract early symptoms and slow down the progression of Parkinson's disease and other α-synucleinopathies.

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P0822 / #2236

POSTERS: C02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

DISCOVERY OF A CHIRAL 2,4-SUBSTITUTED PYRROLO[2,3-D]PYRIMIDINE AS POTENT, SELECTIVE AND ORALLY BIOAVAILABLE LRRK-2 INHIBITOR

Corinne Augelli-Szafran[1], Omar Moukha-Chafiq[1], Jacob Valiyaveettil[1], Hollis Kezar[1], Vandana Gupta[1], Sixue Zhang[1], Theresa Nguyen[1], Robert Galemmo[1], Joseph Maddry[1], Subramaniam Ananthan[1], Andrew West[2], Robert Bostwick[1], Mark Suto[1]
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Aims: We previously reported a novel triazolopyridazine analog, SRI-29132, as a potent LRRK2 inhibitor with kinase selectivity and acceptable brain permeability. Unfortunately, the 6-thioether moiety in this compound was critical for potency but was an oxidative liability. The aim of this study is to identify and develop novel, small molecules as potent, selective and orally bioavailable LRRK-2 inhibitors with no off-target or oxidative liabilities. A detailed structure-activity relationship (SAR) study of a chiral 2,4-substituted pyrrolo[2,3-d]pyrimidine series leading to the discovery of potent, kinase selective and orally bioavailable LRRK2 inhibitors will be described.
Methods: A novel series of LRRK-2 inhibitors was designed, synthesized and evaluated for LRRK-2 activity using our *in vitro* LRRK2 autophosphorylation assay which we developed via Alpha Screen technology. Other research efforts have been based on generic peptide substrates to assess LRRK2 activity whereas autophosphorylation is one of the most biologically relevant actions of LRRK2 to the best of our knowledge. Using this assay, SRI-31255, our original hit from a high throughput screen, was found to have similar potency for blocking human wild type (WT) and mutant G2019S LRRK2 autophosphorylation with IC_{50} values of 520 nM and 427 nM, respectively. We will report these activities for a series of analogs of SRI-31255.
Results: Hit-to-lead optimization studies of SRI-31255 resulted in the identification of lead compound **6** that exhibited excellent LRRK2 inhibition activity, displayed high selectivity across the kinome and has acceptable pharmacokinetic (PK) properties with good brain permeability and no off-target liabilities.
Conclusions: We have identified a brain permeable lead compound **6** for evaluating in proof-of-concept animal studies. This class of compounds serves as a novel lead series for further development of LRRK2 inhibitors for PD therapy.

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P0823 / #393

POSTERS: C02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DOPAMINE, NEUROTRANSMITTERS

CHARACTERISATION OF CVN417: A NOVEL AND SELECTIVE NICOTINIC ALPHA6 RECEPTOR ANTAGONIST FOR THE MODULATION OF MOTOR DYSFUNCTION IN PARKINSON'S DISEASE

Nicola Brice[1], Louisa Christie[1], Anna Rowland[1], Rishi Anand[2], Stephanie Cragg[2], Xiao Xu[1], Keith Page[1], Justin Powell[1], Louise Dickson[1], Helen Hunter[1], Toni Cheung[1], Jason Lawrence[1], Victoria Mulligan[1], Jenna Harvey[1], Martin Teall[1], Roland Burli[1], Lee Dawson[1], Mark Carlton[1]
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Aims: Nicotinic acetylcholine receptor alpha6 (nAChRα6) RNA expression is restricted to midbrain regions and located pre-synaptically on dopaminergic neurons projecting to the striatum, therefore has therapeutic potential in Parkinson's disease. Our aim was to develop a potent and selective antagonist to explore functional nAChRα6 modulation of dopamine release in a disease context.
Methods: A high throughput screen for antagonist activity for nAChRα6 was run and SAR used to develop CVN417. CVN417 was tested in recombinant Ca^{2+} flux and QPatch assays and in rodent locus coeruleus slices where nAChRα6 is enriched. Fast-scan cyclic voltammetry was used in slices to assess effects in rodent striatum. Tacrine-induced jaw tremor was utilised to investigate in vivo outcomes. Human expression was confirmed using our proprietary NETSseq technology.
Results: Novel antagonists of nAChRα6 were optimised, achieving high potency and excellent brain permeability. Activity of CVN417 was confirmed at both rodent and human receptors. In patch clamp studies, CVN417 decreased firing frequency of rat locus coeruleus neurons and in voltammetry studies, CVN417 altered the pulse-number dependence of evoked dopamine release in the rodent striatum. In the tacrine-induced jaw tremor model, there were significant dose-related decreases in the duration of tremor following oral CVN417 administration. Expression in human dopaminergic neurons is modulated by disease.
Conclusions: We have developed CVN417, a novel, highly potent and selective nAChRα6 antagonist. CVN417 shows therapeutic potential by modulating neuronal firing frequency and can enhance the sensitivity of dopamine release to depolarisation in the striatum. In addition, CVN417 reduces duration of tremor in a Parkinson's disease relevant model.

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P0824 / #2180

POSTERS: C02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DOPAMINE, NEUROTRANSMITTERS

LESSONS LEARNED REGARDING LIGAND INDUCED CONFORMATIONAL CHANGES AND STRUCTURE-ACTIVITY RELATIONSHIPS FROM ALL RECENTLY DETERMINED GPCR STRUCTURES OF MONOAMINERGIC LIGAND-RECEPTOR COMPLEXES

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Aims: The monoamine receptors, including dopamine-, serotonin-, histamine-, α- and β-adrenergic receptors, play a vital role in various basal brain functions and are important drug targets in dementia and PD. In recent years there has been a significant increase in the published experimentally determined structures of monoaminergic ligand-receptor complexes. There are now >150 complexes available in the Protein Data Bank (PDB). The aim of this work is to gain insights from detailed comparisons of conformational variability in the ligand-binding region for a relevant subset of complexes in relation to sequence similarity and ligand properties such as binding mode, chemical and pharmacological properties. These insights will be valuable for Structure-Based Drug Design (SBDD) in terms of choice of methods used and how to interpret SBDD findings in relation to measured affinity/efficacy data.
Methods: A multiple sequence alignment was generated for a pharmacologically relevant subset of experimentally determined monoaminergic receptor-ligand complexes and their corresponding structures were superimposed with focus on the binding region. The conformational differences between receptor-ligand complexes were evaluated using standard modeling tools.
Results: Overall, the conformation in the ligand-binding region is conserved for these complexes. However, there are some significant exceptions that reveals ligand-induced conformational changes. The lack of correlation between conformational variability and sequence similarity is especially noticeable within the extracellular loop two (EC2) region.
Conclusions: The shape of the binding region can be significantly affected by the co-crystallized ligand and the subset of ligands explored is limited and biased, regarding chemical structure and pharmacological profile. Using broader selection of ligands for crystallization or Cryo-EM, would most likely reveal new variations of conformational dynamics in the receptors, and thus inform optimal SBDD for effective drug-candidates in dementia and PD.

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P0825 / #1026

POSTERS: C02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DOPAMINE, NEUROTRANSMITTERS

IN VIVO SYSTEMS RESPONSE PROFILE MAPPING OF NOVEL CANDIDATE DRUGS IN DEVELOPMENT FOR TREATMENT OF SYMPTOMS RELATED TO CORTICAL IMPAIRMENT IN PARKINSON'S DISEASE

Susanna Waters[1], Joakim Tedroff[1], Clas Sonesson[1], Sverker Von Unge[1], Stephan Hjorth[1,2], Johan Kullingsjö[1], Daniel Andersson[1], Fredrik Pettersson[1], Nicholas Waters[1]
[1]Integrative Research Laboratories Sweden AB, Irlab, Göteborg, Sweden, [2]Pharmacilitator, Ab, Vallda, Sweden

Aims: The presented work aimed to map systems response profiles of candidate drugs from our cortical enhancer program, and to link response patterns to potential use in clinical symptom domains in Parkinson's disease (PD). IRLAB already sponsors several clinical programs addressing impaired motor function in PD. We use a systems biology approach for drug discovery, collecting multidimensional *in vivo*-pharmacological response profiles on compounds of interest in a standardized fashion. Machine learning techniques enable comparison to clinically well-characterized compounds, and classification/prediction of clinical effect potential of novel compounds.
Methods: Treatment response profiles were generated for CNS reference compounds, including PD drugs, antidepressants, antipsychotics, psychostimulants, procognitive drugs, and candidate drugs IRL942, IRL757 and Phase IIb compound pirepemat. Comparative response profile maps were created by Partial Least Squares-regression (PLS). The experimental methodology is described in Waters 2017, ACS Chem Neurosci 8, 785-797, doi:10.1021/acschemneuro.6b00371.
Results: PLS based on all data collected (gene expression, neurochemistry, behaviour) yielded three significant components, conveniently displayed in 2-D graphs plotting variable weights on PLS component 1 vs. component 2/3. Clinical compounds clustered according to therapeutic class, see (Waters 2017). The cortical enhancers IRL942 and IRL757 were positioned close to pirepemat in a motivation enhancing/procognitive cluster; IRL942 leaning towards procognitive, and IRL757 towards motivation enhancing drugs. Underlying variable weights indicate that activation of subcortical immediate early genes contribute to this distinguishing feature of IRL757.
Conclusions: Systems response profiling/mapping of new candidate drugs suggest a pharmacological differentiation, IRL942 displaying a predominantly procognitive profile, IRL757 expressing additional effects suggesting effects also on symptoms linked to the underlying subcortical degeneration in PD, such as apathy, warranting clinical evaluation. This new class of compounds may have broad utility in neurocognitive disorders.

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P0826 / #2152

POSTERS: C02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CELL TRANSPLANTATION

PERIPHERAL NERVE TISSUE GRAFTS INCREASE DOPAMINERGIC CELL BODIES AND NEURITES IN THE HUMAN SUBSTANTIA NIGRA WITH A UNILATERAL GRAFT

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Aims: To alter disease progression in Parkinson's disease (PD), we examined the safety and feasibility of grafting autologous, injury-activated peripheral nerve tissue (PNT) to provide growth and cell survival promoting factors to the substantia nigra. We examined the cell number and neurite complexity of a 74 year-old male PD participant who received a unilateral reparative (sural) nerve tissue graft into the right SN 54 months earlier.
Methods: Immunohistochemistry for Tyrosine Hydroxylase (TH) was done on every 6th section of the Left (SNL) and Right (SNR) Substantia Nigra. Sholl analysis using the Simple Neurite Tracer and percent area (%A) measurements were done using the ImageJ FIJI program.
Results: Pre-surgery, the participant scored 40 points on the UPDRS scale and two years later scored 35 points. The SNR had a TH %A of 6.35 ± 6.87 while the SNL had a %A of 1.63 ± 1.08. In the SNR, sections with graft present had a %A of 11.12 ± 6.68 while sections without graft present had a %A of 1.58 ±2.1. A clear increase in TH positive fibers was seen in SNR grafted sections compared to the SNL and SNR non-grafted sections. Our studies confirm that the SNR of this patient exhibited more TH-positive cells with more neurite complexity than the contralateral, non-grafted hemisphere.
Conclusions: We present evidence that a unilateral reparative PNT graft into the SNR of a PD participant had significant histological effects on dopaminergic neurons. Further studies include stereological cell counting of the entire SN region, evaluation of neurotrophins produced by grafted tissue, and further characterization of the graft using immunohistochemistry. These studies strongly suggest beneficial effects of the grafted tissue upon the SN in patients with PD.

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P0827 / #1970

POSTERS: C02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CELL TRANSPLANTATION

TREATING PARKINSON'S DISEASE USING CELL THERAPY IN A RAT MODEL

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Aims: Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders. It affects the dopaminergic (DA) neurons within the substantia nigra pars compacta of the midbrain. There is no cure for PD. Cell therapy is considered a promising approach for regenerative medicine. This study aimed to investigate the efficacy of umbilical cord mesenchymal stem cells (MSCs) derived Dopamine progenitors (DAPs) in a rat PD model.
Methods: MSCs were induced to differentiate into DAPs using a neurobasal medium supplemented with growth factors. DAPs were characterized using FACs, immunostaining, and qRT-PCR. DAPs were further differentiated into DA neurons based on the TH staining and DA production. DAPs were then transplanted into 6-OHDA-induced PD in Sprague Dawley rats. Treated animals were subjected to motor function analysis using rotarod and apomorphine-induced rotations. After 5 weeks of transplantation, animals were sacrificed, and brain tissue was subjected to postpartum analysis. The fate of transplanted cells was investigated by cell tracking. Structural changes in the striatum were analyzed by H&E. Expression of DA markers in the brain was examined by immunostaining, western blot, and RT-PCR.
Results: MSC-derived DAPs displayed neural morphology and expressed neural proteins and genes, TUJ1, Vimentin, Nestin, FOXA2, and LMX1B. 6-OHDA-treated animals injected with cells showed significant improvement in motor function. Labeled cells were tracked in the brain SNpc, and H&E and immunostaining showed a significant decrease in the nuclear pyknosis and TH expression in the striatum, respectively, of the transplanted animals. Cell-treated animals also showed upregulation of neuroprotective and neural markers in the brain.
Conclusions: MSC-derived DAPs significantly improved motor function, brain structure, and expression of neural markers in PD rats. These results provide an impetus for clinical studies using DAPs to treat PD.

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P0828 / #1282

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DEEP BRAIN STIMULATION

ANATOMICAL AND MOLECULAR ORGANIZATION OF THE SUBTHALAMIC AREA, INCLUDING THE SUBTHALAMIC AND PARA-SUBTHALAMIC NUCLEI (STN AND PSTN) IN RODENTS AND PRIMATES

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Aims: Aims: The subthalamic nucleus (STN) is crucial for normal motor, limbic and associative function. STN dysregulation has long been correlated with Parkinson´s disease (PD) and additional disorders such as obsessive-compulsive disorder and tremor. Consequently, high-frequency stimulation of the STN is increasing as therapy. However, the anatomical-functional organization of the STN and surrounding structures remains to solve, both to understand symptoms and results of treatment. The aim of our study is to use recent molecular data from our single-cell mouse-based analyses of the STN and neighboring areas (including para-STN (PSTN) and zona incerta (ZI)) for assessment of their spatial organization within the primate brain. Mouse, macaque and human subthalamic areas were analyzed and compared.
Methods: Methods: We recently implemented single-nuclei RNA sequencing (snRNASeq) of the mouse STN followed through with histological analysis of several cluster genes of interest. This led us to identify four distinct spatio-molecularly defined domains within the mouse STN. Further, molecular profiles that dissociated the STN from the adjoining PSTN were identified. Here, we took advantage of this recent knowledge from the mouse to address if the same spatio-molecular profiles and domains can be identified in the macaque and human STN area. Fluorescent *in situ* hybridization was implemented.
Results: Results: Preliminary data support the presence of three to four molecularly distinct domains within the primate STN and unique molecular profiles also within adjoining structures.
Conclusions: Conclusions: Comparative mapping will enable deeper insight into the subthalamic area. We believe that the molecular and anatomical profiles within this clinically important brain area will open new opportunities for understanding how the subthalamus contributes to behavioral regulation and how its dysregulation contributes to parkinsonian disorders, and how it can best be used as treatment target.

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P0829 / #972

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

NEUROPROTECTIVENEUROPROTECTIVE POTENTIAL OF ALOGLIPTIN IN LIPOPOLYSACCHARIDE INDUCED EXPERIMENTAL MODEL OF PARKINSON'S DISEASE

Kajal Bagri, Maanvi Dhureja, Rahul Deshmukh
Maharaja Ranjit Singh Punjab Technical University, Bthinda, Department Of Pharmaceutical Sciences & Technology, Bathinda, India

Aims: To Investigate the neuroprotective potential of Alogliptin in Lipopolysaccharide induced experimental model of PD
Methods: Experimental animals: Wistar rats/ SD (Either sex):250-300g
Inducing agent: Lipopolysaccharide (0.2mg/kg) Intranigral
Investigational agent: Alogliptin (10mg/kg, 20mg/kg, and 40mg/kg)
Results: The present study was designed to explore the neuroprotective potential of alogliptin in LPS-infused experimental model of PD. On the basis of results obtained in the present study, the following salient features can be summarized: üIntranigral LPS results in motor impairments evident in NBW, OFT and HLB test. üLPS produced significant rise in nitrite levels, lipid peroxidation, and decreased levels of antioxidant enzymes include GSH and CAT levels. In line of the above LPS infusion also produced degenerative changes in the basal ganglia includes substantia nigra, striatum as well as in the cortex in rat brains
Conclusions: The present study was designed to explore the neuroprotective potential of alogliptin in LPS-infused experimental model of PD. On the basis of results obtained in the present study, the following salient features can be summarized: Intranigral LPS results in motor impairments evident in NBW, OFT and HLB test. LPS produced significant rise in nitrite levels, lipid peroxidation, and decreased levels of antioxidant enzymes include GSH and CAT levels. In line of the above LPS infusion also produced degenerative changes in the basal ganglia includes substantia nigra, striatum as well as in the cortex in rat brains. Based on the outcomes of the current investigations, it would be safe to conclude that alogliptin has neuroprotective potential and observed increment in the motor activity of LPS-infused rats following alogliptin treatment may be due to its antioxidant potential and ability to prevent the morphological alterations in brain cells.

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POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

NANOBUBBLES IN ORGANOTYPIC BRAIN CULTURES OF SUBSTANTIA NIGRA FOR POTENTIAL BILIRUBIN-DELIVERY IN PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) still faces the unmet clinical need of disease-modifying therapy. We have shown that unconjugated bilirubin (UCB) at specific concentrations prevent dopaminergic neuron (DOPAn) loss in *ex vivo* (organotypic brain cultures of substantia nigra-OBCs-SN) model of PD. Since a carrier is needed to optimize UCB delivery *in vivo*, we tested different polymeric shells of nanobubbles (NBs), consisting of glycol-chitosan (GC), GC-deferoxamine (GC-DFO), and GC-DFO-superparamagnetic iron oxide nanoparticles (GC-DFO-SPIONs).
Methods: We manufactured GC, GC-DFO and GC-DFO-SPIONs, with relative physicochemical characterization. OBCs-SN were exposed to a range of dilution (1:8, 1:64, 1:192) of the NBs formulations. DMSO and rotenone (to reproduce the DOPAn loss of PD) were used as a positive and negative control. NBs safety was evaluated with MTT, LDH, and the DOPAn count. After finding the safe formulations, we continued to load UCB into the NBs and performed treatment in PD model with a wide range of dilution (1:64-1:11428). Statistical analysis was performed to evaluate potential correlations.
Results: The sizes of NBs are between 465-492nm. The pH, viscosity, and osmolarity of nanosuspension are 6, 0.98cP, and 354mOsm, respectively. LDH revealed NBs toxicity at 1:8 dilution for GC and GC-DFO. GC and GC-DFO-SPIONs at >=1:64 dilution as well as GC-DFO at 1:192 dilution did not induce DOPAn loss. However, GC-DFO-SPIONs was excluded due to its agglomeration events. In PD model, DOPAn count reached only 60% vs. DMSO. Meanwhile, preliminary data showed that GC-UCB at 1:192 and GC-DFO-UCB at 1:4572 conferred protection in PD model by reaching 80% and 82% of DOPAn count.
Conclusions: GC at >= 1:64 dilution and GC- DFO at 1:192 dilution are safe for OBCs-SN. Further investigation of NBs-UCB protection on PD model are needed.

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P0831 / #1748

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

POTENTIAL USE OF NATURAL CYANOBACTERIAL AND FUNGAL COMPOUNDS IN THE TREATMENT OF NEUROPATHOLOGICAL CHALLENGES IN THE ENTERIC NERVOUS SYSTEM

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Aims: A common feature of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD) disease is the damage or death of neurons resulting in the loss of motoric and cognitive abilities, respectively. Deposits of neurotoxins like β-Amyloid and α-Synuclein in certain brain regions as well as an increase of oxidative stress and inflammatory components are involved in the pathogenesis of these disorders. There is growing evidence that the gut plays a pivotal role in the development of AD and PD. As already reported, early functional changes within the gut and its intrinsic nervous system, the enteric nervous system (ENS), can be detected many years before the clinical onset of neurodegenerative diseases. Compounds derived from fungi and cyanobacteria with known anti-inflammatory, anti-oxidant and neuroprotective properties might be potential new candidates for an appropriate treatment or prophylaxis.
Methods: Pharmacological effects of C-Phycocyanin from cyanobacteria as well as the fungal metabolites Galiellalactone and Ethyldimethyloxacyclododecindione on the proliferation and differentiation of ENS cells were investigated using immunofluorescence, cell-based assays and neurosphere size distribution. In parallel, we examined cell viability of ENS cells when exposed to neuropathological peptides. qPCR was used to analyze the expressions of oxidative stress and inflammatory genes.
Results: Addition of Galiellalactone and Ethyldimethyloxacyclododecindione to differentiated enteric cells resulted in an increase of living cells. Administration of C-Phycocyanin lead to a beneficial neural stem cell growth in a dose-dependent manner, while neurogenesis was negatively affected. Gene expression analysis revealed altered levels of oxidative stress genes.
Conclusions: Our results show that nature compounds from fungi and cyanobacteria open up an interesting new area of drug research and may be new candidates for the prophylaxis of AD and PD.

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P0832 / #2033

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

FERRITIN CONFERS PROTECTION AGAINST IRON-MEDIATED NEUROTOXICITY IN MPP+-INDUCED MES23.5 DOPAMINERGIC CELLS

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Aims: To investigate the precise cellular mechanisms underlying the role of extracellular ferritin in PD cell models.
Methods: In our study, we used 1-methyl-4-phenylpyridinium ion (MPP^+) to establish a PD cell model in MES23.5 dopaminergic cells. Exogenous Apoferritin or Ferritin was used to investigate their effect in MPP^+-induced MES23.5 dopaminergic cells. The change of cell viability was detected using CCK8 assay. The change of mitochondrial transmembrane potential (△Ψm) and intracellular reactive oxygen species (ROS) level was detected by flow cytometry. Calcein-AM was used in this study to measure labile iron pool (LIP). Western blot was used to detect the expression of ferritin.
Results: Here we demonstrated that the intracellular iron increased response to iron overload in primary cultured astrocytes. These iron-loaded astrocytes released more ferritin in order to buffer extracellular iron. In addition, we found that exogenous Apoferritin or Ferritin pretreatment could significantly inhibit MPP^+-induced cell damage by restoring the cell viability and mitochondrial transmembrane potential (ΔΨm). Furthermore, exogenous Apoferritin and Ferritin might also protect MES23.5 dopaminergic neurons against MPP^+ by decreasing reactive oxygen species (ROS) and inhibiting the increase of the labile iron pool (LIP).
Conclusions: This suggests that astrocytes increased ferritin release respond to iron overload, which might inhibit iron-mediated oxidative damage of dopamine (DA) neurons in Parkinson's disease (PD).

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P0833 / #808

POSTERS: C02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

HUMANIZED MODEL TO STUDY THE ROLE OF KV1.3 BLOCKADE ON MICROGLIA IN NEUROINFLAMMATION

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Aims: Microglia play important roles in neuroinflammation linked to complex neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Several studies have shown that pharmacological blockade of the potassium channel Kv1.3 in rodent microglia reduces neuroinflammation and enhances neuroprotection, indicating its potential as a promising novel therapeutic approach. Although extensive knowledge has been gained about microglia physiology from rodent cell and animal models, these do not capture important aspects of human microglia biology and function, especially regarding processes involved in neurodegeneration. To address this, we have studied the impact of Kv1.3 blockade on human microglia in vitro and in vivo using a xenotransplantation model.
Methods: We induced inflammatory responses *in vitro* in human stem cell (hESC) -derived microglia by LPS or amyloid beta oligomer treatments to study the effects of the Kv1.3 blocker, PAP-1. We also utilized a xenograft mouse model, in which hESC-derived microglia were transplanted into the brain of Rag2 -/- | hCSF1 KI mouse pups. Xenografted mice were injected ICV with amyloid beta oligomers in the absence or presence of PAP-1 to assess the impact of pharmacological Kv1.3 blockade on amyloid beta induced inflammation in both resident mouse and xenografted human microglia.
Results: We observed significantly reduced expression of LPS and amyloid beta-induced inflammatory cytokines by PAP-1 and proprietary compound treatment in human microglia in vitro and in vivo. Interestingly, effects of Kv1.3 blockade differed for mouse and human microglia, supporting the need for humanized models to study microglia cells.
Conclusions: Our results confirm that Kv1.3 channels play a central role in neuroinflammation. Importantly, we demonstrate that mice xenografted with hESC-derived microglia are an impactful model for studying human microglia in neuroinflammation and assessing pharmacological approaches to modulate their activation.

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P0834 / #1500

POSTERS: C02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT:ASTROGLIA

BRAIN REGION SPECIFICITY OF ASTROCYTE-DERIVED EXTRACELLULAR VESICLES: MOLECULAR DETERMINANTS FOR THE PRESERVATION OF MITOCHONDRIAL FUNCTION IN PARKINSON'S DISEASE

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Aims: Astrocytes are key players in the regulation of dopaminergic neuron homeostasis both in health and disease, such as Parkinson's disease (PD). Recently, we demonstrated that astrocyte-derived extracellular vesicles (AS-EVs) from the ventral midbrain (VMB) and the striatum (STR) recover the functions of mitochondrial complex I, inhibited by the PD neurotoxin MPP^+. Interestingly, VMB-AS-EVs, but not STR-AS-EVs, are able to restore ATP production, thus fully recovering mitochondrial functionality [1]. Here we aim to shed light on the molecular mechanisms responsible for this region-specific neuroprotection of AS-EVs.
Methods: EVs were isolated from AS supernatants via differential ultracentrifugation and their cargoes were characterized in terms of proteins (via LC-MS). On the other side, a combination of imaging flow cytometry and mitochondrial assays were employed to assess the relation between EV uptake and their neuroprotective effects in target neurons. Different strategies (e.g., uptake inhibitors, EV shaving etc.) were further exploited to identify the functional molecular component(s) in AS-EVs.
Results: We found that EVs from both VMB and STR enter at similar level in injured dopaminergic neurons, and the EV uptake is mainly due to active endocytosis, rather than membrane fusion. The GO Enrichment Analysis of our EV proteomics data revealed the Integrin binding as one of the most representative Molecular Function, thus suggesting the involvement of critical surface proteins in the process. In the EV lumen, pathways related to mitochondrial activity are specifically enriched in VMB-AS-EVs. Gain- and loss-of-function experiments on relevant candidates will further clarify the underlying mechanisms of EV neuroprotective effects.
Conclusions: These results highlight novel molecular candidates within AS-EVs for the propagation of specific intercellular signaling - within the nigrostriatal system - with neuroprotective implications for PD. **1** doi:10.1002/adhm.202201203.

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P0835 / #1615

POSTERS: C02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

PGRN STABILISATION BY AZP2006 AS A NOVEL THERAPEUTIC STRATEGY FOR GBA1-LINKED PARKINSON'S DISEASE

Dominic Bingham[1], Noelle Callizot[2], Philippe Verwaerde[3], Laura Rouvière[1], Cécilia Estrella[3], Alexandre Henriques[1]
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Aims: The neurotrophic factor progranulin (PGRN), plays a vital role in the development, function, maintenance and survival of mammalian neurons and microglia. PGRN enters lysosomes through interactions with prosaposin (PSAP) where it acts as a chaperone for lysosomal enzymes. Glucosidase Beta Acid 1 (GBA) gene encodes the lysosomal hydrolase β-glucocerebrosidase (GCase), which catalyses the conversion of glucosylceramide into glucose and ceramide. Mutations in this gene are found in approximately 5 – 15 % of Parkinson's Disease (PD) patients. The currently under development molecule, AZP2006 (INN: Ezeprogind) has previously shown to strongly bind to PGRN/PSAP in lysosomes and increases neuroprotection. The present study hypothesised that AZP2006 can rescue the GBA/GBAL444P mutation phenotype by PGRN upregulation/stabilisation
Methods: Here, differentiated SH-SY5Y cell line models were created using CRISPR-Cas9 technology, containing either the GBA/GBAL444P mutation, a PGRN knock-out or a PGRN KO/GBA/GBAL444P, and were treated with either MPP+ or alpha-synuclein.
Results: The GBA/GBAL444P cell line exhibited enlarged lysosomes, increased accumulation of alpha-synuclein and reduced cell survival. Furthermore, following MPP+ and alpha-synuclein treatments, these phenotypes were all exaggerated. However, following treatments with increasing concentrations of AZP2006, a reversal of the MPP+ and alpha-synuclein treatment's effects was observed at around 10 nM AZP2006. Interestingly, at this concentration with alpha-synuclein treatment, cell survival was restored to levels of the untreated WT control.
Conclusions: These results highlight an exciting potential use case for AZP2006 (recently completed Phase 2a clinical development for PSP patients), in treating GBA1-linked Parkinson's disease.

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P0836 / #574

POSTERS: C02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

PTBP1 DELETION DOES NOT INDUCE ASTROCYTE-TO-NEURON CONVERSION

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Aims: A recent study reported that Ptbp1 knockdown in cortex, striatum, and substantia nigra efficiently reprogrammed astrocytes into functional neurons, which rescue motor defects in a mouse model of Parkinson's disease. This approach potentially addresses difficulties associated with directed glial reprogramming. This approach potentially addresses difficulties associated with directed glial reprogramming. However, several concerns remain. First, reduction of Ptbp1 expression in astrocytes in vivo was not shown. Second, lineage relationships between astrocytes and neurons were inferred using GFAP minipromoter constructs, which can show leaky neuronal expression. Third, direct evidence for glia-to-neuron conversion using genetic lineage analysis and/or scRNA-Seq-based trajectory analysis was lacking.
Methods: Here, we conduct genetic lineage and scRNA-Seq analysis of mature astrocytes carrying heterozygous or homozygous mutants of Ptbp1.
Results: We observe efficient and cell-specific disruption of Ptbp1, but no astrocyte-to-neuron conversion in heterozygous or homozygous Ptbp1 mutants. ScRNA-Seq analysis reveals subtle changes in gene expression in mutant astrocytes, but no induction of neuronal-specific genes or neuronal-like electrophysiological properties.
Conclusions: This indicates that astrocyte-to-neuron conversion reported following Ptbp1 knockdown does not reflect the effects of Ptbp1 loss of function.

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P0837 / #1582

POSTERS: C02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

DESCRIPTION OF A NOVEL G-QUADRUPLEX IN SNCA GENOMIC SEQUENCE AS AN INNOVATIVE THERAPEUTIC TARGET IN PARKINSON'S DISEASE

Federica Rey[1], Valentina Pirota[2], Valentina Fantini[3], Filippo Doria[2], Letizia Esposito[1], Rosalinda Di Gerlando[4], Mariella Mella[2], Orietta Pansarasa[4], Mauro Freccero[2], Cristina Cereda[5], Stephana Carelli[1]
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Aims: Many different therapeutic approaches for Parkinson's Disease (PD) have been investigated in the last decade and the downregulation of SNCA gene expression attracted increasing interest in slowing PD pathogenesis. In this context, we propose the targeting of a groundbreaking G-Quadruplex located on the SNCA genome. G-Quadruplex structures (G4s) are non-canonical high-order secondary structures of nucleic acids that occur in specific regions of the genome rich in guanine bases. The selective targeting of G4s is emerging as a novel therapeutic approach in precision medicine for neurodegenerative diseases.
Methods: FRET- and CD-melting experiments were performed to select the best G4-ligand and qPCR stop assay and CD spectra were used to confirm their ability to induce SNCA-G4. Biological validation was performed in SH-SY5Y cells differentiated for 7 days with retinoic acid.
Results: We present the discovery of a new G4, located on the transcription start site of the SNCA gene, that plays a promising role in the modulation of the gene transcription processes. Biophysical studies demonstrated the folding of this sequence into a very stable G4 under physiological conditions, which could be stabilized, and even induced, by well-known G4 ligands. The treatment of differentiated SH-SY5Y cells with a G4-ligand, brings an interesting modulation of SNCA mRNAs and αSyn expression.
Conclusions: Altogether our results emphasize the power of this new G4 as a promising biological target for modulating SNCA expression and αSyn production. Therefore, these preliminary data are extremely helpful for the future development of personalized therapeutic strategies against PD.

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P0839 / #654

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROGENESIS AND IPSC

ENRICHMENT OF IPSC-DERIVED DOPAMINERGIC NEURONS TO STUDY THE PATHOGENESIS OF PARKINSON DISEASE BY COUPLING NEOMYCIN-RESISTANCE TO ENDOGENOUS TYROSINE HYDROXYLASE EXPRESSION

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Aims: Patient-derived induced pluripotent stem cells (iPSC) have transformed our ability to model neurodegenerative disorders. However, despite meticulous efforts to improve protocols to differentiate iPSCs to Parkinson disease (PD)-relevant dopaminergic neurons (DANs), the proportion of mature neurons still varies significantly between batches and between iPSC lines from different individuals. This intrinsic variability hampers reproducibility as well as downstream comparisons. Therefore, new tools are needed to enrich and homogenize DAN yield.
Methods: In three patient-derived iPSC lines we used CRISPR-technology to insert the neomycin resistance gene (*Neo*) into the C-terminus of endogenous *tyrosine hydroxylase (TH)*, encoding the rate-limiting enzyme in dopamine synthesis. Since *Neo* is under the control of the TH promoter, expression is limited to TH-expressing DANs, enabling positive geneticin selection. iPSCs were differentiated with a biphasic WNT-activation protocol and treated with the antibiotic between days 27 and 33. The percentage of TH-positive cells was determined with immunocytochemistry (ICC) and flow cytometry.
Results: High concentrations of geneticin (1000 mg/mL) established the proof-of-concept with the few surviving neurons corresponding to a subgroup of high expressing TH neurons seen by ICC. However, spontaneous clumping of DANs prevented stringent quantification of the differentiation efficacy by ICC, and a flow cytometry-based workflow was incorporated. Geneticin treatment increased the percentage of DANs and preliminary data suggest reduced variability in DAN yield between patient- derived cell lines.
Conclusions: Flow cytometry analysis resulted in a fast, high-throughput quantitative assessment of the percentage of TH positive neurons in differentiated iPSC lines. Expressing neomycin-resistance under the endogenous TH-promoter enabled enrichment of DANs by antibiotic selection. This adaptation will help alleviate the known variability in cell type composition after iPSC differentiation, thereby assisting to untangle the cellular mechanisms underlying PD.

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P0840 / #2175

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROGENESIS AND IPSC

ROLE OF BACH2 IN DOPAMINERGIC NEURON DIFFERENTIATION

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Aims: Oxidative stress is widely recognized as a key player in dopaminergic neuron (DA neuron) degeneration in Parkinson's disease (PD). NRF2 is a pleiotropic transcription factor described as a master regulator of antioxidant cellular response. This NRF2-mediated antioxidant mechanism has been reported to be weaker in neurons than in glial cells. Our transcriptomic and epigenomic profiling of DA neuron differentiation revealed that BACH2, a transcription factor with structural similarity but opposite effects to NRF2, was upregulated with increased activity during DA neuron differentiation while NRF2 expression was downregulated. Given the role of oxidative stress in PD development, our objective was to understand the role of BACH2 as a major factor contributing to the reduced antioxidant response in DA neurons.
Methods: We have used a human induced pluripotent stem cell (iPSC) reporter line expressing mCherry under the tyrosine hydroxylase promoter as an approach to differentiate pure populations of human DA neurons and quantify differentiation efficiency. BACH2 was knocked-down following cell transduction with lentivirus particles containing shBACH2. Effects of BACH2 knockdown in neuronal progenitors and differentiating DA neurons were established following analyses by viability assays, flow cytometry, RT-qPCR and RNA sequencing.
Results: Our findings show that BACH2 is necessary during early DA neuron differentiation, leading to extensive transcriptome changes, whereas the loss of BACH2 during the late differentiation does not affect the cellular viability of DA neurons.
Conclusions: Neuronal BACH2 expression seems to contribute both to relative vulnerability of neurons to oxidative stress and their reliance to astrocytic support but appears to be necessary for proper neuronal development. Further analyses are needed to reveal the possible role of BACH2 as a target for increasing NRF2 activity in neurons.

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P0841 / #2588

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

IS BRADYPHRENIA IN IDIOPATHIC PARKINSONISM IATROGENIC?

Kieran Baker[1], Wenjng Wang[2], Chianna Umamahesan[2], David Taylor[3], André Charlett[4], Sylvia M Dobbs[3], Richard John Dobbs[3], Allan H Young[2], Steven Gilmour[1]
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Aims: Bradyphrenia, slowing of cognitive processing after correction for depression and cognitive function, has been described as a nosological entity within idiopathic parkinsonism (IP).[1] However, since certain exogenous substances influenced bradyphrenia, we question whether it is iatrogenic.
Methods: Reaction time (breaking contact with touch-sensitive-plate), with and without a warning in alerting signal, was measured for right and left index finger,[1] in 60 people with diagnosed-IP and 99 without, of similar age [mean (SD) 65.9 (8.1)] but differing sex distribution (63%, 44% males, respectively). Median (lower-, upper-quartile) for Beck's depression and anxiety inventories were 11 (8, 15) and 12 (5, 18), respectively, with IP and 5 (1, 10) and 4 (2, 7) without (maximum possible scores 63). Mini-mental state examination score was [30 (28, 30) with IP and 30 (30, 30) without (maximum 30). Difference in $\log_e$-transformed reaction times, unwarned minus warned, approximated to a normal distribution, and was designated the 'bradyphrenia-index' (lesser value, greater bradyphrenia).
Results: Variation in bradyphrenia-index was greater within IP than without (mean (data interval) 0.39 (-0.16, 0.93) and 0.38 (0.03, 0.72), respectively, with no significant covariates; F-test for equality of variances, $p<0.001$). No difference remained after adjustment for medicinal associations. Stepwise-variable-elimination showed that those taking monoamine oxidase-B inhibitors, anti-cholinergics and/or catechol-O-methyl-transferase inhibitors had a higher mean (95% CI) bradyphrenia-index [(0.16 (0.06, 0.26), 0.22 (0.00, 0.44) and 0.18 (0.01, 0.35), respectively, p=0.002, 0.055 and 0.033]. Those taking levodopa and/or amantadine had a lower [(-0.15 (-0.25, -0.04) and -0.41 (-0.63, -0.19), p=0.008 and <0.001)]. Effects were irrespective of between-participant dosage variation.
Conclusions: Potential effects on cognitive processing should be considered in choosing anti-parkinsonian medication. Within-recipient dose-response relationships need exploring. [1] Dobbs RJ et. al. Acta Neurol Scand. 1993;87:255-61

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P0842 / #1309

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

SHORT-TERM POSITIVE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON SPEECH OF PATIENTS WITH PARKINSON'S DISEASE – PRELIMINARY RESULTS

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Aims: The objective of this ongoing study is to identify an optimal protocol for transcranial direct current stimulation (tDCS) to improve hypokinetic dysarthria (HD) in patients with Parkinson's disease (PD). We investigate the short-term effects of tDCS using acoustic analysis of speech and based on the results from our previous studies, we focus on stimulation of the right superior temporal gyrus (STG)- auditory feedback area.
Methods: In 14 PD patients with HD, we applied anodal, cathodal and sham tDCS (2 mA) to the right STG with a bitemporal electrode montage using a cross-over design. A protocol consisting of speech tasks was performed prior to and immediately after each stimulation session. Linear mixed models were used for the evaluation of the effects of each stimulation condition on the relative change of acoustic parameters.
Results: Linear mixed model showed a statistically significant effect of the stimulation condition on the relative change of median duration of silences longer than 50 ms ($p = 0.015$). The relative change after the anodal stimulation (mean = -5.9) was significantly lower as compared to the relative change after the sham stimulation (mean = 12.8), $p = 0.014$. Further analysis showed, that anodal stimulation of the right STG induced a significant decrease of this acoustic parameter with a small effect size (Cohen's $d = -0.345$).
Conclusions: The exploratory study showed that anodal tDCS applied over the auditory feedback area may lead to shorter pauses in a speech of PD patients. These positive effects of tDCS on HD in PD will be further explored in our longitudinal study.

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P0843 / #852

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

SINEUPS: A NEW TOOLBOX FOR RNA THERAPEUTICS OF NEURODEGENERATIVE DISEASES.

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Aims: In the field of RNA therapeutics, we propose a new versatile platform to treat neurodegenerative diseases. We previously discovered *Anti-Sense Uchl1 as* the first long non-coding RNA (lncRNA) that enhances the translation of its sense ubiquitin C-terminal hydrolase L1 (*Uchl1*) protein-coding gene, previously associated with Parkinson's disease (PD). *AS Uchl1* is the representative member of a functional class of natural lncRNAs, called SINEUPs, that enhance the translation of their sense mRNAs. Their activity depends on the combination of two domains: the overlapping region, or binding domain (BD), dictates SINEUP specificity, while an embedded inverted SINEB2 element acts as an effector domain (ED) to UP-regulate mRNA translation. SINEUP technology presents several advantages: 1) it induces a 1.5-to-3-fold up-regulation of the target protein, thus limiting side effects due to exaggerated overexpression; 2) it acts on endogenous mRNAs, restricting translation enhancement to the time and space of endogenous gene expression avoiding ectopic protein synthesis; 3) it is scalable, in principle targeting any single mRNA isoform.
Methods: By taking advantage of their modular structure, we artificially engineered their BDs and designed synthetic SINEUPs to enhance the translation of selected target genes that play a crucial role in neurodegenerative diseases.
Results: We successfully enhanced the endogenous expression of target genes of therapeutic value in PD. Representative examples will be discussed, including the activities of *SINEUP-GDNF* to increase endogenous mouse and human GDNF protein levels.
Conclusions: Since the initial discovery, several synthetic SINEUPs have been synthesized and experimentally validated targeting endogenous genes. Here, we provide evidence in support of the use of SINEUPs as a new programmable platform to increase endogenous protein levels of target mRNAs for therapeutic purposes in neurodegenerative diseases.

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P0845 / #2195

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

NON-PARAMETRIC MODELING FOR DOPAMINERGIC TREATMENT EFFECT IN PARKINSON'S DISEASE

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Aims: Disease progression models have successfully been used with longitudinal data from observational cohorts in the field of neurodegenerative diseases. These models recover the natural history of the disease at a population level but are also able to uncover individual heterogeneity which allows for personalized medicine approaches. However, few have been adapted to cohorts where patients follow a treatment due to the complexity of adding this perturbation to the disease evolution. We focus on Parkinson's disease and the dopaminergic treatment. More especially we aim at building a disease progression model with treatment effect in order to explain the variations of drug efficiency between patients at various stages of the disease.
Methods: We use data from the Parkinson's Progression Markers Initiative. Dopaminergic therapy is considered to have a purely symptomatic effect (not disease-modifying). We propose a non-parametric model to account for the differences between ON and OFF states while using a standard disease progression model for the repeated measures in time.
Results: Our model shows that dopaminergic treatment effect is mostly explained by the current disease stage, the dose of the drug and the time since last medication (R^2: 0.69). The model shows that the dose should increase linearly with disease stage to achieve best efficiency, while the treatment effect is felt at full potential about one hour after the medication is taken.
Conclusions: Our results provide useful insight into the variables affecting dopaminergic drug effect on patients. In the future such a model could be used to adjust treatment dose for each patient individually.

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POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

NEUROPROTECTIVE EFFECTS OF FOSGONIMETON ON DOPAMINERGIC NEURONS ARE MEDIATED BY SIGNALING EFFECTORS DOWNSTREAM OF HGF/MET

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Aims: Hepatocyte growth factor (HGF) through its receptor MET promotes neurotrophic and pro-survival effects via a cascade of downstream intracellular signaling pathways including AKT, MEK/ERK, PKC, and CaMKII. We have previously shown that fosgonimeton, a small molecule positive modulator of the HGF/MET system, induces neuroprotective effects in both in vitro and in vivo models of neurodegeneration. We sought to define this mode of action by examining the neuroprotective effects of fosgonimeton on dopaminergic neurons injured with 1-methyl-4-phenylpryidinium (MPP^+) under selective inhibition of individual signaling kinases.
Methods: Rat dopaminergic neurons were treated with vehicle or the active metabolite of fosgonimeton (fosgo-AM) in the absence or presence of one of the following kinase inhibitors: GSK690693 (AKT inhibitor), PD98059 (MEK inhibitor), Calphostin-C (PKC inhibitor), or KN-62 (CaMKII inhibitor). Neurons were then subjected to MPP^+ treatment for 48 hours. Co-immunostaining analysis of tyrosine-hydroxylase (TH) and alpha-synuclein was performed to determine dopaminergic neuron survival, neurite network integrity (total neurite length), and alpha-synuclein aggregation.
Results: Dopaminergic neurons treated with fosgo-AM exhibited significant improvement in neuronal survival, preservation of neurite networks, and reduction of alpha-synuclein aggregation after MPP^+ injury compared to vehicle-treated group. Such effects were lost in the presence of each of the HGF/MET pathway inhibitors assessed, suggesting that the neuroprotective effects of fosgo-AM were mediated by HGF/MET downstream effectors - AKT, MEK, PKC, and CaMKII.
Conclusions: Our data demonstrate that fosgonimeton broadly augments HGF/MET signaling and highlights the involvement of HGF/MET downstream effectors in mediating its neuroprotective effects. The ability of fosgonimeton to promote dopaminergic neuron survival and reduce alpha-synuclein aggregation highlights its potential as a disease-modifying therapeutic for the treatment of Parkinson's disease.

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P0847 / #2029

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

EGULATION OF ZONA INCERTA GABAERGIC NEURONS ON MOTOR BEHAVIOR IN PARKINSON'S DISEASE MODEL MICE

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Aims: Parkinson's disease (PD) is a common neurodegenerative disorder characterized by selective loss of dopaminergic neurons in the substantia nigra and decreased dopamine content in the axon terminals of the striatum. Recent clinical studies have shown that deep brain stimulation of Zona Incerta (ZI) could rescue the motor symptoms of PD patients. ZI mainly consists of inhibitory GABAergic neurons, and has extensive fiber projection with cortex, thalamus, brainstem and basal ganglia. However, the mechanisms involved in ZI stimulation remain unknown.
Methods: We investigate the changes of motor behavior after activation/inhibition of GABAergic neurons of ZI by chemogenetic virus in 6-OHDA-induced PD mice.
Results: We first observed the effects of ZI injection with the inhibitory chemogenetic virus pAAV-GAD67-hM4D(Gi)-mCherry-WPRE on normal C57BL/6 mice. The results showed that unilateral inhibition of ZI GABAergic neurons impaired both the balance ability and motor coordination of normal mice, indicating that inhibition of ZI GABAergic neurons caused parkinsonian motor symptoms. Then we injected the activated chemogenetic virus hM3D on PD mice and observed that both a single and consecutive activation of ZI GABAergic neurons by CNO improved the movement retardance, motor coordination and balance ability of PD mice.
Conclusions: In this study, we identified the role of ZI GABAergic neurons in the regulation of motor behaviors in 6-OHDA-lesioned PD mice. Chemogenetic inhibition of ZI GABAergic neurons causes dyskinesia in normal mice, and activation of these neurons may ameliorate the motor deficits in PD mice.

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P0848 / #1774

POSTERS: C02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

INSULIN RESISTANCE IN THE CEREBRAL CORTEX OF COGNITIVELY IMPAIRED PARKINSON'S DISEASE (PD) CASES IS REDUCED BY EXENATIDE AND THE DUAL INCRETIN RECEPTOR AGONIST DA4-JC

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Aims: We sought to determine if exenatide may contribute to PD treatment by reducing brain insulin resistance and if that effect may be greater with a dual IRA (DA4-JC) activating both major incretin receptors.
Methods: At the Banner Research Institute, fresh frozen tissue was dissected from dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex (IPC) of selected healthy controls, cognitively normal PD cases, PD cases with mild cognitive impairment (PD-MCI), and PD cases with dementia (PD-D), n = 10 for each group. Mean ages of the groups were 83-85 years. Mean postmortem intervals were 5.8-7.4 hours. Responsiveness to 1 or 10 nM insulin with or without 30 min pretreatment with exenatide or DA4-JC (100nM) was determined using the ex vivo protocol of Talbot and Wang et al. (JCI, 2012). Insulin responsiveness was defined as the level of insulin-induced tyrosine phosphorylation of the insulin receptor (IR) at Y960 and Y1151/1152.
Results: DLPFC and IPC insulin resistance was absent in cognitively normal PD cases, but prominent in PD-MCI and especially PD-D cases. With respect to IR Y960, insulin responsiveness was reduced to about 38% of normal in PD-MCI and about 28% in PD-D ($p < 0.01$). With respect to IR Y1150/1151, insulin responsiveness was reduced to 39% in PD-MCI and 13% in PD-D ($p < 0.01$). Both exenatide and DA4-JC markedly increased insulin responsiveness at both IR sites, but DA4-JC was superior, raising responsiveness levels to 94-95% of normal in PD-MCI and 78-85% of normal in PD-D vs.85-89% and 66-69% respectively with exenatide ($p < 0.01$).
Conclusions: Cerebrocortical insulin resistance is a prominent phenomenon in cognitively impaired PD cases and can be markedly reduced by exenatide and especially the dual IRA DA4-JC.

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P0849 / #991

POSTERS: C03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

IMMUNE RESPONSE AND IMMUNIZATION IN PARKINSON'S DISEASE: QSP MODELLING

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Aims: This work aimed to develop quantitative systems pharmacology (QSP) model describing the role of immune response in α-synuclein accumulation, propagation, and dopaminergic neuron loss and effect of antibodies on synuclein pathology.
Methods: QSP model describes synuclein production, distribution and accumulation in brain and distribution to cerebrospinal fluid (CSF). Neurons and microglia uptake and degrade synuclein monomers, oligomers and fibrils. Synuclein interaction with microglia leads to activation and cytokine (IL-1β, TNF-α, IL-6, IL-10) production, MHCII upregulation and T-cell mediated immune response (T-cell infiltration and synthesis of IL-17 and IFNγ). Therapeutic antibodies can prevent synuclein neuronal uptake, microglia inflammatory activation and improve microglial phagocytosis. The model was calibrated using the in vitro data for synuclein uptake and degradation, and on available data for an inflammatory cell count in the CNS in PD patients and PD mouse models with induction of synuclein expression and injection of PFF (preformed fibrils) or MPTP toxicity, as well as on the antibody titers at active immunization.
Results: Our QSP model reproduces data on α-synuclein accumulation in the CNS of PD mice, microglia activation and MHCII upregulation, which helps to recruit T-cells and aggravate inflammation, impair α-synuclein clearance and immune-mediated neurotoxicity. It also reproduces data on reduction of free synuclein in CSF and reduced brain synuclein accumulation after anti α-synuclein antibody MEDI1341 administration or vaccination by PV-1950D. Antibodies restored dopaminergic loss in the model and reduced microgliosis in accordance with *in vivo* data from mice. Simulations for inflammasome inhibitor MCC950 and anti-IL-17A antibody reproduce alleviation of dopaminergic neuronal loss in rodents.
Conclusions: The proposed model can be used for further investigation and analysis of contribution of inflammatory processes in PD and prediction of the efficacy of passive or active immunotherapy or immunomodulation.

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P0849a / #443

POSTERS: C03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

PHASE 1 CLINICAL TRIAL OF ALPHA-SYNUCLEIN PEPTIDE VACCINE UB-312 PART B IN PATIENTS WITH PARKINSON'S DISEASE

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Aims: Alpha-synuclein (aSyn) plays a central role in Parkinson's disease (PD) and is considered a target for disease modification. UB-312 is a synthetic aSyn peptide conjugated to a T-helper peptide and is expected to induce antibodies specifically against pathological aSyn, making UB-312 a potential immunotherapeutic for synucleinopathies. The two-part Phase 1 clinical trial has completed Part A in healthy volunteers. Part A indicated that UB-312 elicited antibody levels sufficient to cross the blood-brain barrier and was generally well tolerated. The ongoing Part B investigates the safety, tolerability, and immunogenicity of UB-312 in PD.
Methods: In Part B, twenty PD participants (Hoehn and Yahr stage $\leq$ III) were enrolled into one of two cohorts (300/100/100 ug and 300/300/300 ug) in a 44-week study. Each cohort was blinded and randomized: 7 active and 3 placebo. Participants received 3 intramuscular injections of either UB-312 or placebo in Weeks 1, 5, and 13. Safety and tolerability were assessed by adverse events, laboratory assessments and clinical examinations. Immunogenicity was assessed by measuring serum and cerebrospinal fluid anti-aSyn antibody concentrations.
Results: Twenty PD patients (mean age 64.1 [SD 9.69] years, 80.0% male) were enrolled. Baseline mean MDS-UPDRS total score was 10.5 (SD 6.07) for Part II and 33.5 (SD 14.98) for Part III. All but one patient received all three vaccinations, and all patients are currently in the study safety follow-up.
Conclusions: Full results expected in 2023.

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P0850 / #2102

POSTERS: C03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

A MULTIYEAR PHASE 1 CLINICAL TRIAL FOR SARGRAMOSTIM THERAPY IN PARKINSON'S DISEASE

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Aims: OBJECTIVES: Incidence of Parkinson's disease (PD) is increasing faster than any other neurodegenerative disorder. Research efforts focus on a better understanding of disease mechanisms; however, novel therapies have not substantively affected disease progression. Current evidence supports the notion that PD is a multifactorial disease for which immune dysfunction and neuroinflammation play a role in driving disease progression. Immunomodulatory therapeutics such as sargramostim to restore immune homeostasis and reduce inflammation represent one strategy to interdict disease progression. Therefore, the primary objective of the current study is to determine safety of sargramostim in PD subjects, with exploratory objectives directed at altering immune responses and clinical efficacy with long-term therapy.
Methods: METHODS: Safety, immunity, and motor outcomes in PD were evaluated during sargramostim (Leukine®) therapy. Hematologic profiles, metabolic panels, regulatory T cell (Treg) numbers and function, and motor evaluations were determined in five PD subjects during a 5-day on, 2-day off sargramostim regimen administered at 3 μg/kg/dose. After two years, treatment was halted for 3 months, and re-initiated for 6 months to determine the effect on disease progression, clinical scores, and immune parameters.
Results: RESULTS: Adverse events for sargramostim included injection site reactions, increased total white cell counts, and bone pain. Treg numbers and motor function improvements were sustained throughout the study. No unexpected adverse events were discernible during therapy, treatment pause or re-initiation. Treg numbers and motor scores returned to baseline during the pause. However, after re-initiation, motor scores improved and Treg numbers and immunosuppressive phenotype was restored.
Conclusions: CONCLUSIONS: Taken together, the data affirms long-term safety, Treg functional stability, and potential clinical efficacy of sargramostim in PD. Confirmation requiring larger numbers of enrolled patients is planned in a phase II evaluation.

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P0851 / #2518

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

NEW POSSIBILITIES OF PARKINSON'S DISEASE THERAPY

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Aims: Parkinson's disease is a disabling and urgent problem that significantly reduces the quality of life of patients and their relatives. Objective: to evaluate the effectiveness of the use of a combination of cortical polypeptides and hypothalamic phospholipids for the correction of motor and cognitive disorders in patients with Parkinson's disease.
Methods: 47 patients (28 men and 19 women) aged 47 to 67 years were deployed, the duration of the disease was 7.1±2.2 years, the severity of the disease on the Hon and Yar scale was 2.4± 0.4. points. To assess the degree of effectiveness of various M. Tinetti scales used, cognitive measures - MMSE, MoCA, Matisse, SCOPA-Cog assessment scales, assessment of the quality of life according to the McDowell index. Patients detect cortical polypeptides and hypothalamic phospholipids within 20 days. The control group consisted of 20 patients treated according to the protocol.
Results: against the background of combined intake, there is an increase in motor activity, a decrease in rigidity, tremor, hypokinesia. Indicators of stability and gait on the M. Tinetti scale are riskily risky by 21.9%. The McDowell index of life disorders decreased by 45 points (from the original 90). Statistically dangerous neurodynamic and operational functions. Increased cognitive function on the MMSE scale showed positive dynamics from 22.9 ± 1.5 to 24.7± 1.5; on the SCOPA-Cog scale – by 12 points, on the Matisse scale – by 8.2% ($p<0.01$). Significantly dangerous tests for the logical memory of the results, as well as tests for counting and thinking.
Conclusions: the dynamics of the studied indicators indicates a positive effect of the combination of polypeptides of the cortex and phospholipids of the hypothalamus on motor and cognitive functions in patients with Parkinson's disease.

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P0852 / #1296

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

NICOTINAMIDE RIBOSIDE ALLEVIATES PARKINSON'S DISEASE SYMPTOMS BUT DOWNREGULATES DOPAMINE METABOLISM

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Aims: Parkinson's disease (PD) associates with a reduction in mitochondrial and proteasome function in the substantia nigra and concomitant depletion of dopamine. Activation of those functions with the NAD^+ precursor nicotinamide riboside (NR) has emerged as a potential therapeutic approach for PD. However, despite recently started clinical trials, studies on NR in PD animal models are scarce. Our aim was to analyze the effect of NAD+ precursor vitamin B3 derivative NR on disease prgression in C. elegans and mouse models of Parkinson's disease.
Methods: We used a-synuclein over-expression in DA neurons and muscle to mimick PD in C. elegans, 26S proteasome inhibitor lactacystin to mimick PD in mice and various proteasome inhibitors in a cell-line model. Among other endpoints we measured mitochondrial number and function, motor function of animals, NAD+ metabolome and DA system integrity and implemented mechanistic analysis using RNAis in C elegans and molecular biology tools in a cell-line model.
Results: We found that in *C. elegans* PD model overexpressing α-synuclein, NR rescued PD-like phenotypes likely by activating the mitochondrial unfolded protein response (UPR^{mt}). However, in a proteasome inhibitor lactacystin-induced mouse model of PD, NR rescued mitochondrial dysfunction and early behavioural deficits, but resulted in decreased levels of dopamine and its related metabolic genes in the substantia nigra. In cell-line model we found that upon proteostasis failure NR increases the acetylation of transcription factor FOXO1, a known regulator of life,- and health span, providing a possible mechanism for the observed long-term effects in adult brain.
Conclusions: Our results suggest that genetic or environmental reduction in proteasome function may be a risk factor upon long-term NR supplementation and suggest for careful monitoring of patients in ongoing NR clinical trials for PD.

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P0853 / #501

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

HER-096 IS A NOVEL BRAIN-PENETRATING PEPTIDOMIMETIC THAT PROMOTES PROTEOSTASIS AND REDUCES NEUROINFLAMMATION IN AGED MOUSE MODEL OF SYNUCLEINOPATHY

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Aims: To develop a next generation, brain-penetrating compound based on unconventional neurotrophic factor CDNF.
Methods: Peptide library screening, lead optimization by chemical peptide modification, in vitro models of blood-brain barrier penetration, neuroprotection and metabolism. In vivo pharmacology studies addressing pharmacokinetics, brain distribution and excretion. Pharmacodynamic effects were studied in an aged mouse alpha-synuclein injection (bilateral substantia nigra) model with glucocerebrosidase (GBA) inhibition by conduritol B-epoxide (every second day i.p.). HER-096 was administered subcutaneously (s.c.) daily or three times of week.
Results: HER-096 was developed based on the active site of CDNF which has been shown to modulate Unfolded Protein Response (UPR) pathway signaling and alleviate ER stress in cells. Via generation of a modified peptide library and lead optimization cycles, HER-096 was selected as the lead candidate. HER-096 is a modified peptide that shows significant tolerance against proteolysis and its main route of elimination is renal excretion unchanged. Subcutaneously delivered HER-096 was found on therapeutic levels in the CSF in rats and dogs, with extended brain half-life compared to plasma. Moreover, s.c. delivered HER-096 modulated target pathway (UPR) activity, protected dopamine neurons, and significantly reduced alpha-synuclein aggregation and microgliosis in a human synucleinopathy-relevant animal model. In the preclinical toxicology program (rats and dogs) no systemic toxicities have been found and the compound will be move to Phase 1 (first-in-human) trial in healthy volunteers in 1H 2023.
Conclusions: Intraputamenal CDNF infusion has previously been tested in a Phase 1 study in moderately advanced Parkinson's disease (PD). A more patient-friendly route of administration will support further development of a disease-modifying therapy for PD and allow access to earlier stage patients. We conclude that HER-096, a CDNF-derived peptidomimetic, is a novel candidate for disease-modification in Parkinson's disease.

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POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

ORALLY ADMINISTERED GLYCOLIC ACID AND D-LACTATE PROTECT AGAINST PARAQUAT- AND ASYN OLIGOMERS-INDUCED DOPAMINERGIC NEURODEGENERATION BUT NOT AGAINST ASYN OVEREXPRESSION IN THE LOCUS COERULEUS OF MICE.

Theresa Straßl[1], Isabel Harbort[2], Yanina Dening[3], Alexandra Chovsepian[3], Viktoria Ruf[4], Wolfgang Oertel[2], Martin Henrich[5], Fanni Geibl[5], Francisco Pan-Montojo[1,3]
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Aims: Parkinson´s disease (PD) has been associated with mitochondrial dysfunction, oxidative stress and increased intracellular calcium concentrations. It has been proposed that these alterations can be caused by the exposure to pesticides, chronic inflammation and several genetic mutations, including mutations or duplication/triplication of the *SNCA* gene leading to the accumulation and aggregation of α-synuclein (ASYN). There are no neuroprotective disease-modifying treatments available. We and others have previously shown that glycolic acid (GA) and D-lactate (DL) can protect dopaminergic neurons against paraquat mediated neurotoxicity *in vitro* and that both substances support mitochondrial function, reduce intracellular calcium levels, and combat oxidative stress.
Methods: Therefore, we tested the neuroprotective potential of both substances against extracellular ASYN-oligomers *in vitro.* In a second set of experiments, both substances were tested in two distinct mouse models of PD: paraquat exposure of mice or viral vector mediated local overexpression of A53T-mutated ASYN in noradrenergic neurons of the locus coeruleus in mice.
Results: Our results show that GA effectively protects against exposure to extracellular ASYN-oligomers *in vitro* and to exposure to paraquat *in vivo*. Treatment with both substances completely protected dopaminergic neurons in the substantia nigra pars compacta of paraquat exposed mice and preserved their motor function. Unfortunately, we did not observe any neuroprotective effects against intracellular A53T ASYN overexpression in injected mice.
Conclusions: Overall, these results suggest that GA and DL could have a neuroprotective effect in idiopathic forms of the disease by slowing down the cell-to-cell progression of the pathology and potentially in some genetic forms of the disease linked to mitochondrial alterations. However, they seem to have a limited effect in those linked to alterations in the expression or the aggregation properties of ASYN.

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P0855 / #1769

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

THE PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED "PRECEDENT" TRIAL OF SAGE-718 IN PATIENTS WITH PARKINSON'S DISEASE COGNITIVE IMPAIRMENT: CLINICAL TRIAL IN PROGRESS

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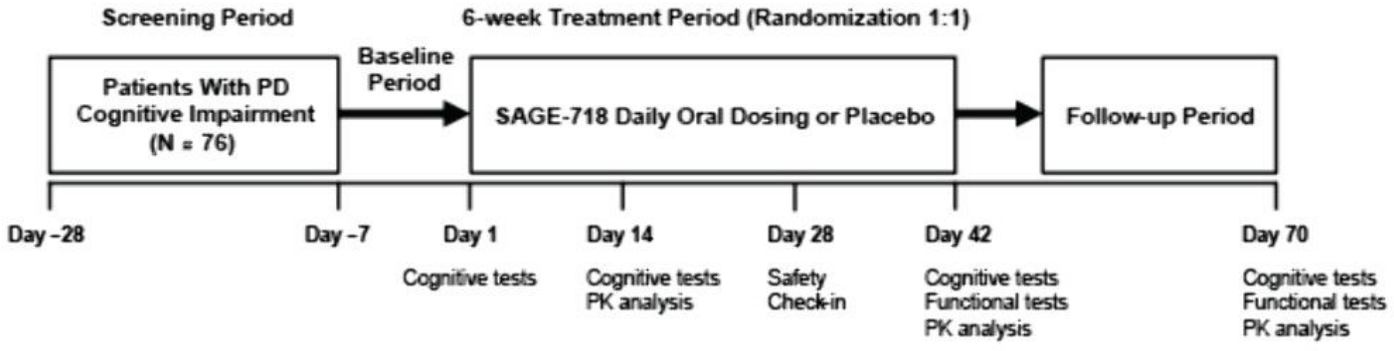
Aims: Parkinson's disease (PD) is a multisystem disorder with diverse clinical features, including neuropsychiatric symptoms and non-motor manifestations alongside motor symptomatology. Cognitive impairment, a common non-motor symptom of PD, may contribute to poor functional outcomes, loss of independence, and increased risk of dementia. Significant unmet needs exist for effective and well-tolerated pharmacotherapies that address cognitive impairment due to PD. Positive modulation of NMDA receptors may improve cognitive deficits. SAGE-718, an investigational NMDA receptor positive allosteric modulator, has been associated with improved cognitive performance in patients with PD and other neurodegenerative diseases. The randomized, placebo-controlled PRECEDENT Study is designed to evaluate the efficacy, safety, and tolerability of SAGE-718 as a potential treatment for cognitive impairment due to PD.
Methods: PRECEDENT (NCT05318937) is a Phase 2, randomized, double-blind, placebo-controlled trial (**Figure**). Approximately 76 patients aged 50–75 years meeting Movement Disorder Society Task Force Criteria for PD Mild Cognitive Impairment with mild-to-moderate motor involvement will be randomized 1:1 to receive SAGE-718 daily oral dosing or placebo for up to 42 days. Primary endpoint: change from baseline in the Wechsler Adult Intelligence Scale-IV Coding score at Day 42. Secondary endpoints: proportion of patients with treatment-emergent adverse events (TEAEs), TEAE severity, and number of patients who withdraw due to AEs. Other endpoints: additional assessments of safety/tolerability, motor symptoms, cognitive performance, and functioning.
Results: PRECEDENT is currently enrolling at sites in the United States.
Conclusions: PRECEDENT is designed to evaluate the efficacy, safety, and tolerability of SAGE-718 in patients with PD cognitive
impairment.

Figure. PRECEDENT Study Design



PD = Parkinson's disease; PK = pharmacokinetics.

Acknowledgments: We thank the patients and their families for helping us reimagine brain health. The PRECEDENT Study is sponsored by Sage Therapeutics, Inc. Medical writing support was provided by Symbiotix, LLC, and funded by Sage Therapeutics, Inc.

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P0856 / #185

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

CHARACTERISTICS OF SAFINAMIDE AS A LEVODOPA ADJUNCT THERAPY IN ASIAN PATIENTS WITH PARKINSON'S DISEASE: A POST-HOC ANALYSIS OF THE SETTLE STUDY

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Aims: Safinamide is a selective and reversible MAO-B inhibitor with a sodium channel inhibitory effect, and it inhibits stimulated glutamate release in the basal ganglia. In the SETTLE study (NCT00627640), safinamide adjunct therapy significantly improved wearing-off in patients with Parkinson's disease (PD) and motor fluctuations. We investigated the characteristics of safinamide as adjunctive therapy in Asian patients.
Methods: This is a post-hoc analysis of SETTLE study, a 24-week, double-blind, randomized, placebo-controlled study. The dose of safinamide was increased from 50 mg to 100 mg if no tolerability issues arose at Week 2. Primary outcome was change from baseline to Week 24 in daily ON-time without troublesome dyskinesia (ON-time). UPDRS Part III, Epworth Sleepiness Scale (ESS), questionnaire for impulsive-compulsive disorders in PD (QUIP), Cogtest PD battery, and PDQ-39 were assessed.
Results: This analysis included 173 Asian patients. At Week 24, safinamide significantly increased daily ON-time relative to placebo by an LS mean of 0.83 hours in Asians. UPDRS Part III was significantly improved in Asians (-2.65 points relative to placebo). No significant difference in ESS and QUIP scores was seen between the safinamide and placebo groups, and no worsening of Cogtest scores was also observed in the safinamide group. The LS mean difference in PDQ-39 summary index (-2.51 points relative to placebo) achieved minimal clinically important difference, although the statistical significance was not observed.
Conclusions: Safinamide as a levodopa adjunct therapy is effective in reducing motor fluctuations without adverse effect on daytime sleep, impulsive disorders and cognitive function in Asian patients.

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P0857 / #141

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

LONG-TERM EFFECTS OF SAFINAMIDE ADJUNCT THERAPY ON LEVODOPA-INDUCED DYSKINESIA IN PARKINSON'S DISEASE: POST-HOC ANALYSIS OF A JAPANESE PHASE III STUDY

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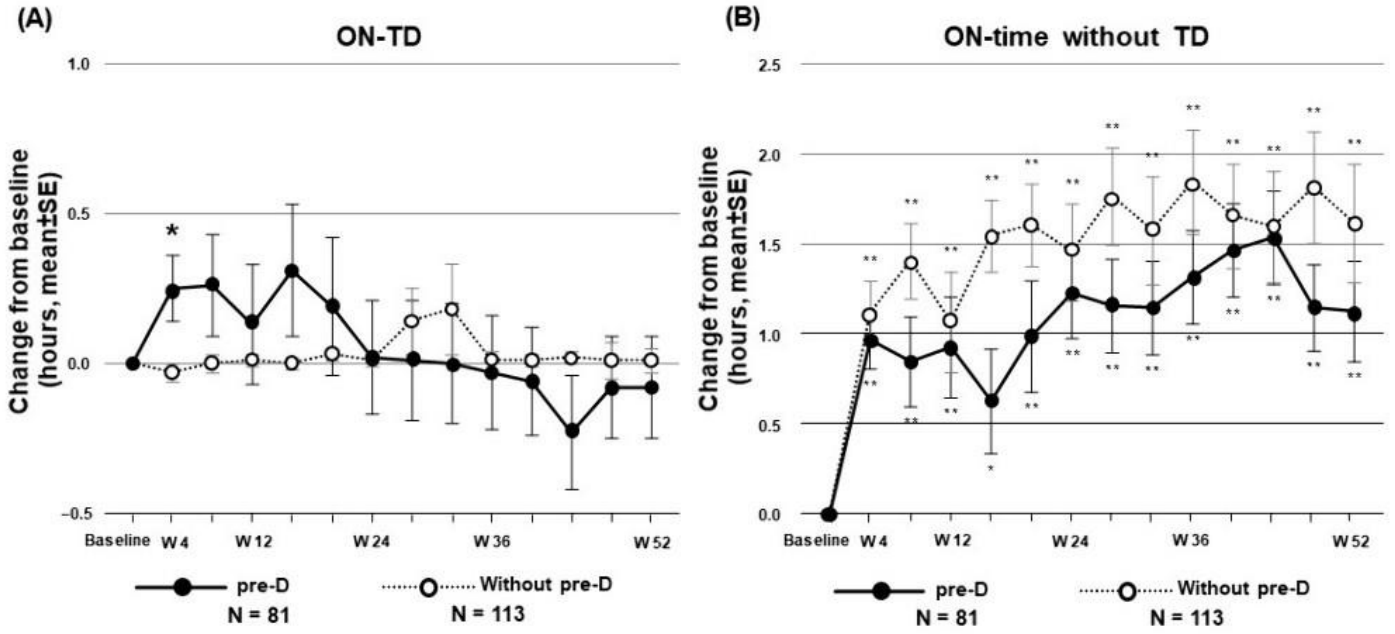
Aims: Safinamide is a selective and reversible MAO-B inhibitor with a sodium channel inhibitory effect. This post-hoc analysis investigated the long-term effects of safinamide on the course of dyskinesia and efficacy outcomes using data from a phase III, open-label 52-week study of safinamide 50 or 100 mg/day in patients with Parkinson's disease and wearing-off.
Methods: Patients (N = 194) were grouped using the Unified Parkinson's Disease Rating Scale (UPDRS) Part IV: with pre-existing dyskinesia (pre-D subgroup; item 32 > 0 at baseline [n = 81]) and without pre-existing dyskinesia (Without pre-D subgroup; item 32 = 0 at baseline [n = 113]).
Results: ON-time with troublesome dyskinesia (ON-TD) increased significantly from baseline to Week 4 in the pre-D subgroup (mean change from baseline: +0.25 ± 0.11 hours) but gradually decreased up to Week 52 (mean change from baseline: −0.08 ± 0.17 hours); ON-TD did not change significantly in the Without pre-D subgroup (Figure 1A). UPDRS Part IV item 32 score increased significantly at Week 52 compared with baseline in the Without pre-D subgroup, but no UPDRS Part IV dyskinesia related-domains changed in the pre-D subgroup. Both subgroups improved in ON-time without TD (Figure 1B), UPDRS Part III, and Part II [OFF-phase]. The cumulative incidence of new or worsening dyskinesia at Week 52 was 32.5% and 5.0% in the pre-D and Without pre-D subgroups, respectively.

Figure 1: Average daily ON-time with troublesome dyskinesia(A) and ON-time without troublesome dyskinesia(B).
ON-TD, ON-time with troublesome dyskinesia; pre-D, pre-existing dyskinesia; SE, standard error; W, week
The p-values indicate the difference at each timepoint vs baseline and were calculated using a paired t-test based on patients who had both evaluations at baseline and each timepoint. *p < 0.05; **p < 0.01



Conclusions: This study suggested that safinamide led to short-term increasing dyskinesia but may be not associated with marked dyskinesia at 52-week follow-up in patients with pre-existing dyskinesia.

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P0858 / #340

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

EARLY RESPONDERS TO SAFINAMIDE IN PATIENTS WITH PARKINSON'S DISEASE AND MOTOR FLUCTUATIONS: A POST-HOC ANALYSIS OF PHASE 3 STUDY

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Aims: Safinamide is a selective and reversible MAO-B inhibitor with a sodium channel inhibitory effect, and it inhibits stimulated glutamate release in the basal ganglia. In the SETTLE study (NCT00627640), safinamide exerted early treatment response as adjunct therapy to levodopa in patients with Parkinson's disease (PD) and motor fluctuations. We characterized the responders to safinamide using SETTLE study.
Methods: This is a post-hoc analysis of SETTLE study, a 24-week, double-blind, randomized, placebo-controlled study. The dose of safinamide was increased from 50 mg to 100 mg at Week 2. Primary outcome was change from baseline to Week 24 in daily ON-time without troublesome dyskinesia (ON-time). Safinamide-treated patients were divided into four subgroups (early/late/transient/poor responders) according to ON-time changes from baseline to Week 2 and to Week 24 with cut-off value of 1 hour (e.g., early responder showed 1-hour increase either at Week 2 or 24).
Results: Of 263 safinamide-treated patients, 39%, 17%, 9%, and 35% were early, late, transient, and poor responders, respectively; the distribution was significantly different in the placebo group (20%, 22%, 14%, and 44%, respectively; n=270, $p < 0.0001$). The early responders in the safinamide group showed remarkable improvement in PDQ-39 at Week 24 (-6.51, 95% CI: -4.40 to -8.62), and they had longer OFF-time, and higher UPDRS part II and III scores at baseline relative to other responders.
Conclusions: Our study revealed the characteristics of responders to safinamide. Patients with longer OFF-time or more motor impairment can benefit from safinamide to improve quality of life.

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P0859 / #2100

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

ISP – A TRANSLATIONAL APPROACH FOR CNS DRUG DISCOVERY APPLIED IN PARKINSON'S DISEASE (PD)

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Aims: Despite great progress in our understanding of the structure and functions of the CNS, discovery and clinical development of new drugs for many CNS disorders has been challenging, especially for neurodegenerative conditions. We aimed to develop a clinical pipeline of first-in-class PD treatments using our proprietary ISP discovery platform. This is a structured machine-learning-aided tool for phenotypic drug screening (Waters 2017, ACS Chem Neurosci 8, 785-797). The screening algorithms were tuned for target effect profiles based on 1) the role of cortical neurotransmission deficiency in the clinical symptomatology, 2) the key role of dopamine in the pathogenesis of motor deficits and the development of involuntary movements.
Methods: Utilizing systems response profiling (Waters 2017) we created three programs: 1) P001/Pirepemat, adding in-depth assessment of cortical neurotransmission by *in vivo*-brain microdialysis, 2) Mesdopetam, adding rodent behavioural/electrophysiological dyskinesia models, 3) Program P003, searching for long-acting full dopamine agonists.
Results: The most advanced P001 compound, pirepemat, regioselectively increased cortical catecholamine transmission, and promoted cortical ACh transmission. In the clinical Phase IIa study, efficacy signals on falls frequency and cognitive measures were observed. Mesdopetam (a dopamine modulator acting on D3-receptors, and a systems profile suggesting DA modulation *in vivo* without adverse motor effects on normal behaviour) was antidyskinetic in rodent models, and displayed significant reduction in On-time with troublesome dyskinesia, measured by Houser diaries, in Phase IIa.
Conclusions: Systematic discovery and evaluation using ISP identified three promising drug candidates for PD treatment, two of which are currently in Phase IIb clinical trials, suggesting translational validity. The P001/Pirepemat project, addressing cortical deficiency in neurodegenerative disorders, displays signals of alleviating cortex-associated symptoms in PD, including falls and apathy. Mesdopetam, a DA D3 antagonist, relieves dyskinesia both preclinically and clinically.

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P0860 / #732

POSTERS: C03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: AGGREGATION INHIBITORS

AGGREGATION AND NEURODEGENERATION: PARTNERS IN CRIME

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Aims: Misfolded proteins and protein aggregation are drivers and accelerators for neurodegenerative diseases, including Alzheimer's Disease (AD) and Parkinson's Disease (PD). Interference with these processes holds promise for new treatment opportunities. An important and essential role are played by iPSC-derived neurons to establish the pathway of aggregation in a dish.
Methods: Apparently Healthy Normal (AHN) iCell® GlutaNeurons and iCell DopaNeurons (AHN engineered SNCA A53T, and PD donor-derived LRRK2 G2019S or GBA N370S) were cultured in 384-well plate format. Cells were seeded with pre-formed TAU fibrils and α-synuclein proteins to drive the development of pathogenic disease-associated forms of TAU and α-synuclein. We evaluated aggregation using different readouts including HTRF and immuno-staining in 384-well plates.
Results: Herein, we show characterization of iPSC-derived cell lines suitable to model neurodegenerative diseases, including PD and AD. We show iCell DopaNeurons express specific markers (LMX1A, FOXA2, TH) indicating a relevant dopaminergic population. We show iCell GlutaNeurons consist of a primarily glutamatergic population, as determined by single cell gene expression analysis, stable expression of excitatory markers (VGAT, VGLUT2, SYN1, and PSD), and formation of active neural networks. These lines were then used to develop cellular assays to measure key cellular pathological phenotypes such as aggregation. We show the development of assays to measure TAU and α-synuclein aggregation using high content imaging tools and readouts employing multiplate readers. These assays have been miniaturized and optimized for use in drug discovery campaigns.
Conclusions: We provide a physiologically relevant assay platform to model PD and AD for drug discovery projects.

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P0861 / #625

POSTERS: C03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: AGGREGATION INHIBITORS

ORCHESTRA: A GLOBAL, RANDOMISED, PHASE II STUDY OF HIGH- AND LOW-DOSE UCB0599, A SMALL-MOLECULE ASYN MISFOLDING INHIBITOR, IN EARLY-STAGE PD

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Aims: UCB0599 is an orally administered, brain-penetrant, small molecule that acts upstream in the pathogenic alpha-synuclein (ASYN) cascade, specifically inhibiting ASYN misfolding. In preclinical Parkinson's disease (PD) models, UCB0599 reduced ASYN pathology, and preserved dopaminergic neurons and motor function. Phase I/Ib studies demonstrated an acceptable safety and tolerability profile. ORCHESTRA (NCT04658186) will assess the efficacy, safety and tolerability of UCB0599 in people with early-stage PD.
Methods: ORCHESTRA is a global, multicentre, double-blind, Phase II study. Patients with early-stage PD are randomised (1:1:1) to receive low-dose UCB0599, high-dose UCB0599 or placebo, for 18 months. Participants (aged 40–75 years) have a confirmed diagnosis of PD with bradykinesia and muscular rigidity and/or resting tremor and modified Hoehn and Yahr stage no greater than 2.5 at Screening. Previous medications for motor symptoms are permitted, only if administered for up to 4 weeks and followed by at least a 3-month washout. Primary endpoint: change in MDS-UPDRS Parts I–III sum score from Baseline to 18 months. Secondary endpoints include: MDS-UPDRS Parts I, II and III sub-scores, DaT-SPECT imaging, time to disease worsening, change in Montreal Cognitive Assessment, time to start of symptomatic treatment and safety/tolerability.
Results: 450 patients will be enrolled from approximately 120 centres in Canada, France, Germany, Italy, Netherlands, Poland, Spain, UK and USA.
Conclusions: ORCHESTRA is the first Phase II study to assess an oral, small molecule inhibitor of ASYN misfolding in PD. UCB0599 is being co-developed by UCB and Novartis as a potential disease-modifying treatment to preserve dopaminergic function and potentially slow/halt PD progression.

On behalf of the ORCHESTRA study investigators

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P0862 / #2407

POSTERS: C03.F. DRUG DEVELOPMENT, CLINICAL TRIALS: ENZYME MODULATORS

EFFECT OF NE3107 ON THE PHARMACOKINETIC PROFILE OF LEVODOPA/CARBIDOPA IN PATIENTS WITH PARKINSON'S DISEASE: A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Aims: Dopaminergic cell death and loss of dopamine cause motor disabilities in Parkinson's disease (PD). Extracellular signal-regulated kinase–nuclear factor-kappa B (ERK-NFκB) signaling mediates chronic inflammation to drive neurodegeneration in PD. Levodopa can restore motor control, but its prolonged use can worsen PD and promote levodopa-induced dyskinesia (LID). Strategies that improve the efficacy of levodopa and reduce its side effects are highly desired. NE3107 is an oral, blood-brain barrier–permeable molecule that binds ERK and inhibits inflammatory signaling pathways. In preclinical studies, NE3107 treatment improved motor control, enhanced levodopa activity, and decreased LID. A phase 2, double-blind, placebo-controlled study was conducted to determine the safety, tolerability, efficacy, and pharmacokinetic (PK) effects of NE3107 in levodopa/carbidopa-treated patients with PD.
Methods: Forty patients were planned to be enrolled and randomized 1:1 to receive 20 mg oral NE3107 twice daily or placebo for 27 days. Patients were 30 to 80 years old with a diagnosis of PD, bradykinesia, and a marked response to levodopa. Eligible patients were taking 300 mg levodopa/carbidopa daily and had a history of motor fluctuations with early morning OFF episodes. PK endpoints evaluated the change from baseline in levodopa maximum serum concentration (Cmax), time to reach Cmax, plasma concentration versus time (AUC), and elimination half-life after 2 weeks of NE3107 treatment. Safety and tolerability endpoints evaluated treatment-emergent and serious adverse events, and efficacy endpoints utilized The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I-III scores and other relevant analyses.
Results: Changes in the PK profile of levodopa before and after NE3107 treatment will be presented at the conference.
Conclusions: This study evaluated the PK interactions between NE3107 and levodopa in patients with PD.

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P0863 / #1111

POSTERS: C03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: DRUG DELIVERY SYSTEMS

DESCRIPTIVE CASE STUDIES OF PATIENTS IN THEIR FIFTH CONSECUTIVE YEAR OF TREATMENT WITH ND0612

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Aims: ND0612 is in development as a continuous SC levodopa/carbidopa delivery system for patients with Parkinson's disease (PD) experiencing motor fluctuations. Primary data from the BeyoND study showed that ND0612 is generally safe up to 1 year of treatment. Here we describe the long-term experience of three individual patients receiving subcutaneous levodopa/carbidopa infusion with ND0612 in an open-label clinical safety study.
Methods: We report three individual cases (1M/2F) from the USA (2 sites) and Israel (1 site). Eligible patients (aged ≥30 years) had a diagnosis of PD (Hoehn & Yahr Stage ≤3) and were experiencing ≥2 hours of OFF time/day despite receiving ≥4 levodopa doses/day and ≥1 other PD medication.
Results: All three cases received continuous ND0612 for 16 h/day. These patients were aged 63-68 years old, BMI 22.8-32.5, Hoehn and Yahr Stage 2-3, and experiencing motor fluctuations for 3-7 years. Patients All three patients showed relevant reductions from baseline in OFF time (reduction of 2.2–5.5 hours at Month 36) and increases in ON time without troublesome dyskinesia (increases of 2.2–7.7 hours at Month 36), which were maintained until last date of efficacy follow-up. All three patients experienced infusion site reactions starting early after treatment initiation. Nodules and bruising were mild to moderate and well tolerated. Local infusion site infections were easily managed and resolved without treatment discontinuation.
Conclusions: Continuing into their fifth year of treatment, these patients exemplify the favorable long-term benefit/risk profile of ND0612 and will serve to inform future patient selection and education.

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P0864 / #1103

POSTERS: C03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: DRUG DELIVERY SYSTEMS

PATIENT REPORTED OUTCOMES WITH CONTINUOUS SUBCUTANEOUS LEVODOPA/CARBIDOPA INFUSION: EXPLORATORY FINDINGS FROM THE ND0612 BEYOND STUDY

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Aims: ND0612 is in development as a continuous, subcutaneous levodopa/carbidopa delivery system for PD patients experiencing motor fluctuations. Primary safety data from the BeyoND study show that treatment with ND0612 is generally safe and well-tolerated for ≥1 year of treatment. We review quality of life and other patient reported outcomes data from the study.
Methods: The BeyoND study is an ongoing open-label Phase 2b study (NCT02726386) evaluating the long-term safety of continuous, subcutaneous levodopa/carbidopa infusion with ND0612 in PD patients with Hoehn & Yahr score of ≤3 during ON and experiencing ≥2 hours daily OFF-time. Exploratory evaluations of efficacy included the PDQ-39, EQ-5D-5L, and Subject Global impression of Improvement (SGI-I). Patient reported outcomes are presented here for 1-year completers (16h and 24h regimens combined) .
Results: 120 of the 214 enrolled patients completed the first year of treatment. At one year, quality of life as assessed by PDQ-39 summary index changed (improved) by -5.8 points vs baseline with the most substantial improvements in the domains of mobility (-9.0), bodily discomfort (-8.4), stigma (-7.9) and activities of daily living (-6.5). A similar pattern of improvement was seen on the EQ-5D-5L Visual Analogue Scale (VAS) score which improved by 8.4 points vs baseline. A high proportion of patients reported improvement on SGI-I, with 74.7% reporting improvement at Month 12.
Conclusions: This open-label study provides preliminary support for the 12-month efficacy of treatment with ND0612 in improving quality of life and global clinical status in patients with PD experiencing motor fluctuations.

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POSTERS: C03.I. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY

COGNITIVE TRAINING & PROGRAM PROMOTING AN ACTIVE, HEALTHY LIFESTYLE FOR PATIENTS WITH IDIOPATHIC REM SLEEP BEHAVIOR DISORDER – A STUDY PROTOCOL

Anja Ophey[1,2], Julia Pauquet[1,2], Sinah Röttgen[3,4], Christopher Doppler[2,3], Aline Seger[2,3], Gereon R. Fink[2,3], Michael Sommerauer[2,3], Elke Kalbe[1]
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Aims: Isolated REM sleep behavior disorder (iRBD) is an early α-synucleinopathy accompanied by an increased risk of pheno-conversion to Parkinson's disease, Lewy Body dementia, or multiple system atrophy. Furthermore, iRBD patients are prone to the development of cognitive impairment. This study investigates the feasibility, short- and long-term effects, and the underlying mechanisms of a cognitive intervention for iRBD patients.
Methods: For the study (DRKS00024898), designed as a delayed-start randomized controlled trial (RCT), 80 patients with polysomnography-proven iRBD and 25 healthy controls will be recruited. The first half of the study is conceptualized as a standard parallel-group RCT. iRBD patients will be randomized to either the intervention group receiving a multi-domain cognitive intervention encompassing computerized cognitive training and psychoeducation on a healthy, active lifestyle for five weeks or a passive control group (CG). Neuropsychological, clinical, and magnetic resonance imaging will be assessed at baseline, post-test, and 6-months follow-up. Following, the open-label "delayed-start" phase of the RCT will start with both the initial intervention group and the delayed-start CG receiving the intervention. Effects will again be assessed immediately after the intervention and at 6-months follow-up. Our primary outcome is a composite score of executive functions. Secondary outcomes include performance in various cognitive domains, non-motor symptoms, motor functioning, and neural parameters.
Results: Regarding feasibility, we will report the number of recruited participants from an existing iRBD cohort, the dropout rates for each time point, and the adherence to and completion of the intervention. Short- and long-term effects of the intervention and potential disease-modifying effects for iRBD patients will be evaluated.
Conclusions: This study will provide first insights into whether cognitive training and psychoeducation on a healthy, active lifestyle may have short- and long-term (neuro-)protective effects for iRBD patients.

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P0866 / #2528

POSTERS: C03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

THE LEARN STUDY: USING PARTICIPANT EXPERIENCE TO IMPROVE TRIAL DESIGN FOR PARKINSON'S DISEASE.

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Aims: A number of advanced medicinal therapeutic products (ATMPS) for the treatment of neurodegenerative diseases are moving to clinical trials. The nature of ATMPs (cell, gene and protein products) mean that many require direct intracranial administration. Combined with the ongoing management of the disease, the requirement for direct CNS administration and complex multi-component assessments results in several unique challenges. Understanding the patient journey during AMTP investigations is important for both mitigating against these challenges and to aid recruitment and retention in clinical trials as candidate ATMPs move forward.
Methods: Semi-structured interviews were conducted with participants and their family members/ care partners following invasive cell and gene therapy or protein infusion clinical trials. Interviews were conducted on-line alone or in dyads, and observed by a second non-participatory researcher. Interviews were transcribed verbatim and analysed thematically using NVivo software.
Results: Experiences of participants were largely positive, expressing strong feelings of working towards the greater good. A common thread relating to negative experiences lay with the difficulties participants faced during specific assessments including brain imaging and anything requiring 'off' medication visits. These related to the importance participants put on additional support in attending study visits being beneficial to their overall experience. Key issues arose once the trial had ended, which included learning about negative outcomes of the trials and the transition from participant back to patient following an intensive study period.
Conclusions: Listening to the voice of lived experience from complex trials is vital to inform the design of efficient, patient-centred studies to maximise recruitment and retention. Simple modifications to trial conduct can significantly enhance the participant experience and advocates for the inclusion of broad and diverse patient experience in the development of future ATMP studies.

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P0867 / #240

POSTERS: C03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: OTHER

THE EFFECTS OF LASER CANE CUES ON THE FREEZING OF GAIT OF PARKINSON'S DISEASE PATIENTS: CAN INCREASING THE LASER LIGHT BEAM WIDTH PLAY A ROLE?

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Aims: To assess the effect of laser cane as a visual cue on the freezing of gait of people with Parkinson's disease and further determine the effect of laser light beam width and color on the freezing of gait.
Methods: 7 known Parkinson's Disease patients were enrolled in this study, all of whom had at least one episode of freezing at at least one clinical visit. These patients underwent gait analysis in 4 stages: walking without a cane, walking with a thin red light laser cane, a thick red light laser cane, and a green light laser cane.
Results: Using laser canes effectively improved nearly all parameters of walking, including right and left stride length, step length, the velocity of movement, and rotation time. Using different colors of laser cane didn't make any significant difference in improving the freezing of gait of our patients. Nevertheless, increasing the laser light beam width significantly improved almost all walking parameters.
Conclusions: This is the first study assessing the effect of laser light beam width on freezing of gait in Parkinson's disease patients and shows promising results in regards to increasing the thickness of laser lights in order to improve walking parameters in Parkinson's disease patients more effectively. Furthermore, this is the second study to evaluate the effect of laser light color, contradicting the previous results by showing no significant correlation between the color of laser light and improvements in walking parameters.

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P0868 / #1940

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

ARTIFICIAL INTELLIGENCE BASED DETECTION OF PARKINSON'S DISEASE IN MAGNETIC RESONANCE IMAGING BRAIN SCANS

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Aims: Candidate neuroprotective treatments for Parkinson's disease (PD) are highlighting the need for early diagnostic tests. Exploratory imaging techniques have suggested that early pathological brain changes may be detectable using dedicated experimental MRI sequences. We explored whether deep learning might be employed to detect such brain changes on routine MRI scans. Deep learning has shown promise in diagnostic medical imaging, and offers the potential of automated diagnosis by detecting patterns that might be invisible to the human eye. These methods have sometimes been criticised for being "black boxes", but emerging explainability methods are allowing better interpretation.
Methods: We trained a convolutional neural network to classify 138 PD and 60 control brain MRI images acquired from the Parkinson's Progression Marker Initiative database. Models were assessed using 5-fold cross-validation. We used Deep SHapley Additive exPlanations (DeepSHAP) to calculate and visualise the contribution of individual pixels to the model's prediction.
Results: A model trained using a combined dataset of axial T2 and proton density MRI scans classified images with 79% accuracy and a Receiver Operating Characteristic area under the curve (AUC) of 0.86. Another model trained on just T2 scans classified images with 81% accuracy and AUC of 0.83. A further model trained on just proton density scans classified images with 84% accuracy and AUC of 0.89. The heatmaps generated using DeepSHAP demonstrated predominant contribution to the prediction in the midbrain slices.
Conclusions: Our models exhibited good diagnostic performance. The explainability method highlighted regions of interest consistent with the known neuropathology of PD, providing a focus for future work. We will validate these models in a large dataset of routinely collected MRI scans from South West England, many of which precede the onset of motor symptoms.

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P0869 / #400

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

VALIDATION OF A JACOBIAN AI-BASED METHOD TO MEASURE CEREBELLAR VOLUME CHANGES IN MULTIPLE SYSTEM ATROPHY

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Aims: The accurate, consistent, and scalable estimation of cerebellar atrophy would be highly beneficial for clinical trials in multiple system atrophy (MSA)[1-3]. This work performs validation of a fully automatic volume change workflow in MSA using Jacobian integration from non-linear warp-fields estimated with a convolutional neural network (CNN)-based 3D T1-weighted (T1W) image analysis workflow.
Methods: We analysed a MSA dataset (N=191, M-STAR clinical trial), with baseline and week-48 T1W scans, baseline images only were segmented to generate cerebellar ROIs[4]. We did not differentiate between placebo and treatment groups. We trained a CNN to perform non-linear registration of serial, affinely aligned, pre-processed image pairs[5]. This provided a voxel-wise, high-resolution warp field in a fraction of the computed time take by traditional methods[6]. Volume change measures were obtained through integrating the Jacobian determinants of the deformation fields within the baseline ROI. A generalised linear model was fit to the annualised volume change using age, sex, total Unified Multiple System Atrophy Rating Scale, and diagnosis (parkinsonian or cerebellar subtype) as covariates.
Results: We compared cerebellar volume change from 1) the proposed Jacobian-CNN method, and 2) a temporally coupled segmentation-based method (ATLAS)[7]. Both methods used the same baseline segmentations[4]. The Jacobian-CNN method reported higher estimates of annualised change from baseline (CNN=2.11%;ATLAS=0.16%) and increased effect size (CNN=2.38;ATLAS=0.16). Reduced sample sizes (power:80%,treatment effect:0.25,alpha=0.05), were obtained compared to both the ATLAS method and the PROMESA study, which used a widely used software, SPM12[8] (CNN N=44;ATLAS N=10186;PROMESA N=297).
Conclusions: The developed framework provides a fully automatic solution for estimating cerebellar volume change with increased sensitivity over comparable methods. Additionally, the framework is flexible and highly scalable, and as such has the potential to be advantageous for future clinical trials. [1]doi:10.1186/s40673-016-0052-4;[2]doi:10.1002/mds.28610;[3]doi:10.1093/brain/awl021;[4]doi:10.1016/j.neuroimage.2009.09.069;[5]doi:10.1002/alz.050068;[6]doi:10.1016/j.neuroimage.2010.09.025;[7]doi:10.1016/j.neuroimage.2010.04.006;[8]doi:10.1016/ S1474-4422(19)30141-3

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P0870 / #1224

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

MRI ESTIMATION OF IRON DEPOSITION IDENTIFIES ELEVATED PALLIDAL AND RUBRAL IRON LEVELS IN PSP COMPARED TO PARKINSON'S DISEASE

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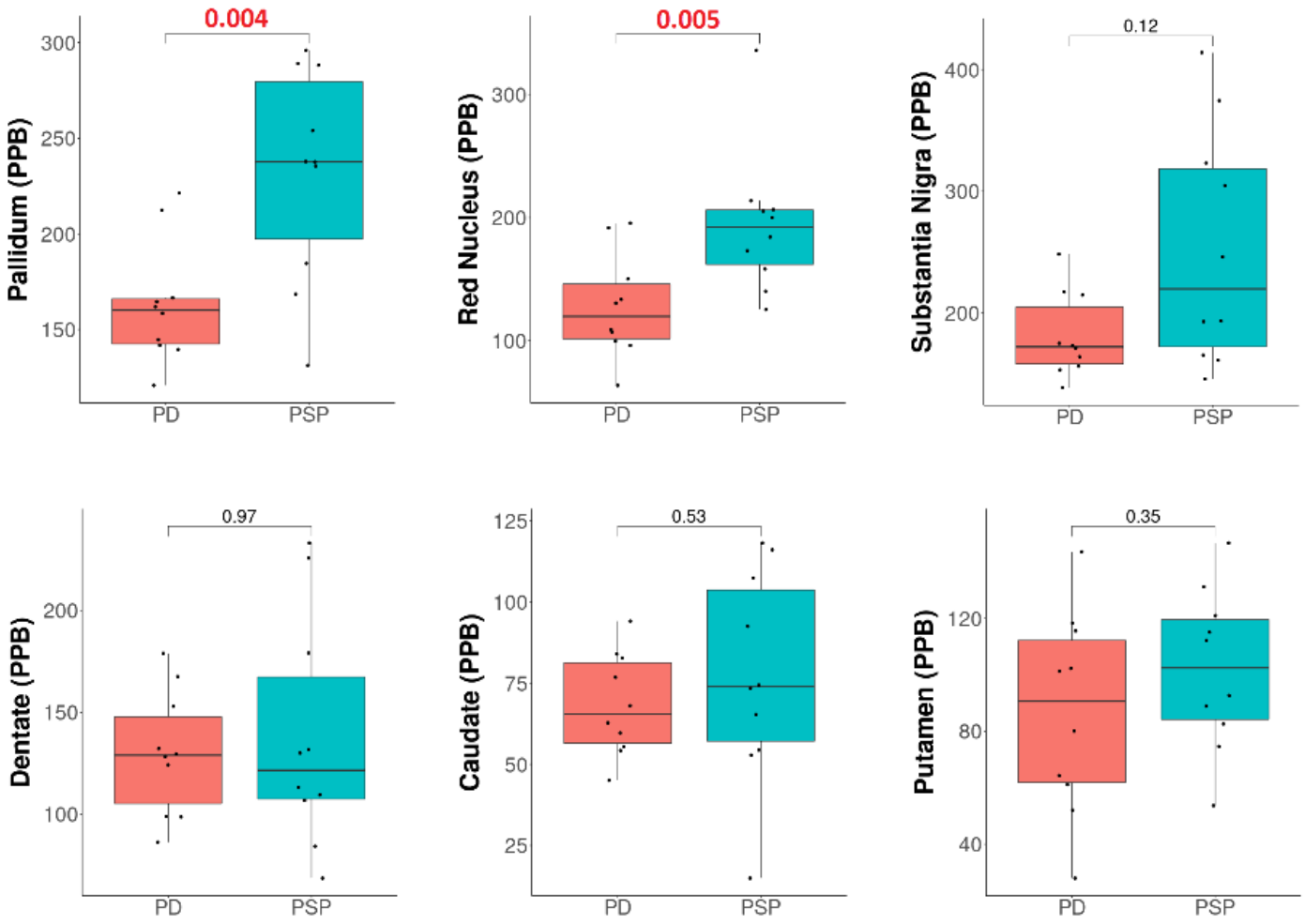
Aims: The overlapping motor and non-motor symptoms of progressive supranuclear palsy (PSP) with Parkinson's Disease (PD) may lead to misdiagnosis. We aimed to assess the usefulness of subcortical iron level in differential diagnosis of PD and PSP.
Methods: Ten PD and ten PSP patients underwent 3.0T MRI (**Table 1**). Subcortical iron deposition measures (robust mean) were derived from quantitative susceptibility mapping (QSM, STI Suite v3). Basal ganglia were segmented using FSL-FIRST whereas substantia nigra (SN), red nucleus (RN) and dentate nucleus (DN) were segmented manually from QSM images. Regional mean iron differences between PD and PSP patients were assessed using two-tailed unpaired Wilcoxon-rank sum tests.

Table 1. Patient Demographics

	PD	PSP
#n	10	10
Age (mean ± SD)	68.9 ± 11.5	67.3 ± 6.2
Sex (female/male)	3/7	5/5
Disease duration (mean ± SD)	6.3 ± 4.7	4.6 ± 3.3
ACE-III (mean ± SD)	88.0 ± 9.0	82.1 ± 7.0

Results: Iron levels were significantly higher in PSP compared PD in RN ($p = 0.005$) and pallidum ($p = 0.004$) as shown in **Figure 1**. In PSP, disease duration was significantly correlated with the increased pallidal values ($p=0.048$) and showed a similar trend in the RN ($p=0.068$).

Figure 1. Comparing QSM-iron level (robust mean) in Pallidum, Red Nucleus, Substantia Nigra, Dentate, Caudate and Putamen between Parkinson's Disease (PD) and progressive superanuclear palsy (PSP). A significant association was found in Red Nucleus and Pallidum using Wilcoxon-rank sum test.



Conclusions: Elevated pallidal and rubral iron levels in PSP compared to PD are consistent with greater extra-nigral pathology in PSP. QSM-MRI iron mapping may have potential in differential diagnosis of PSP and PD.

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P0872 / #581

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

SEX DIFFERENCES IN GRAY MATTER VOLUME AND THEIR INTERACTION WITH AGE IN PROBABLE DEMENTIA WITH LEWY BODIES

Javier Oltra[1], Annegret Habich[2], Christopher G Schwarz[3], Anna Inguanzo[2], Ketil Oppedal[4], Frédéric Blanc[5], Afina W. Lemstra[6], Jakub Hort[7], Barbara Segura[1], Carme Junque[1], Eric Westman[2], Bradley F Boeve[8], Dag Aarsland[9], Kejal Kantarci[3], Daniel Ferreira[2]
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Aims: Sex differences are central to precision medicine. However, few studies have investigated this topic in dementia with Lewy bodies (DLB) through neuroimaging. We investigated sex differences and their interaction with age on gray matter (GM) volumetric measures from magnetic resonance imaging in 165 probable DLB patients.
Methods: The sample consisted of 119 DLB males (68.7±8.4 years) and 46 DLB females (70.02±9.03 years) from three centers from the European-DLB consortium and the Mayo Clinic. GM volumes of 96 brain regions were extracted from T1 acquisitions using SPM12 and MCALT atlases. Residuals from the regions of interest (ROIs) were calculated using multiple linear regression models with intracranial volume, center, and age as predictors. To analyze sex differences and the sex by age interaction, we applied two ANOVA models with ROI as the dependent variable. In model 1 sex was included as the independent variable, while in model 2 sex, age, and the interaction were included as the independent variables.
Results: We found smaller GM volumes in DLB males than in DLB females in the middle frontal, fusiform, middle occipital, middle temporal, and supramarginal cortices; and smaller GM volume in DLB females than in DLB males in the entorhinal cortex. The results showed a significant sex by age interaction in GM volumes in the anterior cingulum, middle frontal, fusiform, supramarginal, and superior temporal cortices. Sex differences were statistically significant at younger ages and tended to be non-significant at older ages. The interaction for the middle frontal cortex remained significant after correcting for multiple comparisons.
Conclusions: Male DLB patients show smaller GM volumes than DLB females in several cortical regions. These sex differences decrease at older ages.

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P0873 / #1102

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

NEUROMELANIN-SENSITIVE MRI REVEALS ITS KEY ROLE IN THE PATHOGENESIS OF PARKINSON'S DISEASE IN THE AAV-HTYR RAT MODEL

Jean-Baptiste Perot[1], Romain Valabregue[1], Lucas Soustelle[2], Anthony Ruze[1], Laura Mouton[1], Nadege Sarrazin[1], Stéphane Lehéricy[1], Miquel Vila[3], Mathieu Santin[1]
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Aims: In Parkinson's disease (PD), the role of neuromelanin (NM), which accumulates in the dopaminergic neurons of the substantia nigra (SN), remains to be elucidated. Recently, an AAV-based rat model expressing human tyrosinase (AAV-hTyr) was developed, recapitulating motor symptoms, Lewy bodies, and dopaminergic neurons degeneration following accumulation of NM in the rat SN. For further understanding of the link between NM, motor symptoms, and neurodegeneration, we describe a longitudinal study including NM-sensitive MRI, multiparametric MRI (R1, R2, R2*, MPF, QSM), motor behavioural test and immunohistochemistry (IHC).
Methods: For this purpose, 40 male rats were injected at 2 months of age in the SN. As neuromelanin is naturally expressed solely in humans, AAV-hTyr were injected unilaterally in right SN and compared with contralateral NM-free SN. Left and right forepaw use test and MRI were performed before and 1-, 2-, 4- and 8-months after injection. A portion of the cohort is euthanized after each time point for transversal IHC.
Results: Our results showed progressive increase in the contrast-to-noise ratio (CNR) between ipsilateral and contralateral SN after injection (one-way ANOVA, $p<0.001$), as measured on NM-sensitive T1-weighted images, indicating NM accumulation. In the meantime, use of the contralateral forepaw is significantly decreasing ($p<0.001$).
Conclusions: Preliminary data hints a key role of NM accumulation in the onset of motor symptoms. Neurodegeneration of the dopaminergic neurons of SN was already shown by IHC in the AAV-hTyr rat model and will be confirmed here. As neurodegeneration induces iron accumulation, our longitudinal NM-MRI and motor results will be compared with multiparametric MRI, especially iron levels as measured with QSM. We aim at unravelling the effect of NM accumulation on iron release, neurodegeneration, and motor symptoms in this model of PD.

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P0874 / #1253

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

LEWY BODY DEMENTIA-RELATED CORTICAL PATTERN IN ISOLATED REM SLEEP BEHAVIOR DISORDER

Jee-Young Lee[1], Jung Hwan Shin[1], Heejung Kim[2], Yu Kyeong Kim[3], Beomseok Jeon[4]
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Aims: To investigate the longitudinal evolution of Dementia with Lewy bodies-Related Cortical Pattern in a prospective cohort of isolated REM sleep behaviour disorder(iRBD) patients.
Methods: In a total of 50 videopolysomnography-confirmed isolated RBD patients, we obtained 3D-T1 3T MRI and clinical and neuropsychological evaluation scores. The Dementia with Lewy Bodies (DLB)-Related Cortical Pattern was derived from 22 DLB patients compared with 44 healthy control data using an approach of principal component analysis. We estimated the DLB-related cortical pattern expression in individual iRBD patients and analyzed the longitudinal evolution of the pattern with repeated scanning at 2 or 4 years of follow-ups. We also analyzed the discriminative predictability of DLB-related cortical pattern expression for future dementia-first versus motor-first phenoconversions.
Results: The DLB-related cortical pattern was characterized by a negative contribution from the temporal, orbitofrontal, and insular cortices and a positive contribution from the precentral and inferior parietal cortices. The DLB-pattern scores correlated with attention and frontal executive dysfunction and visuospatial impairment. In the longitudinal analysis, DLB-related cortical pattern showed an increasing tendency in the dementia-first converters but no significant change in motor-first converters. Differentiation of dementia-first from motor-first conversions was correct in 88.2% with the elevation of DLB-related cortical pattern.
Conclusions: Structural MRI-derived Lewy body disease-related cortical patterns can reflect the longitudinal evolution of Dementia with Lewy bodies in isolated RBD population.

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P0875 / #1762

POSTERS: C04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

ABNORMAL BASAL GANGLIA INTRINSIC ACTIVITY IN PRODROMAL LEWY BODY DISEASE

Lenka Krajcovicova, Patricia Klobusiakova, Ivona Moravkova, Kristina Mitterova, Lubos Brabenec
Central European Institute of Technology - Masaryk University, Applied Neuroscience Research Group, Brno, Czech Republic

Aims: Aim of the study was to assess the changes in amplitude of low frequency fluctuations (ALFF) in subjects with prodromal Lewy body disease (preLBD) as compared to healthy controls (HC).
Methods: We performed resting state functional magnetic resonance imaging (rs-fMRI) in 78 subjects – 48 preLBD (mean age 69,14 +- 6,35 years) and 30 HC (mean age 67,35 +- 7 years). The diagnosis of preLBD was based on published research criteria and all subjects underwent detailed clinical and cognitive examination. Imaging was performed using 3T MRI scanner. Acquired BOLD rs-fMRI data were preprocessed and ALFF was computed in 3 power bands: slow-5 (0.010 ÷ 0.027 Hz); slow-4 (0.027 ÷ 0.073 Hz); and slow-3 (0.073 ÷ 0.198 Hz). ANOVA with factor of group and covariates of age and gender was used for statistical analysis.
Results: The differences in given ALFF band in preLBD as compared to HC were present in following regions: 1) ALFF slow-3. Increased ALFF in caudate bilaterally, right SMA, right SFG/MFG, right middle cingulum, right cerebellum 2) ALFF slow-4. Increased ALFF in caudate bilaterally. 1) ALFF slow-5. Increased ALFF in left putamen and caudate bilaterally.
Conclusions: Using ALFF approach we observed increased activity in preLBD subjects mainly in bilateral caudate (in all frequency bands) and in regions involved motor control (right SMA, cerebellum) as well as in cognitive functions, working memory and attention (right SFG/MFG). These changes were partly specific for frequency band and may represent pathological hyperactivation of basal ganglia and motor control regions in early stages of the disease. Acknowledgments: The study was supported by the grant AZV NU20-04-00294 of the Ministry of Health, Czech Republic.

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P0876 / #263

POSTERS: C04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

NEURAL CORRELATES OF EXECUTIVE FUNCTION IN PATIENTS WITH IRBD VS HEALTHY CONTROLS

Julia Pauquet[1,2], Anja Ophey[1,2], Sinah Röttgen[1,3], Ezequiel Farrher[4], N. Jon Shah[4,5,6,7], Christopher Doppler[1,3], Aline Seger[1,3], Gereon R. Fink[1,3], Michael Sommerauer[1,3], Elke Kalbe[2]
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Aims: Isolated REM sleep behavior disorder (iRBD) is an early α-synucleinopathy and is a prodromal manifestation of Parkinson's disease, Lewy-Body dementia, and multisystem atrophy. iRBD patients already show non-motor symptoms and signs of neurodegenerative processes, resulting, e.g., in executive dysfunctions. Only one study has investigated neural correlates of executive functions in iRBD patients revealing deficits in a dual-task executive measure. We want to further investigate neural correlates of executive functions using the Wisconsin Card Sorting Test (WCST) in iRBD patients compared to healthy controls.
Methods: N = 40 patients with polysomnography-confirmed iRBD who are eligible for magnetic resonance imaging (MRI) will be compared to an age- and sex-matched healthy control group (n = 25) using task-based fMRI. An EPI-based BOLD sequence on a Siemens 3T Prisma MRI scanner equipped with a 64-channel head coil will be used. Patients will perform a digital version of the WCST as a measure of executive functions (including aspects of planning, conceptualization, and set-shifting), which will be presented via Neurobehavioral Systems´ "Presentation" software on a screen. The WCST set-up was built for the present study and will be available via OSF.
Results: Comparisons between iRBD patients and healthy controls of the behavioral performance in the WCST, as well as concurrent neuroimaging will be analyzed and reported. As data collection is still ongoing, we will evaluate and present all data sets available at the time of the conference.
Conclusions: This study will provide new insights into possible alterations of neural processing of executive functions as measured by the WCST in patients with iRBD as compared to healthy controls and will serve as a baseline for intervention studies aiming to strengthen cognitive function.

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P0877 / #2675

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

DISCOVERY OF NOVEL CHEMICAL MATTER TO ENABLE ALPHA-SYNUCLEIN PET TRACER DEVELOPMENT

Robert Drolet[1], Zhizhen Zeng[2], Anthony Roecker[3], Patricia Dockery[2], Idriss Bennacef[2], Yuchuan Wang[2], Kerry Riffer[2], Mona Purcell[2], Hyking Haley[2], Jun Meng[2], Mallory Stenslik[2], Lei Ma[1], John Fay[4], Wenping Li[2], Jacob Marcus[1], Sean Smith[1], Eric Hostetler[2]
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Aims: The accumulation of aggregated a-synuclein in the form of Lewy bodies and Lewy Neurites is a pathological hallmark of Parkinson's disease (PD). Currently, alpha-synuclein deposition can only be studied at autopsy or inferred from plasma/CSF levels. Identification of an alpha-synuclein PET ligand would enable *in vivo* quantification of disease progression and may improve feasibility for long duration disease modification clinical trials in PD. However, high-affinity and selective alpha-synuclein PET ligand candidates do not currently exist. In collaboration with the Michael J. Fox Foundation, and the Ken Griffin Alpha-Synuclein Imaging Award, we sought to advance a viable alpha-synuclein PET tracer candidate towards clinical evaluation in a patient population.
Methods: Radioligand saturation and competitive binding experiments were conducted in postmortem PD and Alzheimer's disease brain tissue to profile PET candidate affinity and selectivity. Autoradiography experiments in postmortem brain tissue was performed on lead radioligand candidates to validate binding to pathological alpha-synuclein. For advanced [C11] or [F18] labeled leads, PET imaging experiments were performed in aged A30P alpha-synuclein overexpressing transgenic mice to assess in vivo brain binding potential. *In Vivo* PET imaging experiments were performed in non-human primates to determine tracer utility for human studies.
Results: In vitro and in vivo experimental data describe the identification and profiling of candidate molecules with subnanomolar potency and selectivity for alpha-synuclein. Lead radioligands have been [18F] or [11C] labeled and demonstrate specific binding to pathological alpha-synuclein in the A30P alpha-synuclein transgenic mouse in vivo PET imaging studies.
Conclusions: Together the data demonstrate the in vitro and in vivo profiling of small molecule radioligands that selectively bind pathological alpha-synuclein in transgenic mice and post-mortem PD brain. Candidate molecules are currently being advanced towards clinical testing.

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P0878 / #322

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

ESTIMATION OF REGIONAL CEREBRAL BLOOD FLOW WITH DYNAMIC 18F-FE-PE2I PET IN EARLY PARKINSONIAN SYNDROMES AND HEALTHY CONTROLS – FIRST RESULTS.

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Aims: ^{18}F-FE-PE2I-PET (FE-PE2I) is highly selective for dopamine transporter (DAT) imaging [Chalon S,2019;Fazio P,2018;Fazio P,2019]. The potential of measuring regional cerebral blood flow (rCBF) in dynamic FE-PE2I for differential diagnosis in parkinsonism has, to our knowledge, not been previously investigated.
Our aim was to explore potential differences in rCBF between healthy controls (HC) and parkinsonian patients using FE-PE2I *R1* as rCBF-proxy, validated by rCBF measured with ^{15}O-H_2O PET (H_2O) in the same subjects.
Methods: Thirty-one *de novo* parkinsonian patients (68.4±7.6 years) and 29 HC (70.1±4.6years) did a dynamic FE-PE2I and H_2O at baseline within a clinical trial (EudraCT-no: 2015–03045-26). Two years later, criteria-based diagnostic reassessment confirmed Parkinson´s disease (PD) in 24 cases, three had atypical parkinsonian syndrome (APS), four had non-idiopathic parkinsonism (n-IP) and all HC remained healthy. The *R1* in FE-PE2I was calculated using the simplified reference tissue model [Lammertsma AA,1996] and the double-integral method [Koopman T, 2019] was used for H_2O; cerebellum was used as reference. Mann-Whitney tests were used for group difference analyses on averaged left/right lobar measurements. Two-tailed $p<0.05$ was considered significant.
Results: rCBF with FE-PE2I in the parietal- and occipital lobes were lower in patients than HC ($p=0.023$, $p=0.026$) and in the parietal-, temporal- and occipital lobes with H_2O ($p=0.002$, $p=0.019$, $p=0.005$). APS had lower rCBF than PD in the parietal lobes with FE-PE2I ($p=0.028$) and in the parietal- and occipital lobes with H_2O ($p=0.014$, $p=0.021$).
Conclusions: The highly selective PET-tracer for DAT, ^{18}F-FE-PE2I, may hold potential for differential diagnosis in early parkinsonian syndromes by allowing for both DAT- and rCBF assessment.

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POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

COMBINED APPROACH IN THE DIAGNOSTIC OF PARKINSON'S DISEASE AND OTHER NEURODEGENERATIONS

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Aims: Millions of people suffer from neurodegenerative disorders worldwide. Parkinson's disease (PD) is among the leading disease. Our aim was to develop and scientifically substantiate set of criteria for early diagnosis of neurodegenerative disorders, including molecular genetic analysis and positron emission tomography (PET).
Methods: For molecular genetic analysis we included 60 patients with sporadic and genetic PD forms. To identify genes (PARK2 and 7, LRRK2 and etc.) we used the MLPA technique. Analysis of the GBA gene was carried out by direct sequencing according to Sanger. For PET with 18F-FDG we had 10 patients with PD and 10 healthy people for determination of diagnostic norm. To do it, we used graphs of the distribution density of the activity of the RFP using the Parsen-Rosenblatt method. When conducting MLPA analysis, none of the 60 patients revealed any mutations, which is apparently due to the low incidence of this mutations among patients of our region with diagnosis of PD. But analysis of the GBA gene revealed 6 different variants in 9 out of 60 examined patients. Using PET, the standard indicators have been established that allow to confidently diagnose PD on the basis of PET examination (and to differentiate with healthy people).
Results: Molecular genetic analysis and PET proved their significance for early preclinical diagnosis of neurodegenerative disorders, such as PD. Analysis in the GBA gene showed a similar frequency of occurrence in a sample of patients from our region as in European populations. Determination of a decrease in the uptake of 18F-flurodopa during PET allows to confirm the disease, regardless of the presence or absence of motor manifestations.
Conclusions: This combined approach could be applied for a study of some other neurological diseases.

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P0880 / #208

POSTERS: C04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: SPECT

CORRELATION BETWEEN CARDIAC SYMPATHETIC IMAGING IN-VIVO AND DISTRIBUTION OF CARDIAC SYMPATHETIC NERVES POST-MORTEM IN PEOPLE WITH COGNITIVE IMPAIRMENT

Gemma Roberts[1], Tuomo Polvikoski[2], Debbie Lett[2], Alan Thomas[2]
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Aims: To validate cardiac I-123-mIBG as a biomarker of sympathetic denervation using cardiac tissue obtained post-mortem. To compare regional cardiac I-123-mIBG uptake with the distribution of sympathetic nerves in cardiac tissue samples.
Methods: Participants in cardiac I-123-mIBG studies were invited to donate tissue after death. Clinical diagnosis was based on symptoms and dopaminergic imaging. Neuropathological diagnosis used consensus criteria. I-123-mIBG scans were acquired with a gamma camera. The scans were evaluated for global and regional tracer uptake using Hermes Medical software. A slice from the left ventricular (LV) wall between apex and valve level was fixed in formalin. 5-7 samples covering the entire circumference of the LV wall were stained for tyrosine hydroxylase. High-res images of the sections were analysed using pixel thresholds to assess the level of staining and thus sympathetic nerve density.
Results: We obtained cardiac tissue from 5 participants. The interval between scan and death was 2.8 to 5.2 years.

Clinical diagnosis	Neuropathological diagnosis	Overall mIBG uptake	Regional mIBG uptake	Regional TH staining pattern
Alzheimer's disease (AD)	AD, limbic-predominant age-related TDP-43 encephalopathy, progressive supranuclear palsy No stellate ganglia(SG) pathology	Normal	Posterior-lateral wall reduced	Lowest in posterior section
Possible dementia with Lewy bodies (DLB)	Amygdala alpha-synucleinopathy. Moderate AD, cerebral amyloid angiopathy (CAA) No SG pathology	Normal	Posterior reduced	Anterior and posterior reduced
AD	Limbic DLB, Moderate AD, CAA, Severe SG alpha-synucleinopathy	Low	Reduced throughout	Reduced throughout
AD	Vascular dementia, cardiac amyloidosis No SG pathology	Normal	Posterior reduced	Reduced in anterior septum and posterior
Probable DLB	Brain tissue not available. Severe SG alpha-synucleinopathy	Low	Reduced throughout	Reduced throughout

Conclusions: Neuropathological diagnosis was in line with mIBG results in all cases. Regional uptake matches reasonably well with the distribution of tyrosine hydroxylase stained nerves.

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P0881 / #1647

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

DETECTING PARKINSON'S DISEASE IN THE SKIN WITH ELECTRON MICROSCOPY

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Aims: The presence of phosphorylated Ser129 alpha-synuclein (pSyn) inclusions, the main pathological hallmarks of Parkinson's disease (PD), has been recently detected in the peripheral autonomic nerve fibers in the skin of PD patients. We propose to combine immuno-protocols with electron microscopy to thoroughly characterize the deposition of pSyn inclusions in dermal nerve fiber bundles. This study will help to determine whether skin biopsies will be a useful tool for the detection of PD pathology.
Methods: We studied the ultrastructure of pSyn inclusions in the nerve fiber bundles in human dermis from PD and control age-matched brain donors using correlative light and electron microscopy. 3-mm cervical skin biopsies were chemically fixed at autopsy and processed for electron microscopy with heavy metal staining and resin-embedding. Ultra-thin sections were cut using an ultramicrotome and collected alternating between sections for immunohistochemistry and electron microscopy. Antibodies against pSyn were used to detect immunopositive regions for later imaging using electron microscopy.
Results: We found that a subset of nerve fiber bundles in PD donors were positive for pSyn and the myelin sheaths surrounding them were severely damaged, while the myelin sheaths in the control patients were nicely preserved. We screened multiple biopsies from both PD and control donors and observed the presence of damaged myelinated nerve fibers only in PD donors.
Conclusions: These abnormalities in the myelin sheaths surrounding the diseased nerve fibers may help to discriminate among PD and control subjects and to understand the involvement of the peripheral innervation in the disease. The same approach will also be used to unravel ultrastructural similarities and differences in the dermal nerve fibers from other synucleinopathies.

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P0882 / #292

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

ALTERED GLUTAMATE SIGNALING IN PARKINSON'S DISEASE PATIENTS WITH REM SLEEP BEHAVIOR DISORDER

Christopher Doppler[1,2], Aline Seger[1,2], Ezequiel Farrher[3], Cláudia Régio Brambilla[3], Lukas Hensel[1,2], Christian Filss[4], Ana Gogishvili[3,5,6], N. Jon Shah[3,7,8,9], Christoph Lerche[3], Bernd Neumaier[10], Karl-Josef Langen[3,4], Gereon R. Fink[1,2], Michael Sommerauer[1,2]
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Aims: Patients with Parkinson's disease (PD) and rapid eye movement (REM) sleep behavior disorder (RBD) often show a more malignant phenotype. As glutamate represents the brain's primary excitatory neurotransmitter and is also involved in the pathophysiology of RBD, we expected glutamate signaling to contribute to the clinical divergence of PD.
Methods: We applied ^{11}C-ABP688 following a bolus-infusion protocol, a PET tracer with highly specific binding to the metabotropic glutamate receptor 5 (mGluR5), and simultaneously measured the levels of glutamate and its metabolites using single voxel stimulated echo acquisition mode (STEAM) MR spectroscopy of the left putamen. Thirty-three Parkinson's disease patients were grouped according to their RBD status as determined by overnight video-polysomnography and compared to 15 age- and sex-matched healthy control (HC) subjects. Total volumes of distribution (V_T) of ^{11}C-ABP688 were estimated in cortical and subcortical brain regions with metabolite-corrected plasma concentrations during steady-state conditions between minutes 45 to 60 of the scan.
Results: V_T of ^{11}C-ABP688 were globally higher in PD patients with RBD compared to patients without RBD (P= 0.004) and HC subjects (P = 0.009), whereas levels of glutamate and its metabolites did not differ between groups and did not correlate with the regional V_T of ^{11}C-ABP688. V_T of ^{11}C-ABP688 correlated with the amount of REM sleep without atonia, a hallmark of RBD (F(1,42) = 5.600, P = 0.023), and with dopaminergic treatment response in PD patients (F(1,30) = 5.823, P = 0.022).
Conclusions: Our results suggest that glutamate signaling in PD patients with RBD is altered as indicated by higher V_T of ^{11}C-ABP688 despite unaffected glutamate metabolism. This receptor-neurotransmitter dysbalance might indicate another mechanism contributing to the heterogeneity of PD and warrants further investigation of drugs targeting mGluR5.

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POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

PERSONALIZED WHOLE-BRAIN MODELS IDENTIFY NOVEL NEUROTRANSMITTER RECEPTOR PATHWAYS UNDERLYING HETEROGENEITY IN PARKINSON'S DISEASE

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Aims: Many non-dopaminergic neurotransmitter systems are implicated in Parkinson's disease (PD), resulting in heterogeneous motor/non-motor symptoms. However, the difficulty of in-vivo receptor imaging has impeded our understanding of neurotransmission dysfunction in PD beyond the classical dopaminergic circuit. Using personalized, whole-brain modeling combining multi-modal neuroimaging, spatial templates of neurotransmitter receptors and clinical assessments, we infer the roles of various neurotransmitter systems in PD neurodegeneration and their association with symptomatic heterogeneity.
Methods: We pre-processed longitudinal neuroimaging data from 6 different modalities (dopaminergic DAT-SPECT, T1 and T2 structural, resting-state functional and diffusion-weighted MRI) for (N=71) Parkinson's patients from the Parkinson's Progression Markers Initiative (PPMI). Using averaged (N=4) post-mortem autoradiography-derived templates for 15 (glutamatergic, GABAergic, cholinergic, adrenergic, serotonergic and dopaminergic) receptors, we fit subject-specific models for the longitudinal rate of change of each neuroimaging modality (GM density, t1/t2 ratio, fALFF, mean diffusivity, fractional anisotropy and dopamine transporter density). Obtained model parameters represent i) direct effects of receptor densities, ii) receptor-mediated neurobiological interactions and iii) propagation of pathology. We then performed singular value decomposition across patients to robustly identify receptor mechanisms correlated with 13 clinical assessments from different domains.
Results:

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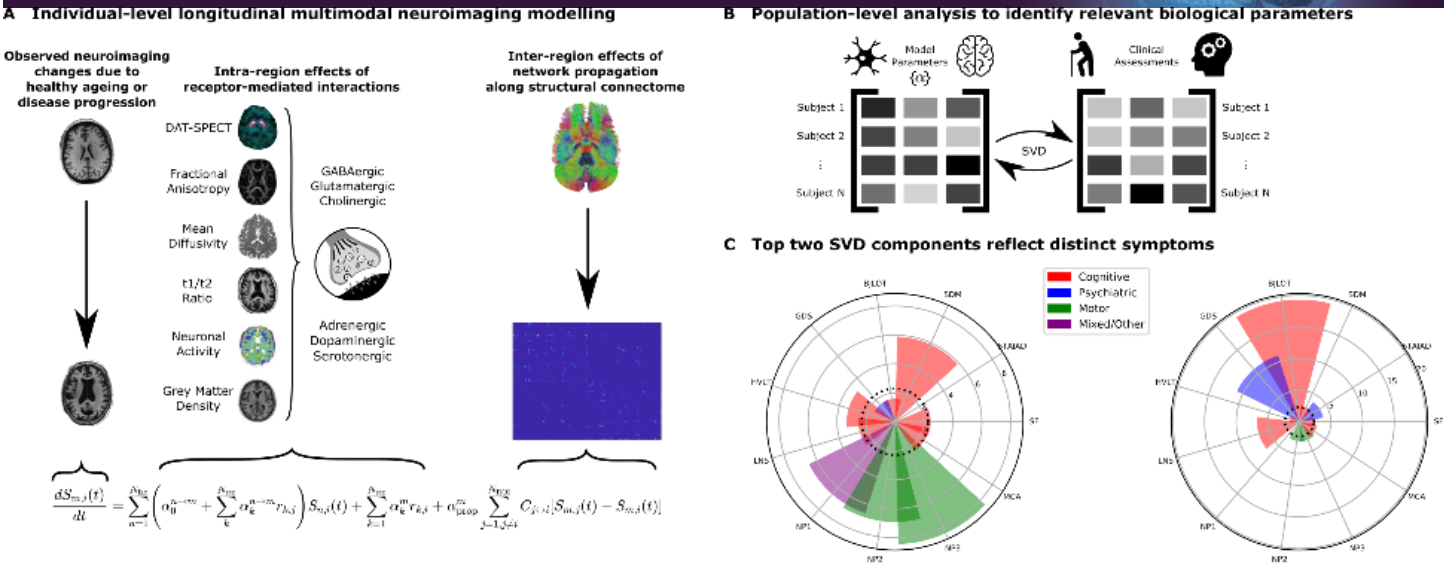

Longitudinal neuroimaging changes are significantly better explained (F-test, P<0.05) by the inclusion of receptor maps in 86%-99% of subjects. Receptor-mediated interactions particularly influence microstructure (t1/t2 and MD). Furthermore, distinct combinations of receptor mechanisms correlate with symptom severity along two axes (47.0% and 14.5% variance explained, respectively; P<0.001) representing i) motor symptoms and psychomotor speed (r=0.89; P<0.001), and ii) visuospatial dysfunction and depression (r=0.85; P<0.001).

Conclusions: This project is the first integration of neurotransmitter receptors, multi-modal neuroimaging and clinical data in an interpretable brain model to identify PD-related mechanistic pathways, constituting a promising step towards personalized and precision neurotransmitter-based treatments.

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P0884 / #1045

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

BILATERAL CHOLINERGIC UPREGULATION ASSOCIATED WITH CA2-CA3 HIPPOCAMPAL ATROPHY IN COGNITIVELY UNIMPAIRED PATIENTS WITH PARKINSON'S DISEASE: A COMBINED MRI-PET STUDY

Camille Legault-Denis[1,2], Étienne Aumont[1,2,3], Kate Onuska[4], T.W. Schmitz[4,5], Aurélie Bussy[6], M. Mallar Chakravarty[6], Jean-Paul Soucy[1], Alain Dagher[1,7], Pedro Rosa-Neto[3,7,8], Marc-André Bédard[1,2,9]
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Aims: Cortical cholinergic denervation has been described in Parkinson's disease (PD) with or without cognitive deficits. However, normal cognition in the latter has been suggested to underly hippocampal cholinergic upregulation as a compensating process. To better describe this feature, cholinergic innervation within the hippocampal subfields was assessed, using MRI segmentation and PET imaging with [^{18}F]-FEOBV.
Methods: The sample consists of six PD patients with normal cognition (PD-NC), six PD patients with mild cognitive impairment (PD-MCI), and six healthy participants (HP). They all underwent a structural T1 MRI (3T) and a high-resolution PET scan with [^{18}F]-FEOBV, a sensitive measure of cholinergic terminal density. Each hippocampus was segmented in five subfields, using the MAGeT-Brain automatic algorithm, and then manually quality-controlled. ANCOVA and Tukey post hoc analyses were performed between the three groups, with corrections for age, total intracranial volume, and partial volume effect.
Results: In comparison with HP subjects, significant volume reductions were observed bilaterally for CA2-CA3 in both PD-NC and PD-MCI. No other hippocampal subfield volumes were found to differ between the three groups. PET imaging revealed higher [^{18}F]-FEOBV uptake in PD-NC than HP, for both right ($p=0.003$) and left ($p=0.007$) CA2-CA3 hippocampal subfields. In contrast, PD-MCI did not show significant [^{18}F]-FEOBV changes compared with HP. Correlational analyses revealed that [^{18}F]-FEOBV uptake in PD-NC increases as a function of CA2-CA3 atrophy (Right: $R=0.62$, $p=0.008$; Left: $R=0.57$, $p=0.014$).
Conclusions: CA2-CA3 hippocampal atrophy was associated in this study with increased [^{18}F]-FEOBV uptake in PD-NC but not in PD-MCI. This supports the hypothesis that cholinergic sprouting may occur in CA2-CA3 to compensate for atrophy. Such a compensation might contribute to the absence of cognitive decline in PD-NC.

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POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

ATROPHY AND HYPOMETABOLISM AT DIFFERENT STAGES OF COGNITIVE DECLINE IN PARKINSON DISEASE.

Jesús Silva-Rodríguez[1], Miguel Labrador-Espinosa[1], María Isabel Reina-Castillo[1], Laura Muñoz-Delgado[1], Pablo Franco[1], Ana María Castellano-Guerrero[1], Daniel Macías-García[1], Silvia Jesús[1], Astrid Adarmes-Gómez[1], Fátima Carrillo[1], Juan Francisco Martín-Rodríguez[1], Florinda Roldán-Lora[2], David García-Solís[3], Pablo Mir[1], Michel Grothe[1]
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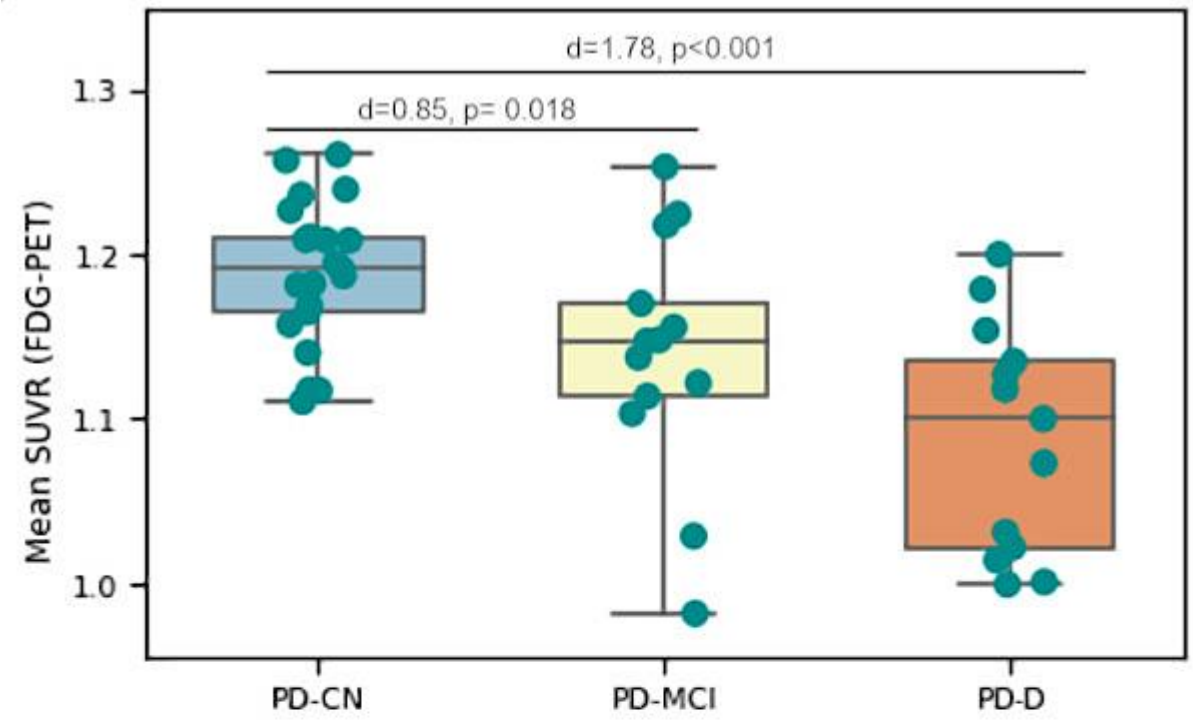
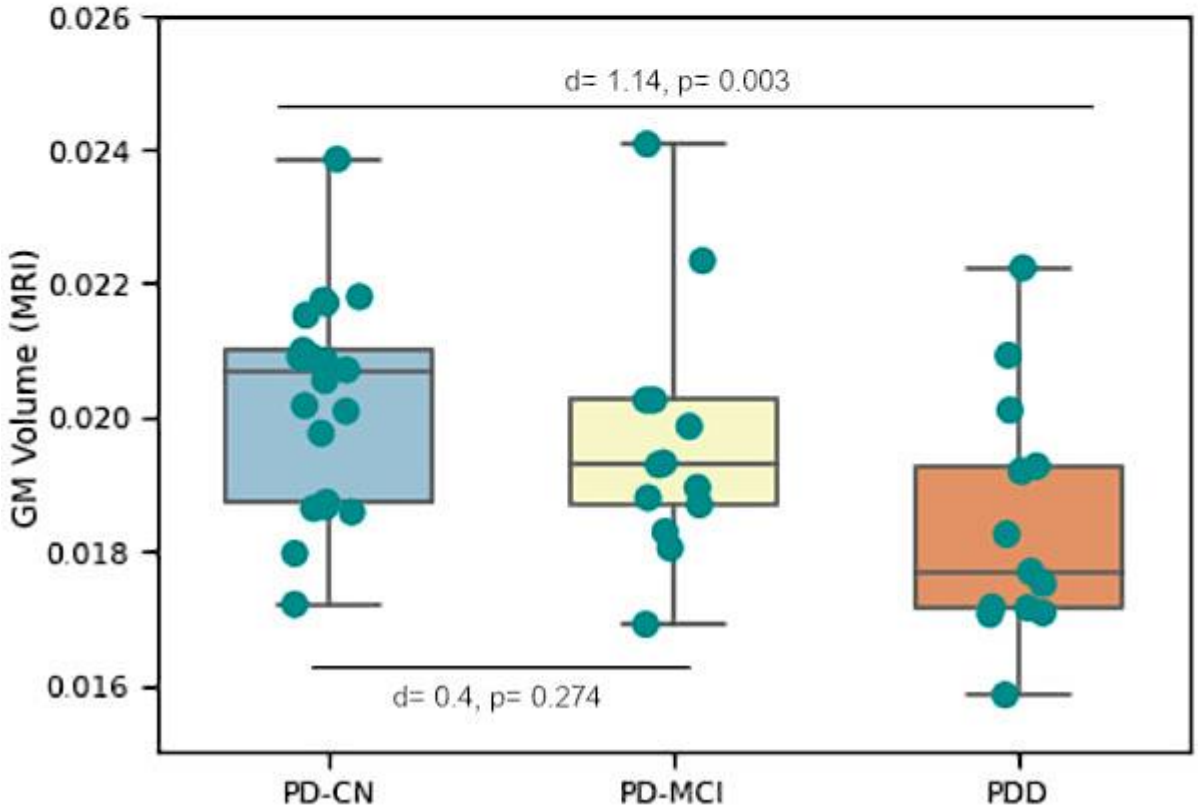
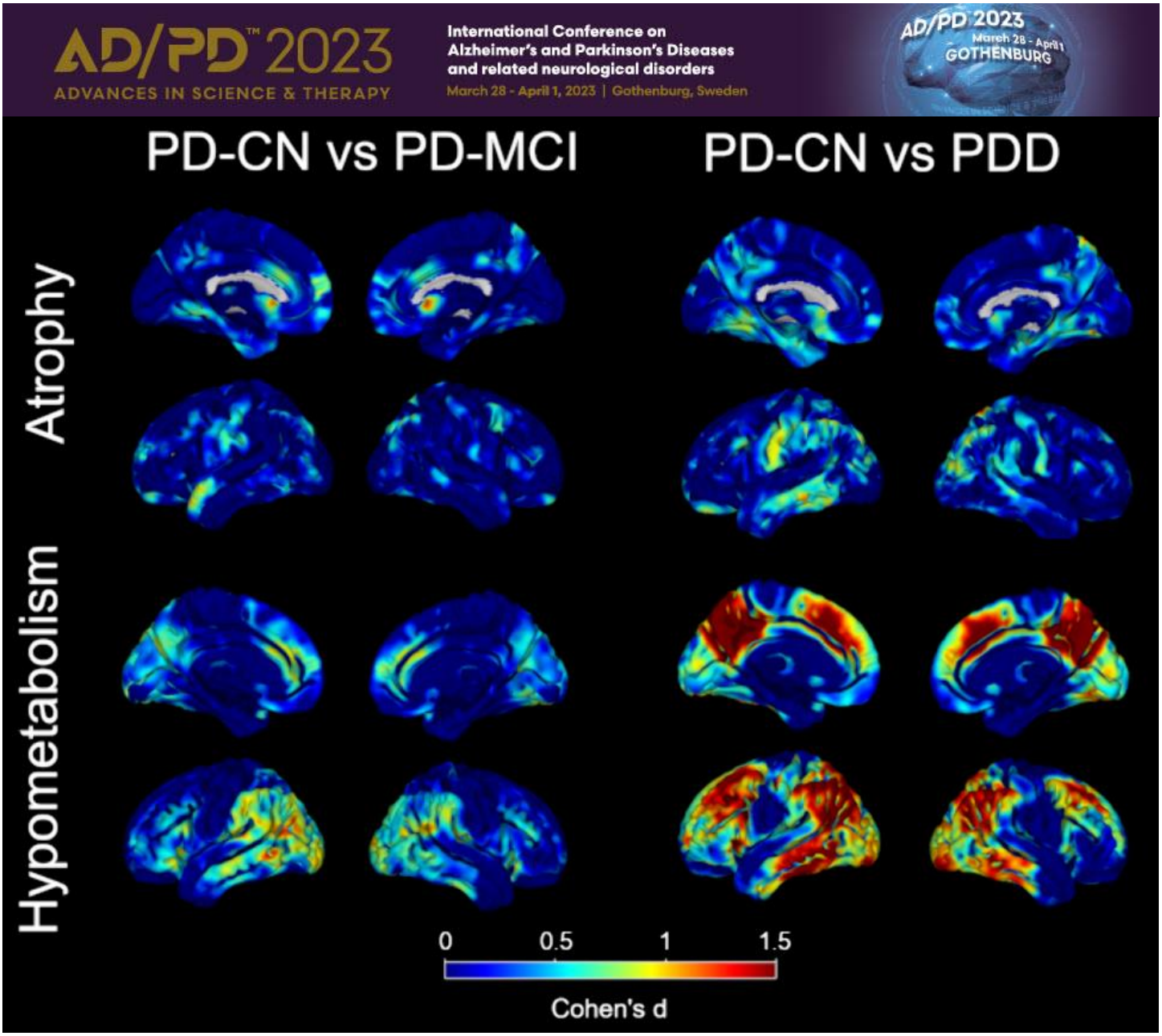
Aims: We aimed to compare the relative sensitivities of quantitatively measured atrophy (MRI) and hypometabolism (FDG-PET) as imaging biomarkers of the cortical neurodegeneration accompanying cognitive decline in Parkinson's Disease (PD).
Methods: 47 PD patients were stratified according to their cognitive status using the PD-Cognitive Rating Scale (PD-CRS): 21 cognitively normal (PD-CN, PD-CRS>81), 12 with mild cognitive impairment (PD-MCI, 81≥PD-CRS>64), and 14 with dementia (PDD, PD-CRS ≤ 64). All patients underwent 3T T1-MRI and FDG-PET. Grey matter volume (GMV) and FDG metabolism were quantified within a posterior-occipital cortical composite region-of-interest found to be sensitive to PD-related cognitive impairments in previous works. Both measurements were contrasted between the cognitively impaired and the PD-CN group. In complementary voxel-wise analyses we assessed modality-specific associations with cognitive impairment in a spatially unbiased manner.
Results: In the PD-MCI group, significant posterior-occipital hypometabolism was observed in comparison to the PD-CN group (d=0.85, p=0.018), but no significant differences were observed in posterior-occipital GMV (d=0.40, p=0.274; Fig.1). The PDD group did show significantly reduced posterior-occipital GMV compared to PD-CN (d=1.14, p=0.003), albeit with a considerably lower effect size compared to posterior-occipital hypometabolism (d=1.78, p<0.001). These results were corroborated in voxel-wise analyses, where both cognitively impaired groups showed more widespread and more pronounced patterns of cortical hypometabolism compared to gray matter atrophy





(Fig.2). ***Fig.1*** ***Fig.2***



Conclusions: Our results suggest that FDG-PET is more sensitive than MRI for the detection of cortical neurodegeneration associated with cognitive decline in PD. This has implications for the design of predictive imaging biomarkers to improve personalized disease prognosis in PD.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

THE PREDICTION OF ALZHEIMER'S DISEASE PATHOLOGY IN PATIENTS WITH DEMENTIA WITH LEWY BODIES USING PLASMA BIOMARKERS

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Aims: Plasma biomarkers have proven to be accurate in assessing Alzheimer disease (AD) pathology, offering a more accessible alternative to cerebrospinal fluid (CSF) and positron emission tomography. AD comorbid pathologic characteristics are common in patients with dementia with Lewy bodies (DLB) and are associated with steeper cognitive decline. Therefore, the aim of this study was to determine if a combination of plasma biomarkers could detect such AD co-pathology in clinically defined DLB patients.
Methods: Participants from the European-DLB (E-DLB) Consortium clinically classified as DLB (n=93), MCI-DLB (n=15) or possible DLB (n=13) were selected based on availability of plasma and CSF biomarkers, MMSE and relevant DLB clinical symptoms. AD pathology positivity was determined by CSF Aβ42/40, or alternatively Aβ42/p-tau, with a prevalence of 52%. Plasma p-tau181 and p-tau231 were measured by in-house SIMOA assays (University of Gothenburg). A logistic regression model for AD pathology in DLB patients was fitted using as predictors p-tau181, p-tau231, age, MMSE score, presence of cognitive fluctuations, parkinsonism, and recurrent visual hallucinations. To determine which predictors were more helpful, bootstrapped internal validation (n=500) was performed with backward variable elimination, at an alpha=0.157 stopping criterion.
Results: During the backward elimination, the model most often selected included plasma p-tau231 and presence of parkinsonism. This model presented an AUC of 87.1% (95% CI 81.0-93.2%), with plasma p-tau231 being positively associated with AD pathology (β-estimate: +0.44, *P*<0.001) and presence of parkinsonism negatively, but not significantly, associated with AD pathology (β-estimate: -1.19, *P*=0.08). Further SIMOA analyses will include plasma Aβ42/40, NfL and GFAP in determining AD pathology in DLB patients.

Conclusions: This multi-centre study demonstrates the importance of plasma biomarkers to highlight AD comorbid pathologic characteristics in DLB patients, with impact for patient management and care.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CROSS-SECTIONAL PROTEOMIC EXPRESSION IN PARKINSON'S DISEASE-RELATED PROTEINS IN DRUG-NAÏVE PATIENTS VS HEALTHY CONTROLS WITH LONGITUDINAL CLINICAL FOLLOW-UP

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Aims: This study aimed to use proteomic profiling of a well-characterized single center longitudinal PD cohort to identify a panel of candidate diagnostic and predictive markers for PD pathology that can help elucidate pathology-associated pathways and mechanisms.
Methods: Aptamer technology (SomaLogic®) was applied to measure protein levels (1305 proteins) in cross-sectional serum samples from 85 diagnosed, drug-naïve PD patients and 93 healthy controls (HC) from the de novo Parkinson's (DeNoPa) cohort at baseline. Statistical analyses included differential expression analysis, feature selection analysis, and pathway clustering analysis. Correlation of baseline protein levels to longitudinal change in clinical symptoms for 8 years was done using linear mixed-effects model analysis.
Results: Findings from the proteomic analysis identified 73 differentially expressed proteins using limma, fourteen of which were confirmed using the feature selection analysis, Boruta. Among the differentially expressed proteins identified, ten proteins—ALCAM, contactin 1, CD36, DUSP3, NCAM-L1, NEGR1, Notch1, TrkB, and tyrosine kinases CSK and BTK— significantly correlated with longitudinal clinical scores including PD progression tracking assessments—Movement disorder Society Unified PD Rating Scale total score and non-motor symptom score, cognitive functioning Montreal Cognitive Assessment, and depression rating scales Geriatric Depression Scale and Beck Depression Inventory—indicating their potential predictive capabilities of different progression types. Known functions of these proteins and their possible relation to PD or its symptoms include biological mechanisms such as cell adhesion, axonal guidance and neuroinflammation, and T-cell activation.
Conclusions: We identified a panel of blood-based biomarkers capable of potentially predicting clinical disease progression of related motor and non-motor PD symptoms. Further insights into the biological mechanisms associated with clinical symptoms were also elucidated, thereby highlighting the need to validate and further investigate these markers and their mechanisms.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

COMBINED PROTEOMIC AND METABOLOMIC CSF PROFILING CAPTURES DISTINCT CSF SIGNATURES ASSOCIATED WITH PARKINSON'S DISEASE

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Aims: CSF analysis is important for the diagnosis of neurological diseases as it is in direct contact with the brain and can reflect disease-related changes at the molecular level. Therefore, our aim was to perform metabolomics as well as proteomics profiling of CSF from participants of the longitudinal Parkinson's disease study "DeNoPa" (six-year longitudinal study with visits at baseline, 24, 48, and 72 months). Furthermore, in addition to "omics" profiling, bioinformatic identification of subgroups based on clinical data was performed and linked to proteomic analysis.
Methods: Metabolites from CSF and plasma samples from the DeNoPa cohort were identify and quantify utilizing the AbsoluteIDQ® p 400 HR Kit from Biocrates. Proteomic profiling was performed utilizing a quantitative label-free mass spectrometry based approach. Subgroup identification analyses were performed using machine learning methods.
Results: Within the metabolome analysis, we detected 37 and 207 metabolites in CSF and plasma, respectively. Several of these metabolites were significantly different between patients and controls especially in one lipid group. Selected differential metabolites are currently validated with independent methods. Univariate and multivariate analyses of the proteomic data revealed distinct protein signature which are currently linked to the clinical data.
Conclusions: The combined metabolite and proteome analysis of CSF opens up a comprehensive view at the molecular level. Several potential metabolite markers were identified, which are currently further validated.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PLASMA CELL-FREE RNA: A PROMISING BIOMARKER FOR PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is the most common neurodegenerative disorder, after Alzheimer disease (AD). We aimed to create a model that can confidently predict PD using plasma cell-free RNA (cfRNA) data.
Methods: We extracted RNA from plasma samples received from the Movement Disorders Clinic at Washington University in Saint Louis. After library preparation and sequencing, data was processed using the standard pipeline including tools such as FastQC, STAR, PICARD, SamTools and Salmon, and applying stringent quality control. We then performed differential expression analyses using DESeq2. We used information on medication use to identify and remove genes whose expression was affected by medication. For predictive model development, data was split into training and testing populations, made up of 70% and 30% of all samples, respectively. We used Lasso regression to model disease status.
Results: We identified 1966 significantly dysregulated genes that were not affected by medication, which is consistent with recent findings in cfRNA in AD. The best predictive model for PD included 30 genes and had an Area Under the Receiving Operating Curve (AUC) of 0.88 in the testing population. The model distinguished PD from AD with 82% specificity, leading to misclassification of 10 out of 56 samples (5 PD cases and 5 controls) in the testing population.
Conclusions: Plasma cfRNA could be a powerful tool for PD prediction, being a minimally invasive biomarker with an accuracy higher or comparable to current CSF biomarkers. We are testing the performance of our model with a variety of neurodegenerative diseases to ensure high specificity for PD.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CHANGES IN THE BLOOD IN PATIENTS AT RISK OF DEVELOPING PARKINSON'S DISEASE AT THE PRODROMAL STAGE

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Aims: The aim of this study was to evaluate changes in the blood in patients at risk of developing Parkinson's disease at the prodromal stage.
Methods: The risk group (n=27) included patients aged 55-75 years according to the results of a neurological examination and upon detection of premotor symptoms - an impairment of olfaction, an impairment in the REM sleep phase and constipation. The control group included patients of the same age (n=20) without these disorders. Real-time qPCR was used to evaluate the expression of a number of genes - PARK7, LAG3, and DRD3, in lymphocytes, and the expression of some microRNA in plasma.
Results: It was shown that in patients at risk, the expression of miR-29a, miR-19a and miR-19b in plasma is reduced by half, and the expression of miR-24 and miR-29 does not change compared to the control group. In addition, the expression of PARK7, LAG3 and DRD3 genes was increased in lymphocytes compared to the control group. Earlier was reported that similar changes were observed in patients diagnosed with PD. PARK7, LAG3 and DRD3 are tightly associated with neurodegeneration and aggregation of alpha-synuclein, and miR-29a, miR-19a, miR-19b correlate with severity of PD. Changes in the expression of miR-24 and miR-29c were detected at late stages of neurodegeneration and it correlated with cognitive impairment in PD. This explains the absence of changes in the expression of these miRNAs at the preclinical stage.
Conclusions: Thus, we found changes in the expression of a number of microRNAs in plasma and the expression of a number of genes in lymphocytes, which are considered as candidates for a diagnostic marker of Parkinson's disease at the prodromal stage. Funding grant agreement: 075-15-2020-795, state contract 13.1902.21.0027 of 29.09.2020, RF-190220X0027.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

GPNMB BIOMARKER LEVELS IN PARKINSON'S DISEASE INDIVIDUALS WITH GBA MUTATIONS

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Aims: We have recently demonstrated that Glycoprotein nonmetastatic melanoma protein B (GPNMB), previously reported as a biomarker for Gaucher's disease (GD), is necessary and sufficient for uptake of fibrillar alpha-synuclein into cells, a mechanism with relevance for the pathophysiology of Parkinson's disease (PD). GD and PD are linked through their relationship to mutations in *GBA*, which encodes beta-glucocerebrosidase, a lysosome-associated enzyme. Individuals who carry homozygous *GBA* mutations develop GD, while those with homozygous or heterozygous mutations in *GBA* have increased risk of developing PD. Both patients with GD and PD exhibit increased plasma GPNMB levels. In this study, we aim to elucidate the connection between biofluid levels of GPNMB and *GBA* mutations in PD patients.
Methods: GPNMB protein levels in 857 PD patients and normal controls were determined via ELISA. Of these individuals, 151 carry at least one mutant allele of *GBA*, the most prevalent being N409S, E365K, and T408M variants (n = 53, 40, and 30, respectively).
Results: Here, we demonstrate an interaction between specific *GBA* variants and GPNMB at the biomarker level.
Conclusions: Our data suggest that GPNMB-*GBA* interactions may inform penetrance of PD in *GBA* mutation carriers.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

EVALUATION OF 1,410 CEREBROSPINAL FLUID SAMPLES FROM THE PPMI COHORT USING A HIGHLY ACCURATE A-SYNUCLEIN SEED AMPLIFICATION ASSAY (AS-SAA).

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Aims: To evaluate αS-SAA performance in CSF samples from a large cohort of patients with PD, individuals at-risk for PD, and healthy controls.
Methods: 1,410 CSF samples from 1,154 participants of the Parkinson Progression Marker Initiative were blindly analyzed using Amprion's αS-SAA, including PD cases (n=566), prodromal cases (n=52, hyposmia and RBD), SWEDD cases (n=55), non-manifesting carriers (NMC, n=318) of PD associated genes (e.g., LRRK2, GBA), and healthy controls (HC, n=163). Participants underwent regular clinical evaluations, dopamine imaging, and longitudinal biofluid collection. Sensitivity and specificity were determined in PD patients and HC, including PD subgroups (sex, genetic variant carriers, subjects with and without olfactory deficits). Frequency of positive CSF αS-SAA results was determined in prodromal subjects and NMCs. Longitudinally collected CSF samples were compared within patients, in some cases spanning over 7 years of follow-up.
Results: Sensitivity and specificity for all PDs was 88%, while specificity for HC was 96%. Sensitivity in sporadic PD with typical olfactory deficit was extremely high (98%), while other groups presented lower sensitivities (67% for LRRK2 carriers, 71% for sporadic PD patients without olfactory deficit, and 39% for LRRK2 carriers without olfactory deficit). Among prodromal and at-risk groups, 86% of RBD and hyposmic cases had a positive αS-SAA result. 8% of NMC (LRRK2 and GBA) were positive. Longitudinal samples showed little variation, with most patients with positive results at baseline remaining positive in follow-up.
Conclusions: Our results confirm the diagnostic accuracy of αS-SAA for PD and demonstrate that αS-SAA is positive in most prodromal cases and a small fraction of at-risk NMCs. These findings along with the variability among subgroups indicate that αS-SAA may be a crucial biomarker to establish homogeneous at-risk cohorts for observational and interventional studies.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

LEVELS OF CSF SEEDED ALPHA-SYNUCLEIN OLIGOMERS REFLECT PARKINSON'S DISEASE SEVERITY

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Aims: The identification of reliable diagnostic biomarkers that correlate with Parkinson's disease (PD) severity is needed for better clinical treatment. Using a novel approach, we explore disease associated alpha-synuclein (αSyn) aggregates as biomarkers of PD clinical course.
Methods: A combination of both seed amplification assay (SAA) and enzyme-linked immunosorbent assay (ELISA) was used to establish a quantitative test readout that mirrors the disease severity of PD patients. At first, we explored two sets of human brain homogenates (pilot and validation sets), and then verified it with three independent human CSF cohorts; one discovery (62 PD, and 34 control) and two validation (49 PD and 48 control; 20 PD and 20 control respectively).
Results: Pilot set analysis showed that oligomers-specific ELISA robustly quantified SAA end product from subjects with PD or DLB with high sensitivity and specificity scores (100%). The validation set of human brain homogenates further showed that seeding activity could be detected earlier with oligomeric ELISA as the test readout rather than SAA alone. More importantly, multiplexing the assays provided robust information about the patients' clinical disease stage. In the discovery cohort, levels of CSF seeded αSyn oligomers correlated with the severity of the clinical symptoms of PD as measured by UPDRS-motor ($r = 0.58$, $p < 0.001$) and H&Y scores ($r = 0.43$, $p < 0.01$). Similar correlations were observed in the two validation cohorts between the concentrations of CSF seeded αSyn oligomers and the respective cohort UPDRS-motor scores.
Conclusions: Our findings suggest that levels of CSF seeded αSyn oligomers are important diagnostic biomarkers for PD that reflect disease stage by correlating with clinical measures of disease severity.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

BETA-GLUCOCEREBROSIDASE PROTEIN LEVELS ARE INCREASED IN THE CSF OF PARKINSON'S DISEASE, ALZHEIMER'S DISEASE, AND DEMENTIA WITH LEWY BODIES PATIENTS

Bárbara Fernandes Gomes[1], Mathias Sauer[2], Sophia Weiner[1], Gunnar Brinkmalm[1], Ann Brinkmalm[1], Johanna Nilsson[1], Bengt Nellgård[3], Keti Dalla[3], Andrea Pilotto[4], Alessandro Padovani[4], Davide Chiasserini[5], Lucilla Parnetti[6], Ulf Andreasson[1,2], Kaj Blennow[1,2], Johan Gobom[1,2], Henrik Zetterberg[1,2,7,8,9]
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Aims: Mutations in beta-glucocerebrosidase (GBA), a lysosomal enzyme, are known to be a major risk factor for Parkinson's disease (PD) and dementia with Lewy bodies (DLB). We developed a targeted mass spectrometric method to measure protein levels of GBA in cerebrospinal fluid (CSF) and used it in a clinical study to determine if GBA is a viable candidate biomarker for DLB. For this, GBA was measured in the CSF of a small clinical cohort.
Methods: Based on previous untargeted mass spectrometry data, a tryptic peptide for GBA (SYFSEEGIGYNIIR) was selected for quantification. A parallel reaction monitoring (PRM)-based method was developed using nano-LC-MS coupled to a high-resolution Quadrupole-Orbitrap hybrid mass spectrometer. CSF samples from two independent cohorts comprised of healthy controls (n=19) and patients with Alzheimer's disease (AD) (n=22), DLB (n=21), PD (n=6) were analyzed.
Results: We show that this assay can successfully detect GBA in 5 µL of CSF. GBA was significantly ($p < 0.05$) increased in PD, AD, and DLB patients (fold change = 1.67, fold change = 1.45, fold change = 1.52, respectively), compared to healthy controls. GBA concentration also shows a correlation with cognitive status, being significantly ($p < 0.05$) increased in patients with mild cognitive impairment, and dementia (fold change = 1.47, fold change = 1.44, respectively), compared to patients with normal cognition.
Conclusions: GBA protein levels are indiscriminately increased in the CSF of PD, AD, and DLB patients, compared to healthy controls, making it a more likely biomarker candidate for general neurodegeneration than a DLB- or PD-specific biomarker.

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POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

CORTICOTROPIN-RELEASING HORMONE PROTEIN LEVELS ARE DECREASED IN THE CSF OF PARKINSON'S DISEASE AND DEMENTIA WITH LEWY BODIES PATIENTS

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Aims: Proteomic data generated by the MIRIADE consortium suggests corticotropin-releasing hormone (CRH) as a potential biomarker for dementia with Lewy bodies (DLB), with the ability to discriminate DLB from Alzheimer's disease (AD) and frontotemporal dementia. The goal of this study was to develop a targeted mass spectrometric assay to measure CRH in CSF and evaluate its biomarker potential by analyzing a small cohort of patients.
Methods: Based on data from the PeptideAtlas database (Human CSF 2014-09 build), the tryptic peptide CRH 82 – 101 (SPAAPLSPASSLLAGGSGSR) was selected for quantification. A method was developed based on parallel reaction monitoring (PRM) using nano-LC-MS with a high-resolution Quadrupole-Orbitrap hybrid mass spectrometer, that enabled measurement of CRH in 5 µL of CSF. This method was used to analyze CSF samples from two independent cohorts comprised of healthy controls (n=19) and patients with AD (n=22), DLB (n=21), and Parkinson's disease (PD) (n=6).
Results: We determined this assay can successfully detect and quantify CRH in 5 µl CSF with a CV<10%. CRH was significantly ($p < 0.05$) decreased in the CSF of PD and DLB patients (fold change=-1.8 and -1.9, respectively), compared with healthy controls. In addition, CRH levels in both PD and DLB were significantly different from AD samples (fold change = -2.11 and -2.05, respectively).
Conclusions: CRH is decreased in PD and DLB patients, and can discriminate both these diseases from AD, making it a potential biomarker for these two synucleinopathies.

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P0897 / #580

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

A METABOLOMIC BLOOD TEST FOR PARKINSON'S DISEASE.

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Aims: The goal of our project is to identify a blood metabolomic test for Parkinson's disease, especially at an early stage.
Methods: Plasma samples from 100 PD and 25 age and gender matched healthy controls, from the Parkinson's Disease Biomarker Program, were utilized for analysis of 1863 metabolites using high resolution mass spectrometry (General Metabolics, Inc.). We conducted an unbiased evaluation of the metabolites to enable prediction of PD from normal controls.
Results: We identified a panel of 20 metabolites that enabled high accuracy for predicting PD (91%) with AUROC of 0.96. In addition, our model was able to accurately predict the presence of PD in early stage/drug naive subjects with high accuracy of 92%.
Conclusions: These data suggest that a blood test for PD is possible using metabolomic biomarkers. New studies are in progress to validate these findings.

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P0898 / #868

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PROTEOMIC ANALYSIS OF CEREBROSPINAL FLUID OF PATIENTS WITH PARKINSON'S DISEASE, ATYPICAL PARKINSONISM AND CONTROLS

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Aims: The diagnosis of Parkinson's disease (PD) and atypical Parkinsonian syndromes (APS) is challenging due to overlapping clinical phenotypes. We aimed to identify protein signatures in cerebrospinal fluid (CSF) to differentiate PD, APS, and controls (Ctrl).
Methods: CSF samples were collected from patients with PD (n=50), APS (n=47) and age-matched controls without neurodegeneration (n=44). The APS group included Multiple system atrophy (MSA; n=16), Dementia with Lewy bodies (DLB; n=7), Corticobasal degeneration (CBD; n=8) and Progressive supranuclear palsy (PSP; n=16). Mass spectrometry experiments were performed on a Q-Orbitrap platform (Q-Exactive Plus) in a data-dependent acquisition (DDA) mode. Differential expression analyses were conducted with customized scripts (in R and Perseus). Three different imputation methods (MinProb, Man, K-nn) were applied to cover missing values.
Results: Pre-processing identified a total of 575/497 proteins (in R/Perseus, respectively). In PD vs. Ctrl 16/11 proteins were found differentially expressed (DE). Their functional enrichment showed pathways related to acute-phase response, platelet degranulation and neutrophil activation. DE analyses revealed 14 significant proteins for non-PD-synucleinopathies vs Ctrl and 53 for non-PD-synucleinopathies vs PD. Functional annotation of those upregulated DE proteins showed pathway enrichment for plasminogen coagulation, protein activation cascade and immune response.
Conclusions: Our proteomic analysis revealed several DE proteins in CSF that are involved in acute phase, inflammatory and immune responses, arguing for a contribution of these pathways in the pathogenesis of synucleinopathies. The value of individual proteins as biomarker needs to be validated in studies with larger cohorts.

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P0899 / #548

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

FACTORS INFLUENCING THE RT-QUIC ASSAY FOR ALPHA-SYNUCLEIN

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Aims: The Real-Time Quaking Induced Conversion (RT-QuIC) assay has shown great potential to detect aggregates of α-synuclein (α-Syn) in cerebrospinal fluid (CSF) of subjects with dementia with Lewy bodies (DLB). Our aim was to define the factors affecting the performance of the assay.
Methods: RT-QuIC reactions were performed at 37 degrees using a pH of 7.4, six 1mm beads and shaking following the protocol of Fairfoul et al. (2016). Reactions were seeded with 10µL of pooled CSF from subjects with DLB or subjective cognitive decline (SCD) and run in triplicates. Different RT-QuIC parameters such as temperature, sample volume, recombinant protein and beads were varied and compared to this reference condition. The number of positive replicates showing aggregation, the lag-phase and fluorescence were used as outcome measures.
Results: The reference condition (N=6) showed aggregation in all DLB replicates and in one out of three SCD replicates. Increasing temperature or CSF volume prevented aggregation in all DLB replicates while a different recombinant protein produced aggregation in all SCD replicates. Different shaking settings, adding NaCl to the buffer or a lower pH reduced the number of positive DLB replicates. Adding SDS to the buffer increased the variation in lag-phase between DLB replicates from 11% to 42%. Adding one extra bead to each well reduced the maximum fluorescence by 66%. However, the use of zirconium/silica instead of glass beads reduced the variation in maximum fluorescence (zirconium/silica (N=6) intra/inter-assay variation: 34.1%/36.8%; glass (N=6) 44.2%/50.5%).
Conclusions: We identified that temperature, CSF volume and type of recombinant protein impact performance of the α-Syn RT-QuIC assay most. Buffer additives, shaking settings, bead number and material can be varied during optimization. Currently we are clinically validating the RT-QuIC assay.

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P0900 / #1234

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

SYNUCLEIN SAA UTILIZATION BY DIAGNOSTIC CODES

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Aims: Detection of misfolding synuclein aggregates in cerebrospinal fluid (CSF) by α-synuclein (αSyn) seed amplification assay (αS-SAA) correlates with high accuracy in Parkinson disease, dementia with Lewy Bodies, and multiple system atrophy. Clinical value of αS-SAA may therefore be realized through specific rule-in/rule-out and confirmatory applications such as MCI, dementia/Alzheimer's disease, atypical Parkinson's disease, Lewy body variant of Alzheimer's disease, and movement disorders. In this study, diagnostic/clinical test results were examined to evaluate utility of the αS-SAA test as used in the clinical setting
Methods: Diagnostic Codes (ICD-10) from 54 CSF patient samples were reviewed by a medical director for clinical significance/quality and compared against their "detected" or "not detected" result.
Results: 9 patientss had no codes and were rejected from analysis. From the remaining 45 patients there were 26 unique codes. Aggregation of these codes revealed the following detection rates: 18% "Other dementia" (n = 11), 0% PD (n = 9), 100% PD-LBD (n = 2), 17% DLB (n = 6), 100% AD-DLB (n = 2), 0% AD (n = 1), 40% MCI (n = 5), and 0% other symptoms (n = 9). Additionally, 7 distinct codes were associated with "detected" and 17 with "not detected." Based on clinical review, these data likely represent distinct opportunities for αS-SAA to contribute to improvement in management.
Conclusions: αS-SAA test results and codes from 54 patients highlight clinical utility presumptively for: 1. Rule-out of PD 2. Confirmation of DLB, 3. Re-evaluation of DLB, 4. Rule-in/rule-out of synucleinopathy component of AD 5. Distinguishing between MCI-DLB vs MCI-AD. Physicians may utilize these data for either continuing with a treatment plan or supporting suspicion of a diagnosis/modifying treatment plan. Future data from clinical providers will continue to improve utilization.

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P0901 / #796

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

COMPLEMENT SYSTEM CHANGES IN BLOOD IN PARKINSON'S DISEASE AND PROGRESSIVE SUPRANUCLEAR PALSY/CORTICOBASAL SYNDROME

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Aims: Parkinson's Disease (PD) is a clinically diagnosed neurodegenerative disorder. It is often challenging to differentiate early PD from atypical parkinsonian disorders such as the Four-repeat (4R-) Tauopathies Progressive Supranuclear Palsy and Corticobasal Syndrome. Diagnostic biomarkers are necessary, and several proteomic studies have suggested the complement system is altered in PD plasma, but validation studies are lacking. The aim of this study was to investigate whether peripheral blood levels of complement proteins could be used as diagnostic biomarkers for PD versus healthy controls, and whether they could aid in differential diagnosis between PD and 4R-Tauopathies.
Methods: Plasma from 148 individuals (PD, 4R-Tauopathies, and healthy controls (HC)) from the Swedish Biopark cohort were used to quantify 12 complement proteins with immunoassays, and CH50 classical pathway complement activity was quantified in sera from further 78 individuals (PD and HC).
Results: Complement factors C1q and C3 in plasma were lower in individuals with 4R-Tauopathies (ANOVA, p=0.0041, p=0.0057 respectively) compared to both PD and HC. None of the analysed complement proteins were altered between PD and HC, however a few proteins correlated with clinical parameters within the PD group. Most notably, levels of C3 correlated with non-motor symptoms in female patients. We did not find a difference in classical complement activity in PD serum compared with HC, but we did find a correlation with mental fatigue severity.
Conclusions: In conclusion, individuals with 4R-Tauopathies displayed lower concentrations of plasma C1q and C3 compared with PD and HC. Neither complement levels nor CH50 activity were significantly altered in PD versus HC, but both may be associated with PD symptom severity.

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P0902 / #1853

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PLASMA P-TAU181 LEVELS IN CLINICALLY DIAGNOSED ALZHEIMER'S DISEASE WITH SMALL VESSEL (SVAD) COMPARED WITH AD

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Aims: The fundamental pathological process in the development and progression of AD is amyloid(Aβ) deposition and Tau toxicity. Cerebral small vessel disease can develop cognitive impairment and dementia independently and in collaboration with Alzheimer pathology. Thus, the detection of Alzheimer's biomarkers might be useful for distinguishing the basic pathology of AD dementia from concurrent vascular diseases.
Methods: 334 EDTA plasma samples of patients admitted to the UBC Hospital Clinic for Alzheimer's disease between 2008 – 2018, and 25 samples of matched aged healthy control with normal cognition were included. The cohort was sorted into 5 diagnostic groups: healthy control, "No Cognitive Impairment" (NCI), non- AD neurodegenerative disease (non -AD NDD), AD, and small vessel diseases with AD (SVAD) according to clinical and neuroimaging findings. The samples were assayed by using a developed p-tau181 specific Simoa
Results: A subgroup of 40 patients (Female = 15) with small vessels disease and AD were compared with other groups. Mean age of SVAD cases (78.8 ± 7.7) was higher than any of the other diagnostic groups ($p<0.001$). The plasma p-tau181 concentrations of cases with SVAD were twice more than control and about three times more than NCI and other neurodegenerative diseases groups ($p<0.001$) and slightly more than plasma p-tau181 in AD cases.
Conclusions: The plasma p-tau181 levels in SVAD cases were significantly more than control and NCI cases. We found a slight difference in p-tau181 levels between SVAD and AD cases. Further studies with larger clinical sample need to investigate the effects of SVD on plasma p-tau181 concentrations in AD.

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P0903 / #2045

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

IS IT POSSIBLE TO DIAGNOSE PARKINSON'S DISEASE WITH THE HELP OF DEHYDROEPIANDROSTERONE SULFATE ?

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Aims: Aim of our study was to compare the level of dehydroepiandrosterone sulfate (DHEA-S) in blood plazma in patinents with Parkinson's disease dementia
Methods: We examined 60 patients with PD, who were divided into 30 patients depending on the presence or absence of dementia. As a control, we also examined on a voluntary basis 30 healthy persons recognized as such by a special commission. Thus, patients with cognitive impairments were defined by us as the main group, and in the absence of non-motor manifestations of PD, in particular, dementia, the comparison group. Serum dehydroepiandrosterone sulfate values were obtained, the state of cognitive function was assessed using the following scales: MMSE, MOCA, CDR
Results: Analysis of the distribution of the mean value of the blood biomarker in the examined patients and healthy individuals revealed the following feature. Investigation of the level of dehydroepiandrosterone sulfate progressively decreased, reaching its minimum value in patients of the main group. The comparative group in this case occupied a borderline value. Dehydroepiandrosterone (DHEA), another important endogenous antiglucocorticoid, has procognitive properties. According to the results of the study, it was found that a decrease in DHEAS by 40-50% indicated the development of chronic cerebral ischemia in the patient, a 10-fold decrease in DHEAS made it possible to establish the development of an early form of the disease, while a decrease in more than 10 times about the developed Alzheimer's disease.
Conclusions: The diagnostic efficacy of dehydroepiandrosterone sulfate in the blood serum of patients, was established for the early diagnosis of dementia and monitoring the effectiveness of therapy, identifying a risk group in PD.

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P0904 / #1692

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

PEPTIDOMIC ANALYSIS IN CSF IDENTIFIES CHANGED N-TERMINAL PROCESSING OF MAJOR PRION PROTEIN AS A POTENTIAL BIOMARKER IN PARKINSON'S DISEASE

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Aims: Symptoms of Parkinson's disease develop gradually and can in the early stages be hard to recognize and distinguish from those of other parkinsonian disorders. Data suggest as many as 25% of patients who have received a clinical diagnosis of Parkinson's disease may be misdiagnosed. Therefore, specific biomarkers of Parkinson's disease would benefit patients, caregivers, and researchers alike. In this study, we used an unbiased mass spectrometry-based approach with the aim to discover potential new biomarkers of parkinsonian disorders.
Methods: To identify new biomarkers, we performed an explorative TMT endopeptidomic analysis of cerebrospinal fluid from patients with Parkinson's disease, and other parkinsonian disorders**:** corticobasal degeneration, multiple system atrophy, and progressive supranuclear palsy (*n* = 67). A PRM method was established and used to validate the findings in a second cohort.
Results: Among the peptides that showed the most significant differences in Parkinson's disease were several from the N-terminal region of major prion protein (PrP), which were all decreased compared to healthy controls and also compared to subjects with corticobasal degeneration, multiple system atrophy, and progressive supranuclear palsy (Figure 1). The follow-up study validated the findings of decreased abundances of PrP 23-31 and PrP 23-34 in Parkinson's disease.
Conclusions: Endogenous peptides in CSF from the N-terminal region of major prion protein are decreased in Parkinson's disease. These peptides have potential to indicate Parkinson's disease in clinical samples and, possibly, to distinguish between Parkinson's disease and other parkinsonian disorders. Our results suggests that N-terminal processing of major prion protein may be involved in the pathophysiology of Parkinson's disease.

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P0905 / #701

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

A NOVEL ELISA IMMUNOASSAY FOR THE DETECTION OF N-TERMINAL A-SYNUCLEIN IN CSF OF PATIENTS WITH DIFFERENT SYNUCLEINOPATHIES

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Aims: Alpha-synuclein (α-Syn) is the hallmark protein in Parkinson disease (PD), PD with dementia (PDD), Dementia with Lewy bodies (DLB) and Multiple System Atrophy (MSA) collectively called "synucleinopathies". The clinical use of measuring α-Syn into CSF as a diagnostic biomarker for these disorders is limited so far, due to significant overlap. However, most relevant studies, use immunoassay methods targeting the C-terminal α-Syn. We developed a novel immunoassay targeting N-terminal region and explored the clinical performance in a cohort of patients with different synucleinopathies vs. controls.
Methods: A novel prototype N-terminal α-Syn ELISA was used using monoclonal antibody (mAb) 16A6 (aa 1-60; detector) and mAb 24G6 (aa 91-110; capture). The C-terminal α-synuclein fragment was additionally measured using the commercial Euroimmun α-Syn ELISA (Cat#EQ6545-9601-L). A total of 52 CSF samples (13 PD, 6 PDD, 10 DLB, 12 MSA and 11 control subjects) were included in the study.
Results: The detection range of the novel N-terminal α-Syn ELISA was between 25 and 400 pg/mL, while the inter-run precision was between 1.1 and 3.1%. The assay is specific for α-Syn, without cross-reactivity with β or γ synuclein up to a concentration of 10^4 pg/mL. All clinical samples were detected within the measuring range as shown in the Figure. Statistical significant difference was found for the PDD (p=0.0416) and marginal for DLB (p=0.0656) groups compared to controls, while this was not evident with the commercial

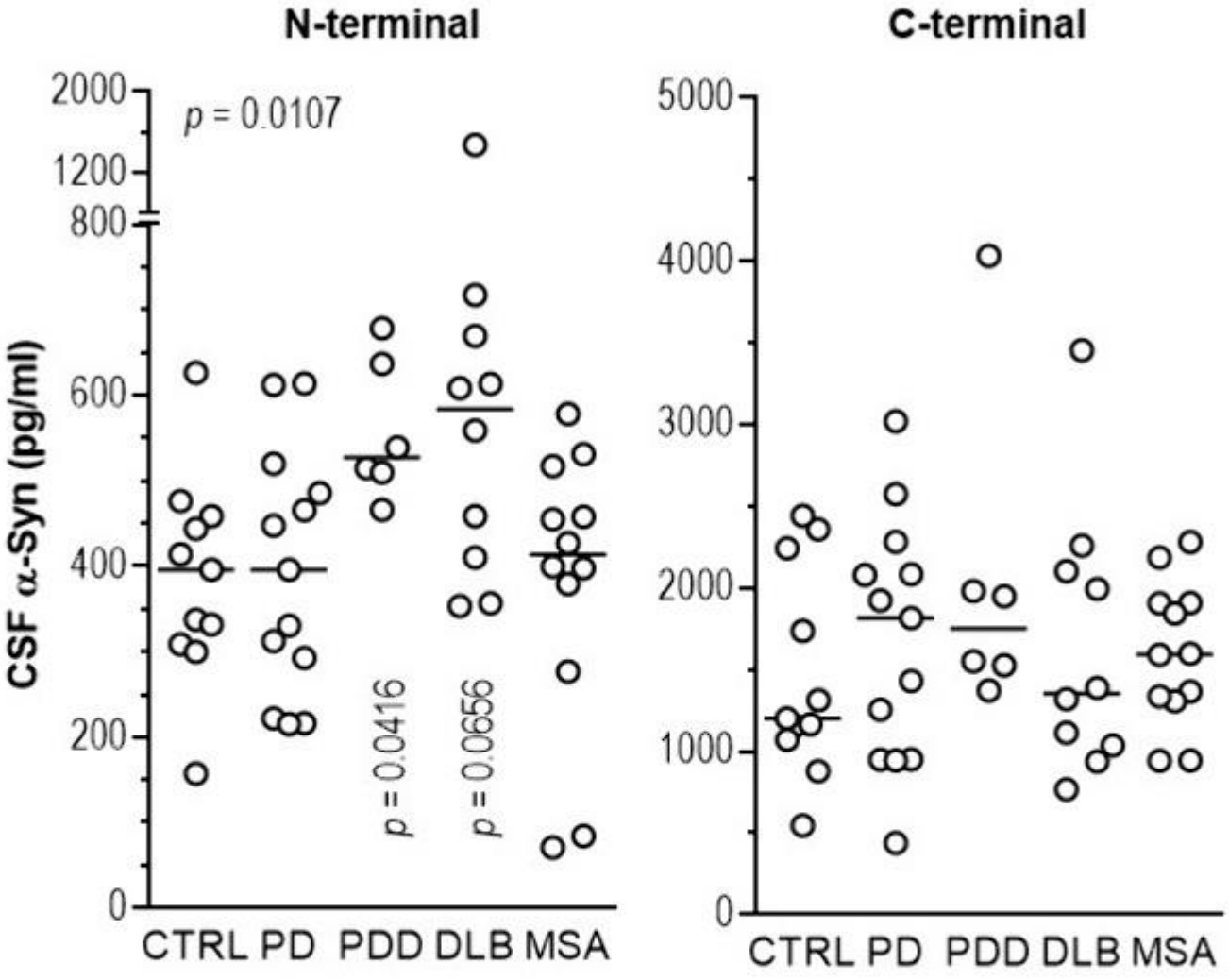

Figure: Scatterplot of CSF α-Syn levels in the studied groups, measured by the two ELISAs. Significant results were observed only in measurements performed by the N-terminal ELISA. The horizontally placed p value is the result of the Kruskal-Wallis test. The vertically placed p values are the results of Dunn's post-hoc tests for comparison between patient groups and controls (CTRL) (significant 0.0416 for PDD vs CTRL and marginally significant 0.0656 for DLB vs CTRL; all others non-significant)

ELISA.

Conclusions: N-terminal α-synuclein measured into CSF may be a promising potential biomarker for synucleinpathies. Further confirmation is needed.

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P0906 / #2338

POSTERS: C04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

EEG MICROSTATES IN DEMENTIA WITH LEWY BODIES: 1 YEAR FOLLOW UP

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Aims: EEG microstates (MS) represent transient, quasi-stable patterns of EEG and are considered as potential biomarker for mild cognitive impairment with Lewy bodies (MCI-LB). Our one-year-old work showed that probable MCI-LB subjects had higher occurrence of all MS compared to healthy controls (HC) and current study should deepen our understanding of correlation between MS dynamics and disease progression in drug naïve probable MCI-LB. Source imaging of MS was additionally performed.
Methods: Altogether, 24 probable MCI-LB and 24 H were assessed at baseline and at 1 year FU using validated scales and questionnaires. All subjects underwent 5 minutes of eyes-closed resting-state evaluation with 256-channel scalp EEG at baseline and at FU. T1 MRI was performed. The microstates analysis was based on the clustering of EEG topographies, using a k-means approach. Mean MS occurrence was used as our temporal parameter of interest and correlated with behavioral outcomes
Results: MCI-LB subjects did not progress in cognitive, motor and behavioral symptoms and nobody converted into DLB. Despite of mean occurrence increase of all MS at baseline in MCI-LB group, results were less or no significant at FU visit, compared to HC. Significant correlations were found between baseline MS1-occ and dominant α frequency and variability, MS3-occ and geriatric depression scale, MS4-occ and excessive sleep scale, while these correlations were less insignificant at FU visit. Eight and six out of 24 MCI-LB subjects dropped significantly in MS1-occ and MS2-occ.
Conclusions: We identified 5 MSs that reflect major brain networks. Increased MS occurrence in MCI-LB at baseline was correlated with core and supportive symptoms of the disease. However, in current study occurrence dropped reflecting decreases in network hyperconnectivity with prodromal DLB progression. This was particularly prominent in the visual and cingulo-opercular networks.

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P0908 / #969

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

CORRELATION OF COGNITIVE FUNCTIONS AND KINEMATIC FEATURES OF PATIENTS WITH PARKINSON'S DISEASE WITH AND WITHOUT DOPAMINERGIC THERAPIES

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Aims: To analyze the correlation between gait and balance kinematic features in Off and On therapeutic conditions and cognitive performances in patients with fluctuating Parkinson's disease (PD).
Methods: Forty PD candidates for device-aided therapies due to the suboptimal control of motor fluctuations underwent an extensive neuropsychological assessment investigating reasoning, long-term memory, short-term memory, attention, frontal executive functions, language, and visual-spatial abilities, reported as the sum of the Z-scores obtained by each pertinent test raw score according to normative data. Gait and balance parameters were derived in both Off (an overnight withdrawal of dopaminergic therapy) and On (45 minutes after a 1.5x patient's morning dose of levodopa intake) therapeutic condition by means of the Opal (APDM)™ motion sensors. A battery of standardized tests was performed: Two-minute walk test; Timed-up and go test (TUG test); Sway test; 360 degrees Turn Test. Spearman correlation analyses were performed to explore correlations between kinematic and cognitive features. Given the multiple analysis, we considered only strong correlations (i.e., $p<0.001$).
Results: Highly significant correlations were found between: 1) turn velocity at the TUG test in Off and short-term memory (0.541; $p<0.001$); 2) the Off vs. On difference in TUG test duration and short-term memory (-0.564; $p<0.001$); and 3) the Off vs. On difference in TUG test duration and language (-0.743; $p<0.001$).
Conclusions: We found that specific measures of gait impairment and their response to levodopa are strongly correlated with distinct patterns of cognitive impairment in PD, highlighting the potentiality of kinematic features as proxy of dopaminergic and non-dopaminergic pathological processes, especially when assessed in Off and On therapeutic conditions. Functional MRI measures of brain connectivity from these patients might contribute to clarifying specific patterns of abnormal neurotransmission.

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P0909 / #1991

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

LONG TERM COGNITIVE OUTCOME OF PRODROMAL AND MILD DEMENTIA WITH LEWY BODIES

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Aims: The cognitive course of dementia with Lewy bodies (DLB) from its early stages is poorly understood. In the dementia stage, its association with Alzheimer's disease (AD) accelerates cognitive decline. The aim of this study is to analyse the long-term cognitive evolution of early stages of DLB.
Methods: Participants of the AlphaLewyMA cohort study were recruited for either mild cognitive impairment (MCI) or mild dementia with a suspicion of DLB or AD. Thirty-one healthy controls were also recruited. All participants were followed up for a minimum of 5 years. The diagnosis considered was that made at the last visit. Using a beta regression, we compared the longitudinal scores of the Mini-mental State Examination (MSSE) of 110 DLB patients, 57 AD patients, 19 DLB+AD patients, 30 patients with other cognitive diseases, and 31 healthy subjects.
Results: The mean follow-up of the participants was 4.9 years (SD ±2.1). During the follow-up, 22 died, 7 went to a nursing home. Using beta regression, the decline of DLB patients is milder than that of AD and DLB+AD patients (P<0.001). The variability of MMSE measured by the standard deviation of the MMSE of each subject is greater for AD (average SD ±4.53) and DLB+AD (SD ±4.80) than for DLB (SD ±2.67). Year-to-year variability is greater in DLB (SD ±2.14) than in AD (SD ±1.73) or DLB+AD (SD ±1.44).
Conclusions: Early stages of dual disease DLB+AD and AD worsen faster than early stages DLB patients. The slope of the evolution of DLB patients is little declining. Year-to-year variability in MMSE indicates cognitive fluctuations. The next step is to know what the evolution of specific cognitive functions and brain volume and connectivity is.

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P0910 / #785

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

DATA-DRIVEN EVIDENCE FOR DISTINCT FRONTO-SUBCORTICAL AND POSTERIOR-CORTICAL TRAJECTORIES OF DOMAIN-SPECIFIC COGNITIVE DECLINE IN PARKINSON'S DISEASE

Michel Grothe[1,2], Miguel Labrador-Espinosa[1,2], Silvia Jesús[1,2], Florinda Roldán-Lora[3], Miquel Aguilar Barberá[4], Pau Pastor[4], Sonia Escalante Arroyo[5], Berta Solano Vila[6], Anna Cots Foraster[6], Javier Ruiz Martínez[7], Francisco Carrillo Padilla[8], Mercedes Pueyo Morlans[8], Isabel González Aramburu[9], Jon Infante Ceberio[9], Jorge Hernández Vara[10], Oriol De Fábregues-Boixar[10], Teresa De Deus Fonticoba[11], Berta Pascual-Sedano[2,12,13], Study Group Coppadis[1], Pablo Martínez-Martín[2], Jaime Kulisevsky[2,12], Diego Santos-García[14], Pablo Mir[1,2]
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Aims: To use a novel data-driven approach, Subtype and Stage inference (SuStain), for identifying distinct subtypes of domain-specific cognitive decline in Parkinson's disease (PD), and study their respective risks for developing dementia.
Methods: We studied 683 nondemented PD patients and 204 healthy controls from the multicentric COPPADIS study. Individual item scores of the PD-Cognitive Rating Scale (PD-CRS) were converted to age- and education-adjusted w-scores with reference to the healthy controls and then modeled with SuStain, which estimates distinct trajectories of domain-specific cognitive decline from the cross-sectional data points. Identified subtypes were characterized in terms of clinical features, regional brain atrophy on MRI (in a subset), and risk of developing dementia over 2y follow-up.
Results: SuStain found cross-validated evidence for the existence of two distinct subtypes of cognitive decline among PD patients (S1, N=194; S2, N=189), together with a third group of unimpaired patients (S0, N=300). S1 showed initial impairment in attention and working memory, followed by clock drawing performance, whereas S2 initially showed selective impairment in clock drawing and copy performance, followed by attention deficits (Fig. 1). Subtypes did not differ in global cognition (MMSE), but S1 was overall more impaired in the "fronto-subcortical" PD-CRS summary score, and S2 more impaired in the "posterior-cortical" score (both $p<0.001$). S1 had a higher proportion of females ($p=0.003$), but subtypes did not differ in any other clinical features. Exploratory MRI analysis showed slightly more pronounced temporal cortical atrophy in S2 (Fig. 2), but both subtypes had similarly increased risk of developing dementia (S0: 1%, S1: 11%, S2: 7%; $p(S1,S2)=0.50$).

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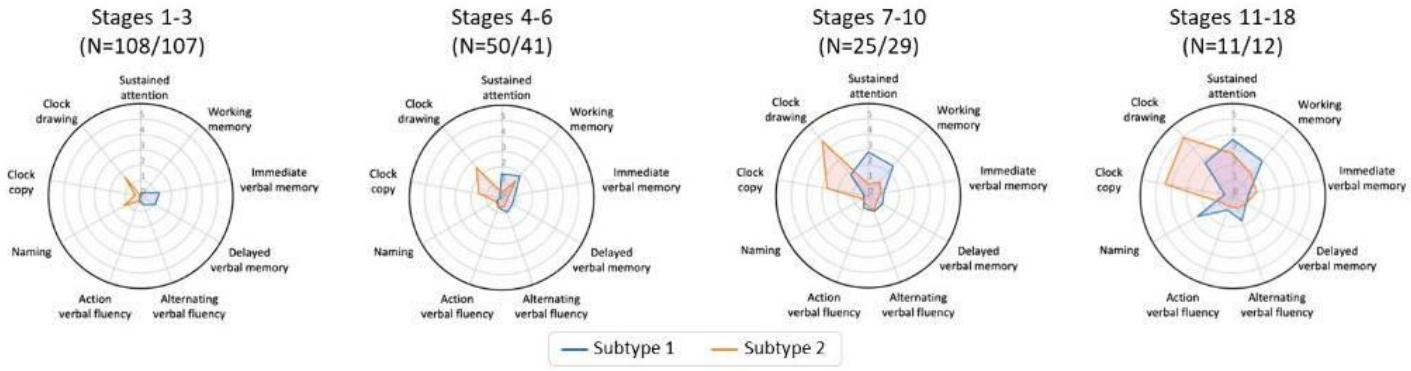
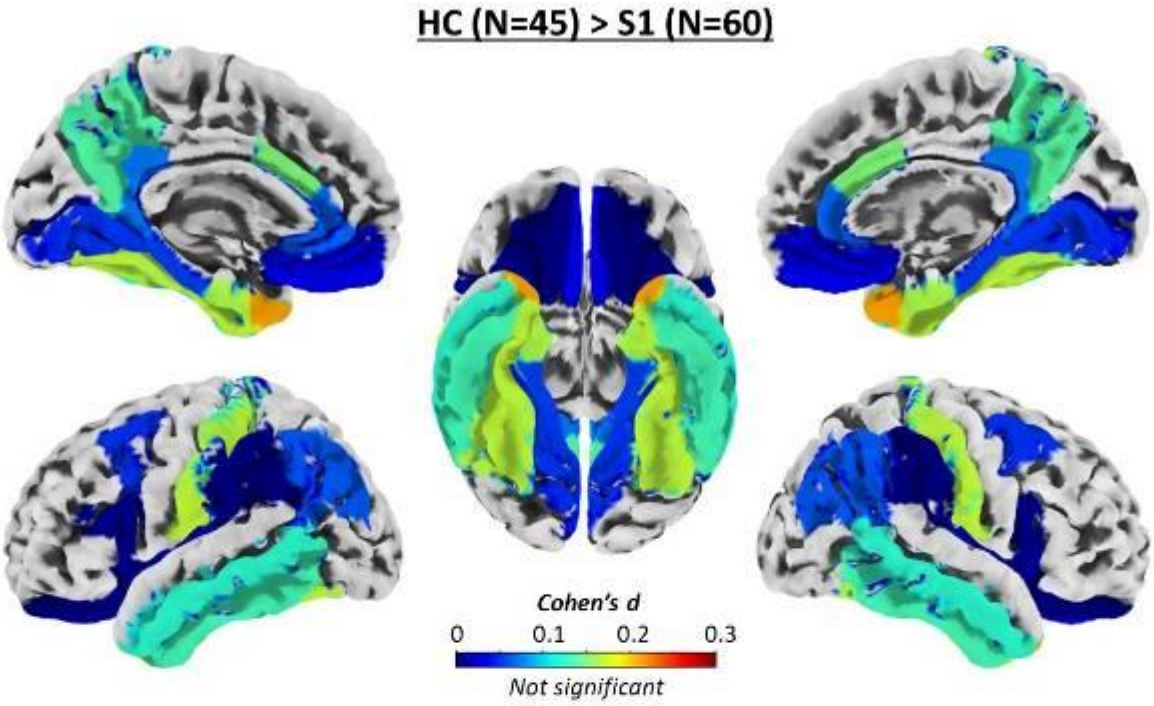
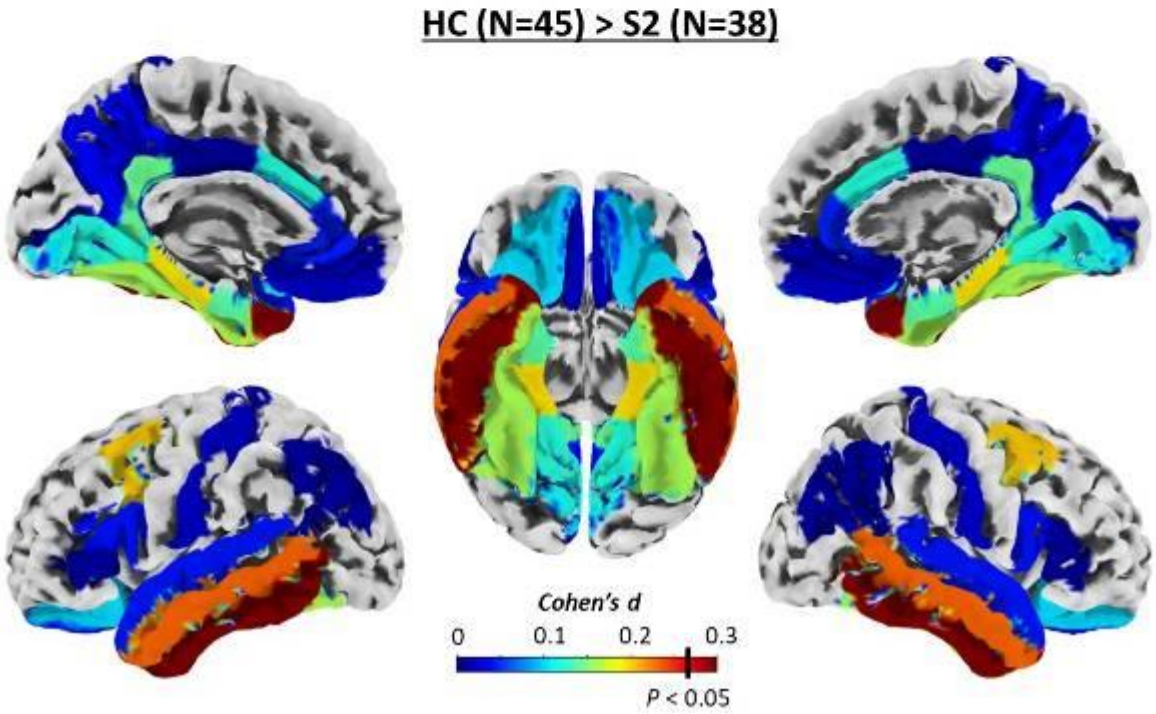
Subtype-specific progression of cognitive impairments across estimated stages







Conclusions: This large-scale data-driven analysis confirms the existence of distinct "fronto-subcortical" and "posterior-cortical" cognitive subtypes in PD, which showed similarly increased short-term risks of developing dementia.

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P0911 / #968

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

SUSTAINED ATTENTION IN MILD COGNITIVE IMPAIRMENT WITH LEWY BODIES AND ALZHEIMER'S DISEASE.

Calum Hamilton[1], Peter Gallagher[1], Joanna Ciafone[1], Louise Allan[2], Nicola Barnett[1], Sally Barker[1], Paul Donaghy[1], Rory Durcan[1], Sarah Lawley[1], John O'Brien[3], Gemma Roberts[1], John Paul Taylor[1], Alan Thomas[1]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]University of Exeter, Department Of Health And Community Services, Exeter, United Kingdom, [3]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom

Aims: Fluctuating attention is a characteristic diagnostic feature of dementia with Lewy bodies (DLB) and its cognitive prodrome mild cognitive impairment (MCI) with Lewy bodies (MCI-LB), and sustained attention is typically more impaired in DLB than in Alzheimer's disease. However, this may be difficult to assess in people with MCI when attentional dysfunctions are mild and may be compensated for in a brief testing session. We therefore aimed to assess the utility of a continuous performance task, requiring sustained attention for several minutes, for detecting fluctuation-like attentional lapses in MCI-LB.
Methods: We collected data from 54 people with MCI-LB, 35 with MCI due to Alzheimer's disease (MCI-AD), and 31 cognitively healthy older adults, including response times on successful reaction trials, and errors of omission (missed responses to valid stimuli) or commission (false positive responses to invalid stimuli). We modelled performance trajectories as a short-term longitudinal process to examine positive or negative adaptations to the task.
Results: Response times on successful trials were broadly similar across all groups. However, there were considerable differences in error rates. MCI-LB made more omission errors than MCI-AD from the task outset (OR 2.3, 95% CI: 1.1-4.7), and also made progressively more frequent commission errors over the task duration. Within MCI-LB, omission errors were associated with the presence of clinical parkinsonism (OR 1.9, 95% CI: 1.3-2.9) and cognitive fluctuations (OR 4.3, 95% CI: 2.2-8.8).
Conclusions: Sustained attention deficits in MCI-LB may be better characterised by attentional lapses and emergent failures in inhibitory control than by slowed responses, with implications for selection of outcome measures in MCI.

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P0912 / #1721

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

BEHAVIOURAL VARIANT DEMENTIA WITH LEWY BODIES - AN OVERLOOKED SYNDROME?

Antoinette O'Connor[1,2], Shane Lyons[1,2], Martha Finnegan[2,3], John Walsh[4], Sean O'Dowd[1,2]
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Aims: Objective The core clinical features of dementia with Lewy Bodies (DLB) are well described, however diagnosis of DLB is significantly delayed compared to other neurodegenerative dementias[1]. We describe the clinical heterogeneity of DLB – heterogeneity which may contribute to diagnostic delays.
Methods: Methods We report three cases of behavioural onset DLB that were initially diagnosed with frontotemporal dementia.
Results: Results Case 1 developed prominent apathy and executive dysfunction with relative sparing of memory and posterior function at 65. Over the following year behavioural disinhibition was reported, but it was only at 68 that features suggestive of DLB (parkinsonism and cognitive fluctuations) emerged. **Case 2** developed behavioural disinhibition and loss of empathy at 56, with emergence of ritualistic behaviour and apathy soon after. Parkinsonism and REMBD were present from symptom onset, but visual hallucinosis only emerged late in the disease course. **Case 3** presented with behavioural disinhibition, apathy and dietary change (new sweet tooth) at the age 58. Over the following year extracampine hallucinations, REMBD and parkinsonism were reported. **Results of investigations:** Dopamine Agonist Transporter (DAT) scans were initially normal or borderline in two cases, but repeat scanning became abnormal in both. DAT scan, performed 18 months into clinical syndrome, was abnormal in Case 3.
Conclusions: Conclusion: Atypical presentations may contribute to diagnostic delays in DLB as well as the greater frequency of initial misdiagnosis[1]. We present three cases of behavioural-onset DLB, that initially met criteria for possible frontotemporal dementia. This series highlights the clinical heterogeneity of DLB and the need for ongoing monitoring for features suggestive of alpha-synucleinopathy in those presenting with a behavioural-onset syndrome. **References** 1. Surendranathan, A. *et al.* Clinical diagnosis of Lewy body dementia. *BJPsych Open* **6**, e61 (2020).

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P0913 / #1391

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

MEMORY OUTCOME IN PRODROMAL AND MILD DEMENTIA WITH LEWY BODIES AND ALZHEIMER'S DISEASE: A LONGITUDINAL STUDY

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Strasbourg University Hospital, Memory Center For Ressources And Research, Strasbourg, France

Aims: The aim of our study was to clarify the characteristics and evolution of the memory profile of patients with prodromal and mild dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). To our knowledge, no such study has been conducted to date.
Methods: We collected verbal memory (FCSRT) and visual memory (DMS48) scores from 91 DLB patients, 28 AD patients, 15 patients with both conditions (DLB/AD) and 18 healthy control subjects (HCS) at their inclusion visit, at 12, 24 and 48 months.
Results: On the FCSRT, DLB patients had better total recall ($p < .001$), delayed total recall ($p < .001$) and recognition ($p = .031$) performances than AD patients, as well as less loss of information over time ($p = .023$). On the DMS48, the differences between these two groups were not statistically significant ($p > .05$), although there was a trend ($p < .08$). Longitudinally, the verbal and visual memory performances of DLB patients were stable over 48 months, unlike AD patients.
Conclusions: Four indicators are relevant to distinguish DLB and AD patients in terms of memory performance: DLB patients benefit greatly from semantic cueing on the FCSRT, their recognition and consolidation abilities are well-preserved in verbal memory, and finally, their verbal and visual memory performance remains remarkably stable over four years. However, performance differences between DLB and AD patients are less obvious on the DMS48, both qualitatively (memory profile) and quantitatively (severity of impairment), indicating the lesser relevance of this test in distinguishing the two diseases.

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P0914 / #2365

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

STEP LENGTH ALTERATIONS AS PROMISING MARKERS OF PRODROMAL NEURODEGENERATION IN IRBD

Cinzia Zatti[1], Andrea Pilotto[1], Clint Hansen[2], Andrea Rizzardi[1], Marcello Catania[1], Robbin Romijnders[2], Maria Pasolini[3], Eva Schaeffer[2], Daniela Berg[2], Walter Maetzler[2], Alessandro Padovani[1,3]
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Aims: Idiopathic REM sleep behavioral Disorder (iRBD) is a condition characterized by an increased risk of conversion to Parkinson's disease (PD) and other alpha-synucleinopathies. Aim of the study was to identify subtle gait alterations in iRBD compared to controls and PD patients.
Methods: The prospective study included consecutively individuals with PSG- confirmed iRBD, drug-naïve PD patients and healthy controls. Each individual underwent a multidimensional assessment including evaluation of motor and non-motor symptoms, cognitive status and comorbidity. PD and iRBD individuals underwent additional dopamine binding imaging. All individuals underwent a gait assessment using mobile health technology (MHT) in supervised condition at normal and fast pace and during dual-task performance.
Results: The study included 19 individuals with iRBDs, 45 drug-naïve PD patients and 80 controls. No iRBD showed a subthreshold parkinsonism as defined by the prominent parkinsonian features of PD (MDS-UPDRS-III iRBD 2.63 $\pm$ 1.98, PD 13.9 $\pm$ 7.4); sixteen of them underwent I123-FP-CIT imaging which excluded a reduced presynaptic dopaminergic binding capacity. MHT showed an increased step time and decreased step length in PD compared to controls in all gait conditions. Persons with iRBD exhibited shorter step length compared to HC in normal ($p=0.012$) and a dual task gait ($p=0.02$) with intermediate values compared to de novo PD ($p=0.02$) .
Conclusions: MHT identified subtle gait alterations in RBD patients at risk for neurodegeneration, even in absence of dopaminergic imaging alterations. Further longitudinal studies are warranted to evaluate the value of MHT in defining the risk of conversion and track the subtle motor progression in prodromal phases of PD.

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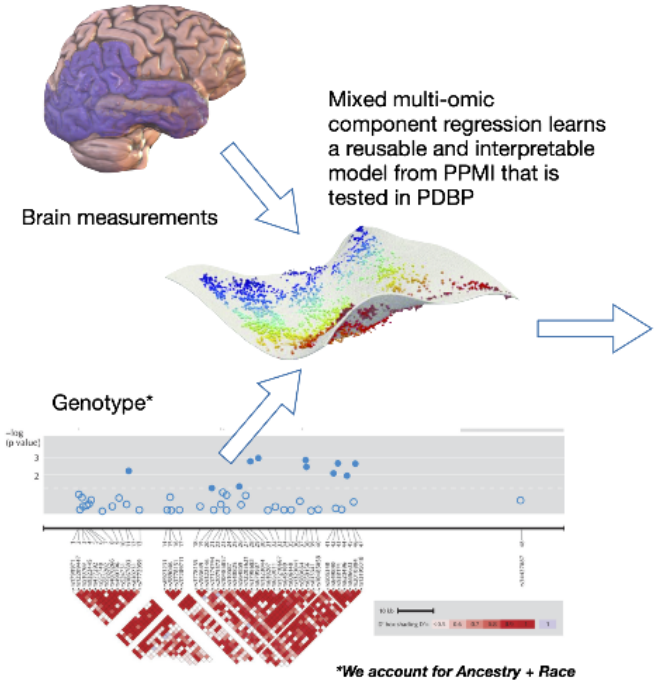
P0915 / #342

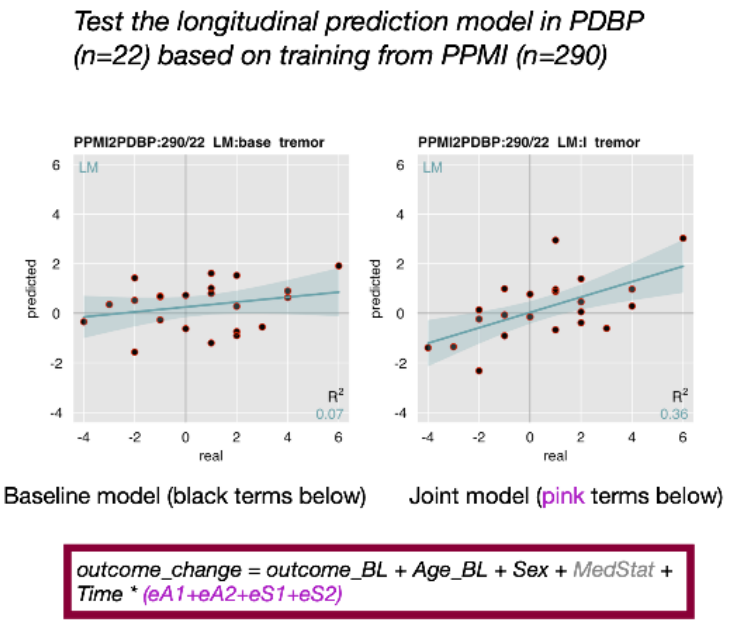
POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

GENETIC RISK VARIANTS AND BASELINE BRAIN PHENOTYPE JOINTLY PREDICT LONGITUDINAL SYMPTOM CHANGE IN SPORADIC PD: VALIDATION FROM PPMI TO PDBP

Brian Avants[1], Roger Gunn[1], Alexandra Reardon[1], Taylor Gosselin[1], Linda Polfus[2], Hamed Masnadi-Shirazi[2], Adam Chamberlin[2], Anant Dadu[3], Faraz Faghri[3], Michael Nalls[3], Jacob Hesterman[1]
[1]Invicro, Image Analysis, needham, United States of America, [2]Ambry Genetics, Bioinformatics Structural Biology, Aliso Viejo, United States of America, [3]Data Tecnica International, Data Science, Glen Echo, United States of America

Aims: Multi-omic covariation between clinical scores, Parkinsons's Disease (PD) risk SNPs and neuroanatomy may encode differences in PD clinical progression. We demonstrate that multi-omic variations in sporadic PD improve prediction of longitudinal change in clinical measurements from baseine data.
Methods: PD risk SNPs (n=120 based on prior GWAS), baseline demographic and longitudinal clinical data were assembled from Accelerating Medicines Partnership PD (AMP-PD). Model training used Parkinson's Progression Markers Initiative (PPMI) data with evaluation in PD Biomarkers Program (PDBP) data. Early stage sporadic PD subjects were selected for consistent ancestry/race. T1-weighted (T1w) neuroimaging was processed via ANTsX [1] yielding tabular measurements of cortical thickness and volume**.** PPMI data (n=295, two time points minimum per subject) was used to cross-validate/tune a novel multi-omic prediction approach [2] that identifies a low-dimensional space linking baseline (first visit) brain structure, genetics and baseline clinical scores. The top two SNP-related and anatomy-related latent variables were then included with baseline clinical scores, age, sex and treatment status (on/off) in a regression model predicting change from baseline in a 1-4 year timeframe. The model was evaluated in independent PDBP data (n=22).
Results: Of 16 clinical outcomes in PDBP, 7 demonstrate Bonferroni-corrected significance beyond the clinical model. R^2 increases by 4% to 16% (improvement ratio 2% to > 50%) due to joint value from imaging and genetics; tremor prediction particularly
benefits.





Conclusions: Baseline multi-omic models improve prediction of clinical scores longitudinally including tremor, rigidity and UPDRS part 1 patient scores. Such a model may enhance patient selection & enable end users to target subjects that progress more rapidly in motor, cognitive symptoms or both. These results further suggest a complex interaction between genotype, phenotype and clinical progression. [1] doi: 10.1038/s41598-021-87564-6 [2] doi: 10.1038/s43588-021-00029-8

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P0916 / #1623

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

EX VIVO TARGET ENGAGEMENT OF ALPHA-SYNUCLEIN-OLIGOMER-ELIMINATING COMPOUNDS IN HUMAN BRAIN HOMOGENATES BY SFIDA ASSAY

Tuyen Bujnicki[1], Sandra Kienast[1], Marc Sevenich[2], Bettina Kass[2], Janine Kutzsche[1], Antje Willuweit[2,3], Dieter Willbold[1,4]
[1]Forschungszentrum Jülich GmbH, Ibi-7: Structural Biochemistry, Jülich, Germany, [2]Priavoid GmbH, Drug Discovery, Düsseldorf, Germany, [3]Forschungszentrum Jülich, Institute Of Neuroscience And Medicine (inm-4), Jülich, Germany, [4]Heinrich-Heine-Universität Düsseldorf, Institut Für Physikalische Biologie, Düsseldorf, Germany

Aims: Brain homogenates from PD patients as a more physiological source of aggregated alpha-synuclein (aSyn) from a complex matrix were used to investigate the target engagement of phage display selected peptides. For this purpose, we performed the surface-based fluorescence intensity distribution analysis (sFIDA) for detection and quantitation of aSyn oligomers and aggregates with single particle sensitivity. The ability of the peptides to reduce the aSyn oligomer amount in the brain homogenates was determined.
Methods: Brain homogenates of several PD patients were incubated with the phage display selected peptides and were subsequently analyzed by sFIDA assay to determine the concentration of the aSyn oligomers and aggregates.
Results: We could show, that some of the peptides have an aSyn oligomer-eliminating ability. By addition of the peptides to the brain homogenates, we observed a reduction of the aSyn oligomer concentration.
Conclusions: Screening of oligomer-eliminating compounds *ex vivo* might predict *in vivo* efficacy with greater accuracy than a purely *in vitro* approach and could also enhance the translational value from animal to clinical trials. Thus, sFIDA proofs a useful tool to investigate quantitatively the effect of oligomer targeting drugs.

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P0917 / #1120

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PERIPHERAL TISSUE BIOMARKER FOR DIAGNOSIS OF SYNUCLEINOPATHIES AND TAUOPATHIES

Shu Chen, Wen Wang, Connor Bargar
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Aims: Synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), and tauopathies such as Alzheimer's disease (AD) and progressive supranuclear palsy (PSP) are characterized by the deposition of misfolded protein aggregates in affected brains. Currently, definite diagnosis of these disorders relies on the examination of autopsied brains. The overall objective of our study is to develop diagnostic biomarkers for synucleinopathies and tauopathies using easily accessible peripheral tissues.
Methods: We have utilized real-time quaking-induced conversion (RT-QuIC) technology to detect the seeding activity of alpha-synuclein (aSyn) or tau aggregates in peripheral tissues as a diagnostic biomarker.
Results: Ultrasensitive and specific detection of seeding activity of aSyn aggregates was achieved with streamlined aSyn RT-QuIC assay using neuropathologically confirmed PD and DLB cases across different tissue types including the brain, skin, salivary gland, and colon. To evaluate the performance of aSyn RT-QuIC for pre-mortem specimens, we performed aSyn RT-QuIC analyses of skin biopsy and olfactory mucosa (OM) collected from patients affected by PD and MSA. Our results have shown that aSyn seeding activity is detectable by RT-QuIC in the skin and OM from living patients, with a sensitivity up to 90% and 70%, respectively. The seeding activity of the peripheral αSyn aggregates correlated with disease duration and severity, and burden of non-motor syndromes in PD patients. Moreover, we have recently developed a novel tau RT-QuIC assay able to detect tau seeding activity in the skin of AD and PSP cases. These assays have also enabled detection of co-pathologies using skin samples.
Conclusions: Our study has demonstrated that the seeding activity of aSyn/tau detected via RT-QuIC may serve as a biomarker using easily accessible peripheral tissues for diagnosis of synucleinopathies and tauopathies.

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P0918 / #2394

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

RELATIONSHIP BETWEEN GAIT AND VOICE IN PARKINSON'S DISEASE

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Aims: Hypokinetic dysarthria and gait disturbance are major sympotms of Parkinson's disease (PD). These symptoms significantly influence activities of daily living (ADL) of PD patient. The aim of this study is to investigate relationship between gait and voice in PD
Methods: A total 139 (107 PD patients and 32 control groups) of PD patients and control groups were consecutively recruited. Voice analysis was done by korean vowel vocalization, which was consisted of sustained vowel vocalization, vowel vocalization in 5 seconds, high frequency speech and low ferequency speech. Gait was analyzed by 'GAITrite' during forward and backward walking. PD patients were distributed based on presence of freezing of gait (FoG).
Results: PD patients showed lower frequency in voice analysis than control group. There is no difference in voice analysis between PD patient with FoG and PD patient without FoG. Forward gait showed no difference between PD patients and control group, but backward gait revealed lots of differences. Those differences were prominent in PD patient with FoG than PD patient without FoG. Correlation analysis revealed no relation between voice and gait in control group. However, in PD patients there was significant relation between high frequency speech and several gait character of PD patient with FoG.
Conclusions: Voice and gait showed difference between PD patient and control group, which was mainly derived from characteristic of PD patient with FoG. Correlation between voice and gait was showed in PD patient, especially PD patient with FoG, which will need further evaluation

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P0919 / #783

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

SEGMENTAL BODY COMPOSITION BY BIOIMPEDANCE VECTOR ANALYSIS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Aims: To examine the alterations of segmental body fluid and lean mass in mild cognitive impairment with Alzheimer's pathology (MCI) and Alzheimer's disease dementia (AD).
Methods: A multi-frequency segmental bioimpedance analysis was employed to provide body composition and bioimpedance variables for each body segment from 365 cognitively normal (CN), 123 MCI, and 30 AD participants. These variables were compared between the cognitive groups and examined the correlations with neuropsychological tests such as the Mini-Mental State Examination and Seoul Neuropsychological Screening Battery. Bioimpedance vector analysis (BIVA) was used to describe the relative position of R-Xc graphs generated from the cognitive groups.
Results: Individuals with AD were slightly older, more depressive, and had significantly poorer cognitive abilities than those with CN; the MCI group showed intermediate results. The whole-body compositions exhibited no significant differences between the three groups and weak correlations with the cognitive tests. Nevertheless, we found the patterns of increasing water volume and decreasing body cell mass in individuals with lower cognitive performance. BIVA method upheld the finding of lower soft tissues and over-hydration status in the AD and MCI groups compared with the CN persons. These results were more consistent in the lower extremities in men with the significant Mahalanobis Distance of 0.40 and 0.86 (p-value < 0.05) from the MCI and AD to the CN groups, respectively.
Conclusions: Reductions in body cell mass or body cell strength together with abnormal cellular water distribution are related to the cognitive states of AD and MCI. These patterns are prominent in the lower extremities compared with the upper extremities and more consistent in men than in women. More studies are needed to examine the over-hydration status in individuals with AD and MCI.

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P0920 / #2208

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

ASSOCIATION OF EARLY WEIGHT CHANGE WITH COGNITIVE DECLINE IN PATIENTS WITH PARKINSON DISEASE

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Aims: To examine whether early weight change is associated with subsequent deterioration in cognitive function, including overall performance and specific domains, in Parkinson's disease(PD).
Methods: In this cohort, early PD patients underwent annual non-motor assessments covering neuropsychiatric, sleep-related, and autonomic symptoms for up to 8 years of follow-up. Cognitive function was measured using the Montreal Cognitive Assessment(MoCA) and detailed neuropsychological testing. Linear mixed-effects models were applied to investigate the association of early weight change with longitudinal evolution of cognitive and other non-motor symptoms.
Results: 358 early PD patients were classified into weight loss(decrease of>3% body weight during the first year;n=98), weight maintenance(within±3%;n=201), and weight gain(increase of>3%;n=59) groups. The weight loss group showed a significantly faster decline in MoCA scores than the weight maintenance group(β=−0.19, 95% confidence interval[CI] −0.28 to −0.10). With respect to specific cognitive domains, the weight loss group showed a steeper decline in sematic fluency test scores(β=−0.37, 95% CI −0.66 to −0.08) and MoCA phonemic fluency scores(β=−0.18, 95% CI −0.31 to −0.05) and, to a lesser extent, Letter-Number Sequencing scores(β=−0.07, 95% CI −0.14 to 0.01) compared to the weight maintenance group. Conversely, the weight gain group showed a slower decline in the Symbol-Digit Modalities Test scores(β=0.34, 95% CI 0.05 to 0.63), although no association was found with longitudinal changes in MoCA scores. We did not find any significant effects of weight change on the progression of other non-motor symptoms.
Conclusions: Early weight loss was associated with a faster progression of decline in global cognitive function and executive function in PD patients, whereas early weight gain was associated with a slower progression of decline in processing speed and attention. The impact of early weight change on non-motor symptoms appeared specific to cognition.

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P0921 / #177

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

DISCREPANCY BETWEEN SELF-AWARENESS AND OBJECTIVE MEASUREMENTS OF OLFACTORY FUNCTION IN PATIENTS WITH PARKINSON'S DISEASE

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Aims: Importance of non-motor symptoms of Parkinson's disease (PD) such as REM sleep behavior disorder, constipation, affective disorders and hypo/anosmia is getting emphasized as those are known prodromal biomarkers of PD. olfaction is sensitive biomarker reflecting underlying neurodegeneration but there are lots of discrepancy of self-reporting olfactory function scale and the laboratory data in clinical practice. This study is performed to elucidate the correlations between self-awareness of olfactory function and objective olfactory test and investigate factors influencing the differences in PD.
Methods: Cross-sectional clinical study was performed with 164 newly diagnosed non-demented drug-naive PD. Basic epidemiological and clinical data were collected. Self-rating olfaction scale by visual assessment of rating) and Korean version Sniffin' stick test II (KVSS II) results were compared. Above 80% of self-rating score was considered as normal by self-rating and The KVSS-II TDI score ranged from 1 to 20 for anosmia, 20.25–27 for hyposmia, and ≥27.25 for normosmia
Results: 47 (28%) of the subjects had normosmia on KVSS II. Among 117 (72%) subjects had hypo/anosmia on KVSS II, 69 (59%) patients reported having normal olfaction by self-rating (VAS >8). Subjective self-rating olfactory function of PD patients showed correlation with TDI total score ($p=0.021$) and threshold ($p<0.001$), but not with discrimination ($p=0.362$) and identification ($p=0.547$) score on KVSS II.
Conclusions: Odor identification and discrimination requires complicated process within central nervous system Odor identification might be attributable to cognitive function and is representatively affected in various neurodegenerative disorders. Self-awareness of olfactory function is largely determined by perception of the smell, while more complicated odor process was not perceived by the subjects in this study. Self-rating scale to check olfactory function is not suitable to detect prodromal non-motor symptoms in elderly PD patients.

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P0922 / #1149

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

SEED AMPLIFICATION ASSAY FOR THE ACCURATE DIFFERENTIATION BETWEEN MSA AND LBDS.

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Aims: The goal of this project is to establish a new robust and accurate αS-SAA to detect and differentiate multiple system atrophy (MSA) from Lewy body diseases (LBDs). Constraints include >90% sensitivity for LBDs and >90% specificity, while shortening the assay runtime from 6.5 days to 24h.
Methods: 170CSF samples (83PD, 60 healthy control (HC), 22 isolated REM sleep behavior disorder (iRBD), and 5MSA) were analyzed with the original and 24h-assay conditions. Two cohorts of MSA were blindly analyzed; a clinically diagnosed cohort (n=49) and a well characterized research MSA cohort (17MSA, 14 controls (CTRL)). Blinded brain tissue samples (postmortem cingulate cortex, n=23) from 5PD, 12MSA, 1 Alzheimer's disease (AD), and 5HC, were homogenized and analyzed.
Results: The original and 24h-assay agreed on 96% of the 170CSF samples. The 24h-assay showed 94% sensitivity for all synucleinopathies [PD(95%), MSA(75%), iRBD(96%)], 95% specificity, and 95% accuracy. The 24h-assay detected 38 (79%) positives out of 49MSA cases (1 inconclusive). Of the positives, 25(66%) were MSA-like and 13(34%) LBD-like. All synucleinopathy brains were positive, all 12MSAs were determined MSA-like and all 5PDs were LBD-like, resulting in 100% agreement with pathological diagnosis. HC and AD brain samples were negative. The 24h-assay detected αSyn seeds in 17(89.5%) of the 19MSA well characterized patients, of which 13(76%) were MSA-like. 13CTRL had a conclusive negative result (100% specificity), and one was inconclusive.
Conclusions: Amprion's R&D 24h αS-SAA maintained the high assay sensitivity for PD reported with our original conditions and significantly increased sensitivity for clinical MSA samples (35 to 79%). Clinical misdiagnosis probably underestimates the sensitivity, since the 24h-assay agreed 100% with pathologically confirmed brain samples and ~90% with MSA samples from a well characterized research cohort.

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POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

PATIENT COHORT DIVERSITY: A PERSPECTIVE ON PARKINSON'S DISEASE

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Aims: To improve diagnosis of neurodegenerative diseases, there is still a need for biomarkers allowing early or differential diagnosis. An important aspect for biomarker studies is the definition of appropriate patient cohort. However, this is a challenge in many neurodegenerative diseases due to the complexity and the lack of diagnostic tools. For example, Parkinson's disease (PD) cannot be generalized due to different subtypes. Therefore, strategies are required enabling identification of PD patient's subgroups and, if necessary, controls based on clinical data. Here we present a strategy for defining cohorts using comprehensive bioinformatics analyses of corresponding clinical data.
Methods: Data set of clinical variables of four time points from the DeNoPa study was processed and formatted. Initially, different clustering analysis were performed comprising k-means, hierarchical clustering, density-based clustering and sparse k-means followed by classification with random-forest, subsequently analyzed using permutation feature importance.
Results: Within the PD cohort, two clusters could be clearly distinguished for all four time points. Interestingly, in the baseline dataset, only two of the included variables were needed to determine the clusters with a cross-validation accuracy of 85%. Furthermore, clusters were not fixed across time points, as patients switch between clusters over time. Comparison of the clusters across the different time points revealed patients to be classified into three groups: A) patients always in cluster 1, B) patients always in cluster 2 and C) patients switching between clusters at least once during the course of the study.
Conclusions: Comprehensive analyses confirmed that there are subgroups within the PD cohort based on analysis of clinical data, with two main subgroups identified. These findings are currently being used for differential analysis and interpretation of proteomic data.

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P0924 / #2352

POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

MYOCARDIAL SYMPATHETIC DENERVATION BIOMARKERS FOR EARLY DETECTION OF PRODROMAL DLB

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Aims: Because of the time course of detecting DLB symptoms and signs, DLB is poorly diagnosed and hardly differentiate from AD, especially in early stage of dementia without the core clinical features of DLB.
We investigated patients with a clinical diagnosis of amnestic mild cognitive impairment (MCI) and early AD whether they had cardiac sympathetic denervation, detected by cardiac 123I-MIBG scintigraphy. And we also assessed presynaptic nigrostriatal dopaminergic system by 18F FP-CIT-PET imaging to distinguish between DLB and AD.
Methods: Thirty patients (72±9.0 yrs old: M:F 17:13) with a clinical diagnosis of amnestic MCI and early AD (CDR 0.5/SOB 3) who have been had visual hallucination and/or suspicious fluctuating cognition history without parkinsonism (n=20, prodromal DLB group) and who have not been had visual hallucination and/or suspicious fluctuating cognition history (n=10, eAD group) enrolled in this study. 123I-Metaiodobenzylguanidine (MIBG) uptake was assessed using the ratio of the heart to the upper mediastinum (H/M ratio), and we also assessed presynaptic nigrostriatal dopaminergic system by 18F FP-CIT-PET imaging to distinguish between prodromal DLB and eAD. Autonomic function tests and orthostatic vital signs were recorded.
Results: The H/M ratio were decreased in pDLB group, and the mean H/M ratio was significantly lower (early/delayed uptake:1.72±0.61/1.65±0.63) compared with eAD group (early/delayed uptake:2.36±0.50/2.15±0.29) in 123I-MIBG scintigraphy ($p<0.05$). Presynaptic nigrostriatal dopaminergic deficits were founded in 18F FP CIT PET and orthostatic hypotension was evident only in pDLB group regardless of spontaneous Parkinsonism (n=17, 85%).

Conclusions: Myocardial postganglionic sympathetic denervation and autonomic dysfunctions especially orthostatic hypotension can be good biomarkers to predict DLB before core clinical symptoms appear, and may useful to distinguish from AD even in early stage. This study is under long term follow up.

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POSTERS: C04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

IPSILATERAL PARAFOVEAL RETINA LAYER THINNING IN EARLY PARKINSON'S DISEASE WITH UNILATERAL SYMPTOMS

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Aims: This study aimed to investigate the asymmetric parafoveal retinal thinning in early Parkinson's disease (PD) patients and to evaluate whether corresponding laterality exists for both motor phenotypes and retina thinning among early PD.
Methods: This prospective study included fifty-four eyes of 27 patients with *de novo* PD or early stage of PD presenting unilateral motor symptoms with Hoehn-Yahr (H-Y) stage 1. Comprehensive Ophthalmologic examinations and neurologic examinations including optical coherence tomography (OCT) and N-(3-[18F]fluoropropyl)-2-carbomethoxy-3-(4-iodophenyl) nortropane PET were done. Retinal layer thickness was measured in subfields of the 1-, 2.22-, and 3.45-mm Early Treatment of Diabetic Retinopathy Study (ETDRS) circle. We analyzed differences between retina layer thickness in both sides among same patient.
Results: We found this asymmetric laterality of parafoveal retinal layer thinning correlates with unilateral parkinsonism with same side. We categorized coincident patient subgroups with which homolateral parkinsonism and retinal thinning in each ETDRS areas. Among all ETDRS areas of this same directional subgroup, retinal thickness difference and more thinning of same sided retina in eight parafoveal area without central area ($p < 0.05$ for all).
Conclusions: Corresponding laterality was observed for parafoveal retinal thinning and motor phenotype in the early stages of PD. This implies possibility of a common pathologic dopaminergic degeneration process for both retina and brain which starts very early in PD. And also, asymmetrically ipsilateral parafoveal retina layer thinning might be considered a potential biomarker of PD and could be valuable for early PD diagnosis.

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P0926 / #2272

POSTERS: C05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

DIFFERENCES IN COGNITIVE PROFILE BETWEEN GBA-POSITIVE AND GBA-NEGATIVE PARKINSON DISEASE PATIENTS

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Aims: Variants in the *GBA* gene increase the risk of developing Parkinson disease (PD) in healthy carriers, and can determine a slightly more severe form of the disease, with more frequent and severe cognitive involvement. We aim at characterizing the cognitive profile of *GBA*-positive and *GBA*-negative Parkinson patients
Methods: Participants were recruited through the RAPSODI study, an online, browser-based assessment platform. They were asked to complete the CogTrack cognitive test. The test measures pattern separation ability, simple reaction time, choice reaction time, digit vigilance reaction time, spatial working memory and numeric working memory. Participants sent to us a saliva sample for sequencing of the *GBA* gene, carried out with Oxford Nanopore Technology full gene sequencing.
Results: 30 GBA-positive PD patients and 150 *GBA*-negative PD patients completed the assessment. The two groups were homogeneous for sex, and the *GBA*-positive included younger individuals (mean age 58.5 ± 9.0 vs 64.3 ± 8.8) *GBA*-positive PD patients showed a significantly worse performance in pattern separation ability (p-value 0.033) and choice reaction time (p-value 0.006).
Conclusions: This study supports previous observations that *GBA*-positive PD patients have more frequent cognitive involvement compared to non-carriers.

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P0927 / #2563

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

META-ANALYSIS OF RARE PARKINSON'S VARIANTS IN MILLIONS OF PEOPLE

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Aims: To conduct a robust assessment of rare and causal variants associated with PD, since many are under heavy debate for their true association with PD.
Methods: Gene and variant selection Biallelic, exonic, and splicing variants were selected from 23andMe data and then further prioritized for variants related to PD, Lewy body dementia, and GBA. 21 additional genes were included (PMID: 31521533). Data sources Results from 23andMe data (3,090,507 people) were replicated using sequencing data from the Accelerating Medicines Partnership - Parkinson's disease Initiative (AMP-PD) and the UK Biobank (UKB). AMP-PD comprises 4,007 people, UKB data covers 200,648 people, resulting in 36,216 cases and 3,103,134 controls for all 3 data sets. Statistical analyses We used RVTests for single variant association testing, using mainly sex, age, and PCs 1-5 as covariates. METAL was used for meta-analysis and results were annotated with ANNOVAR. Power calculations were conducted using the R package genpwr.
Results: We identified a list of 874 variants of interest in 31 genes, 692 of which were present in 23andMe, 644 in UK Biobank (UKB), and 301 in Accelerating Medicines Partnership Parkinson's disease (AMP-PD). We confirmed variants which are robustly associated with PD and identified variants in PD genes that were not yet linked to PD. We also provide a list of suggested PD variants with sufficient statistical power that were not confirmed in this analysis.
Conclusions: Assessing rare variants is crucial to improve our understanding of disease development and heritability, but many complications arise when working with such low frequencies. Here, we provide a robust assessment of rare variants and their association with PD which serves as a great tool for the wider PD community.

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P0928 / #261

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

MICROARRAY GENOTYPING IDENTIFIES NEW LOCI ASSOCIATED WITH DEMENTIA IN PARKINSON'S DISEASE

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Aims: Dementia is one of the most disabling nonmotor symptoms of Parkinson's disease (PD). However, the risk factors contributing to its development remain unclear. We aimed to investigate novel genetic variants that are associated with the development of dementia in PD (PDD).
Methods: Microarray genotyping platform were designed to contain genetic variants with biological plausibility for dementia in PD, suggested by our previous genome-wide association study (GWAS) using ethnicity-specific Korean Chip (K-CHIP), other previous GWAS, or genetic studies using next-generation sequencing. Microarray genotyping was performed in 313 PD patients with dementia, 321 PD patients without dementia, and 635 healthy controls. The primary analysis was performed using a multiple logistic regression model adjusted for age and sex.
Results: The *SNCA* single nucleotide polymorphism (SNP) rs11931074 was determined to be most significantly associated with PD (odds ratio = 0.66, 95% confidence interval = 0.56 – 0.78, $P = 7.75 \times 10^{-7}$). In the analysis performed for patients with PD only, *MUL1* SNP rs3738128 (odds ratio = 2.52, 95% confidence interval = 1.68 – 3.79, $P = 8.75 \times 10^{-6}$) was found to be most significantly associated with dementia in PD. SNPs in *ZHX2* and *ERP29* were also associated with dementia in PD.
Conclusions: This microarray genomic study identified new loci of *MUL1* associated with dementia in PD, suggesting an essential role of mitochondrial dysfunction in the development of dementia in patients with PD.

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P0929 / #777

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

ASSOCIATIONS BETWEEN PATHWAY-SPECIFIC POLYGENIC RISK SCORES AND CLINICAL OUTCOMES IN PARKINSON'S DISEASE

Manuela Tan[1], Sara Bandres-Ciga[2], Hirotaka Iwaki[2,3], Yuri Sosero[4,5], Ziv Gan-Or[4,5,6], Lasse Pihlstrøm[1]
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Aims: There is striking variability observed across individual Parkinson's disease (PD) patients in regards to clinical outcomes and progression. We hypothesize this variability may be driven by differences in the underlying molecular pathogenesis. We used polygenic risk scores (PRS) to study key biological pathways that have been previously implicated in PD risk, and to understand how these may relate to clinical outcomes. We investigated 8 selected pathways: alpha-synuclein pathway, adaptive immunity, innate immunity, lysosomal pathway, endocytic membrane-trafficking pathway, mitochondrial pathway, microglial open chromatin SNPs, and monocyte open chromatin SNPs.
Methods: The PRS is a score for each individual based on the weighted sum of their risk alleles. We used allele weights from the PD GWAS by Chang (2017) to create PRSs, to avoid overlap with the testing datasets. We generated PRSs using variants with a p-value of < 0.05 and allele frequency $> 1\%$. We investigated the following clinical outcomes: age at onset, MDS-UPDRS Part II, MDS-UPDRS Part III, progression to Hoehn and Yahr stage 3 or greater, Montreal Cognitive Assessment, cognitive impairment, PDQ8, and REM Sleep Behaviour Disorder.
Results: We meta-analysed data from 17 European-ancestry cohorts. There were no pathways that were significantly associated with any clinical outcomes after adjusting for multiple testing (Benjamini and Hochberg FDR). We found that the endocytic membrane trafficking pathway was nominally associated with younger age at onset ($p = 0.009$). The alpha synuclein pathway was also nominally associated with younger age at onset ($p = 0.04$).
Conclusions: Our results thus far indicate that pathway-specific PRS based on PD risk are not associated with clinical outcomes. This is in line with other large genetic studies which indicate minimal overlap between the genetics of PD risk and PD progression.

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P0930 / #2542

POSTERS: C05.D. GENETICS, EPIDEMIOLOGY: AGING

TSDS - NEUROPATHOLOGY IN A NON-SELECTED POPULATION

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Aims: Objectives: The Tampere Sudden Death Series is a non-selected autopsy cohort that has the potential to unravel the aetiology behind the initiation of the neuropathology associated with common brain diseases causing dementia - such as alpha-synuclein in Parkinson's disease/dementia with Lewy bodies, TDP43 in limbic-predominant age-related TDP43 encephalopathy (LATE), and amyloid beta and tau in Alzheimer's disease and primary age-related tauopathy (PART).
Methods: The Tampere Sudden Death Series is a Finnish autopsy series of individuals that died out of hospital, representing an unselected cohort of almost 600 cases. Brain regions included are cerebellar cortex, frontal cortex, hippocampus, insula-putamen, pons and substantia nigra. Measuring the neuropathology of dementia disorders, initially investigating alpha-synuclein, using standard immunohistochemistry with the reliable 5G4 antibody, allows us to visualise when Lewy pathology first emerges and whether patterns imitate diseased brains. Further statistical analyses can reveal genetic associations and match these or differentiate from known disease-causing risk factors.
Results: The results are far-reaching due to the multitude of complimentary data existing for this unselected cohort (genome wide, metabolomics, and epigenetic data) and will lead to a better understanding of the prevalence of common neuropathological changes across age groups, especially in middle aged groups.
Conclusions: This information will be vital, when therapies become available, as they will most likely have to be started at very early stages of the disease process.

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P0931 / #2165

POSTERS: C05.D. GENETICS, EPIDEMIOLOGY: AGING

REM SLEEP BEHAVIOR DISORDER AND SHORT SLEEP DURATION AMONG PARKINSON'S DISEASE PATIENTS ARE ASSOCIATED WITH EPIGENETIC MARKERS OF INFLAMMATION AND AGE ACCELERATION

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Aims: Parkinson's disease (PD) patients with REM sleep Behavior Disorder (RBD) may progress faster. No previous research has analyzed the association between RBD and epigenetic age acceleration (EAA) or DNA-methylation-based (DNAm) inflammatory biomarkers. Furthermore, it is unknown whether short sleep duration among PD patients, known to be associated with negative health outcomes in the general aging population, has an influence on EAA.
Methods: Second-generation EEA and DNAm estimates for inflammation (blood cell composition and C-reactive protein (CRP)) were calculated using the blood methylome of 636 PD patients. Linear regression analyses were performed comparing PD patients with or without probable RBD, and between PD patients with a short (<6) and a normal (7-9 hours) sleep duration. We adjusted our analysis for age at blood draw, race, education, smoking status, and sex, and for EAA also for estimated cell composition. We calculated the False Discovery Rate (FDR) to account for multiple testing.
Results: RBD in PD was suggestively associated with an increased EAA (DunedinPACE: 0.03/yr, 95%CI: 0.00-0.06, P:0.06, P-FDR:0.24). Short sleep duration among PD patients was associated with an increased DNAm log-CRP (0.31, 95%CI: 0.12-0.51, P:0.002, P-FDR 0.02), lower CD4T (-0.03, 95%CI: -0.05- -0.01, P:0.01, P-FDR: 0.03), and an increased EAA (Grim AA: 1.53 yrs, 95%CI: 0.06-3.00, P:0.04, P-FDR: 0.06; DunedinPoAm: 0.04/yr, 95%CI: 0.02-0.07, P:0.002, P-FDR:0.01; DunedinPACE: 0.07/yr, 95%CI: 0.02-0.12, P:0.01, P-FDR:0.01). None of these differences were seen in 222 control subjects without PD for sleep duration.
Conclusions: Our preliminary findings suggest that differences in EAA and white blood cell composition with RBD status in PD patients. PD patients with a short sleep duration showed increases in inflammatory markers and in EAA possibly suggesting a worse prognosis for PD patients with short sleep duration.

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P0933 / #2763

POSTERS: C05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

ASSOCIATING CIRCULATING CAFFEINE METABOLITES WITH PARKINSON'S DISEASE RISKS IN A LARGE EUROPEAN PROSPECTIVE COHORT: AN UNTARGETED METABOLOMICS APPROACH

Yunjia Lai[1], Yujia Zhao[2], Douglas Walker[3], Christina Lill[4,5], Bastiaan Bloem[6], Sirwan Darweesh[6], Gary Miller[1], Susan Peters[2], Roel Vermeulen[2,7]
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Aims: Objectives: Parkinson's disease (PD) cases over age 65 are mostly sporadic, with new studies suggesting a predominance of environmental risk factors over genetics in PD etiology. Dietary caffeine has been associated with a decreased risk of PD. However, the underlying mechanism remains elusive, partially due to lack of objective markers of caffeine intake. Our study aimed to illuminate the role of caffeine exposure in PD through an exposomic framework in a large cohort.
Methods: Methods: We conducted a nested case-control study within the European Prospective Investigation into Cancer and Nutrition (EPIC). In total, 351 incident PD cases were selected, each matched to one control by age at recruitment, sex, and study center. Plasma was collected at recruitment, which was on average 7.8 years before case diagnosis. We leveraged a mass spectrometry-based platform for detection and annotation of caffeine biotransformants. We estimated the odds ratios (ORs) for one unit increase of the natural log of peak intensities and PD incidence through conditional logistic regression.
Results: Results: We detected 14 unique caffeine metabolites in circulating plasma. Among these, we detected 1,3,7-trimethyldihydrouric acid, a novel caffeine metabolite first discovered through our *in vitro* enzyme-based exposomic pipeline. While analyses are ongoing for all 14 compounds, our first statistics are indicative for a prospective caffeine-PD link. Specifically, the ORs for PD incidence per one unit increase of log peak abundances were found to be decreased for caffeine (0.89, 95% CI 0.81-0.97) and theophylline (0.84, 95% CI 0.81-0.97), while interestingly, 5-acetylamino-6-formylamino-3-methyluracil had an opposite trend (1.28, 95% CI 1.01-1.61).
Conclusions: Conclusion: We detected 14 caffeine metabolites in a large human cohort, which may provide additional biochemical evidence of the epidemiological connection between caffeine consumption and Parkinson's disease vulnerability.

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P0934 / #1672

POSTERS: C05.G. GENETICS, EPIDEMIOLOGY: OTHER

USING TRAINING TO BUILD RESEARCH MOMENTUM IN THE GLOBAL PARKINSON'S GENETICS PROGRAM (GP2)

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Aims: To establish a virtual 'center of excellence' with resources and expertise to serve the training needs of the Global Parkinson's Genetics Program (GP2; www.gp2.org) and its collaborators.
Methods: The Training, Networking and Communication working group has broadly divided opportunities for 'individuals' and 'groups' to achieve breadth and impact. For groups, we developed a free and accessible web-based learning platform (https://training.gp2.org/) to establish foundational knowledge of PD genetics and related topics. For individuals, tailored research training opportunities (short courses; master's, PhD, sabbaticals, and mentorship programs) have been created, prioritizing clinicians, scientists and researchers from traditionally underrepresented regions in PD research.
Results: To date, seven web-based courses in PD genetics, medical statistics, bioinformatics, and using Terra for analysis have been launched to over 600 students in the learning platform. Courses in introduction to python, functional biology, and advanced bioinformatics are in development. More than 30 trainees have been supported to attend graduate courses in bioinformatics and data science at the Foundation for Advanced Education in the Sciences at the NIH. Four PhD and seven master's fellowships have been awarded to individuals in Africa, Asia and Latin America, and sabbatical training opportunities at GP2 centers are being offered. A trainee network with 118 members from around the world provides streamline opportunities, direct expertise to the places where needed, and facilitates access to data and analyses across GP2.
Conclusions: Training the next generation of PD researchers worldwide is a priority for GP2. Over the coming years, our reach will expand to ensure that needs are met and research capacity is generated where it is needed to further our understanding of the genetic basis of PD.

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P0935 / #1880

POSTERS: C05.G. GENETICS, EPIDEMIOLOGY: OTHER

STUDYING SELECTIVE VULNERABILITY IN PARKINSON'S DISEASE USING SPATIAL TRANSCRIPTOMICS: TECHNICAL APPRAISAL AND OPTIMISATION

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Aims: Transcriptomics techniques, such as bulk and single-cell RNA sequencing, have enabled the study of selective vulnerability in Parkinson's disease (PD) through the analysis of gene expression profiles in specific cell type within a tissue. However, spatial organisation of cells is lost using these techniques. Recent advancement in spatial transcriptomics technology means that gene expression can be precisely mapped to individual cell populations within an anatomical region. Therefore, we aim to assess the feasibility of spatial transcriptomics on archival formalin-fixed paraffin-embedded (FFPE) human brain tissues using the novel Visium Spatial Gene Expression technology.
Methods: FFPE blocks containing the substantia nigra and entorhinal cortex from 3 PD and 3 aged-controls were obtained from the Oxford Brain Bank. Degree of RNA fragmentation of the tissue was assessed using the DV200 metric. Tissue sections were mounted on spatially barcoded slides from the Visium Spatial Gene Expression kit and stained with H&E. Following library construction and sequencing, gene expression data was visualised and analysed using the Loupe Browser.
Results: Following sequencing, an average of approximately 340 unique genes were detected per barcoded spot (range 7-1077). Expression-based clustering analysis revealed up to 8 clusters which maps well to distinct anatomical regions. Spearman correlation identified the median number of unique genes per spot significantly correlates with time in fixation (Rho=-0.78, p=0.0016), but not DV200 (Rho=0.17, p=0.5573) or post-mortem interval (Rho=0.24, p=0.4132).
Conclusions: This study demonstrates it is feasible to use archival FFPE brain tissues for spatial transcriptomics despite high degree of RNA fragmentation as measured by DV200. Future work should aim to use samples with a post-mortem formalin fixation time of less than 3-4 weeks.

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P0936 / #1209

POSTERS: C05.G. GENETICS, EPIDEMIOLOGY: OTHER

GENETIC FACTORS INFLUENCING THE OCCURENCE OF LEVODOPA MOTOR COMPLICATIONS IN PARKINSON'S DISEASE

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Aims: We aimed to determine the frequency of selected polymorphisms of *COMT, DRD2*, *ANKK1* and *DAT* genes in a large group of PD patients and to investigate the association of selected polymorphisms and occurrence of motor complications. Also, we wanted to examine the effect of haplotypes integrating selected polymorphisms of *ANKK1/DRD2* genes on the motor complications frequency.
Methods: Serbian PD patients (N=234), treated with levodopa for at least two years, were genotyped for the rs4680 in *COMT*, rs6277, rs1076560, and rs2283265 in *DRD2*, and rs1800497 and rs2734849 polymorphisms in *ANKK1* genes. Also, variable number of tandem repeats polymorphism in the *DAT* gene was examined.
Results: Dyskinesia was more frequent among AA rs4680 COMT carriers than AG and GG rs4680 COMT carriers. GGAAA and AGGAA *ANKK1/DRD2* haplotypes were revealed as vulnerability factors for motor fluctuations occurence.
Conclusions: Our results may suggest a role of genetic factors in development of motor complications. These results should be considered as positive preliminary evidence which need to be addressed in further longitudinal studies with larger cohort.

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P0937 / #2765

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: _-SYNUCLEIN

THE INDUCTION OF SENESCENCE IN NEURONAL CELL MODELS OF ALPHA-SYNUCLEIN PATHOLOGY

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Aims: Cellular senescence is characterized as an irreversible cell-cycle arrest connected with prominent changes in cellular morphology and metabolism. Senescent cells accumulate during aging and promote a variety of age-related diseases. Previous studies suggested that senescence is involved in the pathobiology of Parkinson's disease (PD) but the interconnection between cell growth arrest and neurodegeneration of dopaminergic neurons remains largely underexplored. In our study, we target the question regarding the potential link between the senescence induction and the pathological hallmark of PD; alpha-synuclein (a-syn) aggregation.
Methods: We generated neuronal model cell lines stably overexpressing a-syn (wild type or its PD related mutated variant A53T). Following experiments included detailed analysis of senescence markers induction (p16Ink4a, p21Waf-1/Cip1 and components of senescence-associated secretory phenotype) in generated cell lines. We compared the readouts in conditions without stress or in stress conditions (including oxidative stress induced by H2O2 or rotenone).
Results: Our data suggest the senescence markers induction in the both cell lines overexpressing wild type or A53T variant of a-syn already in the conditions without additional stress induction. We observed more prominent senescence features in the cell model with A53T variant of a-syn. The stress conditions increased the induction of senescence markers after both H2O2 or rotenone treatment.
Conclusions: Our results confirmed the connection between a-syn overexpression and senescence induction. Next, we plan to analyze the senescence response in neurons using specific senescence reporters which are currently being prepared in our laboratory. The link between the mechanisms related to PD-related pathology and permanent cell growth arrest might open new treatment strategies for PD towards the senescent cells clearance including senolytic drugs. This project was supported by: APVV-19-0585, APVV-20-0331, VEGA2/0158/21, SASPRO 2_1085/01/02.

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P0938 / #828

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: _-SYNUCLEIN

VALIDATION OF BIOCHEMICAL ASSAYS TO QUANTIFY LEVELS OF A-SYNUCLEIN PATHOLOGY IN HPFF SEEDED PRIMARY CULTURES

Marianne Borgers, Sofie Versweyveld, Bruno Vasconcelos, Aurélie Schwartzentruber, Brian Hrupka, Marc Mercken, Bianca Van Broeck
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Aims: Validate pS129 aggregated alpha-Synuclein (aSynuclein) and phospho-independent aggregated aSynuclein sandwich immunoassays for the detection of aSynuclein pathology in primary cultures.
Methods: Primary hippocampal cultures of C57BL/6JOlaHsd (carries a deletion at the aSynuclein locus, referred to as aSynuclein Knock-out) and Wild type (WT) mice were seeded at DIV9 with human preformed fibrils (hPFF) leading to the formation of aSynuclein pathology in WT cultures. The intracellular induced aSynuclein pathology consists of aggregated rodent aSynuclein proteins that are phosphorylated at S129. As a control, cultures were as well seeded at DIV20 to have hPFF present without the induction of aSynuclein pathology. Lysates of DIV21 were ultracentrifuged to separate aggregated and soluble aSynuclein and verified by SDS-PAGE/Western blot. All fractions were analyzed in sandwich immunoassays.
Results: hPFF was found in the culture lysates that could contribute to signals obtained in the sandwich immunoassays. hPFF are not phosphorylated at pS129 and therefor the pS129 aggregated aSynuclein sandwich immunoassay specifically detected the induced aSynuclein pathology. The applied hPFF in the culture lysates was found to be modified at the C-terminus during the incubation time on the cultures. This modification led to the loss of the antibody's epitope that is used in the phospho-independent aSynuclein sandwich immunoassay. Therefore, the phospho-independent aggregation assay also specifically detected the induced aSynuclein pathology.
Conclusions: pS129 aggregated aSynuclein and phospho-independent aggregated aSynuclein sandwich immunoassays were found to detect specifically the induced aSynuclein pathology in WT primary hippocampal cultures after PFF seeding.

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P0939 / #243

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: _-SYNUCLEIN

ENTERIC BIOMARKERS OF PARKINSON'S DISEASE

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Aims: Lewy bodies comprised mainly of alpha-Synuclein (αSyn) in the brain are the hallmark of Parkinson's disease (PD) but are also found in enteric nervous tissue. Gastrointestinal symptoms including constipation are among the earliest and most consistent prodromal symptoms of PD. This suggests that PD pathology begins in the gut before spreading to the brain. We hypothesize that biomarkers of early PD pathology are easily accessible in the gut before significant neurodegeneration has occurred in the brain. Because colonoscopy for cancer screening is recommended for everyone between the ages of 45 and 75, this standard of care procedure could be expanded to also screen for such biomarkers in enteric nervous tissue.
Methods: We used a humanized synucleinopathy mouse model and analyzed motor and gastrointestinal function in addition to changes in αSyn expression, subcellular distribution, and post translational modifications in brain and gut tissue. We similarly analyzed biopsies of human subjects collected in the rectum, sigmoid colon, cecum, and terminal ileum from PD patients and healthy controls.
Results: In mice, we found significant impairments to GI and motor function, along with biochemical changes in αSyn. We detected similar changes in human biopsies.
Conclusions: We conclude that biochemical analysis of αSyn in the gut is possible using biopsies taken during routine screening colonoscopies, and that biochemical changes in αSyn can be detected in tissue from PD patients. Therefore, early gut pathology is a promising target for future PD research that may lead to earlier diagnosis and potentially preventative care. Future work will expand on these findings.

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P0940 / #1621

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: _-SYNUCLEIN

SNCA-AS1, ANTISENSE TRANSCRIPT TO THE SNCA GENE, REGULATES ALPHA-SYNUCLEIN AND SYNAPTIC MODULATION WITH POSSIBLE IMPLICATIONS IN PARKINSON'S DISEASE AND AGING

Letizia Esposito[1], Federica Rey[1], Erika Maghraby[1], Letizia Messa[1], Cecilia Pandini[2], Gianvincenzo Zuccotti[1], Stephana Carelli[1], Cristina Cereda[1]
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Aims: SNCA protein product, alpha-synuclein (alpha-syn), is widely renowned for its role in synaptogenesis and implication in both Parkinson's Disease (PD) and aging, but research efforts are needed to clarify its physiological functions. SNCA-AS1, the antisense transcript to the SNCA gene, has been found up-regulated in PBMCs of patients affected by sporadic PD and its transcriptional modification is implicated in synapse-related genes expression. This work aims to report how SNCA-AS1 affects both synaptic processes and alpha-syn's expression.
Methods: SH-SY5Y cells stably transfected with SNCA-AS1 to overexpress the gene, whereas the knock-down model was performed via CRISPR-dCas9. Real Time-PCR and western blot were used to verify SNCA-AS1's effects on SNCA's expression and synapses-related markers. SNCA half-life was assessed via Actinomycin D treatment. Alpha-syn's expression was evaluated in presence of Cycloheximide. TEM and SEM were performed to analyze morphological aspects of synapses during the neural differentiation.
Results: The overexpression of SNCA-AS1 in SH-SY5Y cells upregulates both alpha-syn's mRNA and protein, whilst its knock-down decreases both targets. This strongly impacts on neurites' extension and synapses' morphological ultrastructural aspect, as assessed by SEM and TEM. Through specific molecular signatures SNCA-AS1 causes transcriptional modification in synaptic modulation pathways recapitulating an aging-related decline, as confirmed by RNA-Seq studies. Moreover, we demonstrate that the SNCA-AS1 overexpression reduces the half-life of SNCA mRNA, contrary to what happens in the knock-down model. Lastly, we report that SNCA-AS1 overexpressing cells release alpha-syn in the medium.
Conclusions: Our results show that SNCA-AS1 impacts alpha-syn expression, synapses biology and PD-related genes.

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P0941 / #1011

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: _-SYNUCLEIN

NEURONAL ACTIVITY DRIVES AUTOPHAGIC SECRETION OF A-SYNUCLEIN IN INTRACELLULAR CALCIUM- AND AMPHISOME FORMATION-DEPENDENT MANNERS

Yoshitsugu Nakamura, Taiki Sawai, Kensuke Kakiuchi, Shigeki Arawaka
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Aims: Extracellular α-synuclein (α-syn) secretion is a key step in cell-to-cell transmission of α-syn pathology in α-synucleinopathies, including Parkinson's disease and dementia with Lewy bodies. However, the mechanism that regulates α-syn secretion in neurons is not fully understood. Our aim is to elucidate how neuronal activity regulates α-syn secretion.
Methods: Mouse primary cortical neurons or SH-SY5Y cell line stably expressing wild-type α-syn were treated with chemical reagent, siRNA-mediated knockdown or cDNA overexpression. We measured α-syn proteins in conditioned medium.
Results: We find that increasing neuronal activity by glutamate or KCl, and elevating intracellular Ca2+ concentration using A23187, enhance α-syn secretion in mouse primary cortical neurons. Glutamate- and A23187-induced α-syn secretions are antagonized by intracellular Ca2+ chelator BAPTA-AM. Rapamycin-mediated mTOR inhibition increases α-syn and p62 secretions, but these increases are suppressed by heterozygous deficiency of Beclin 1. Glutamate-induced α-syn and p62 secretions are abrogated by siRNA-mediated knockdown of Atg5 in SH-SY5Y cells. Glutamate treatment facilitates autophagy flux without promoting autophagy-inducing AMP-activated protein kinase or p70S6 kinase phosphorylation in primary neurons in a manner sensitive to BAPTA-AM. Facilitation of amphisome formation by overexpression of Rab7 increases α-syn and p62 secretions. Blockade of amphisome formation by tetanus toxin and inhibition of amphisome trafficking to the plasma membrane by siRNA-mediated knockdown of Rab8a significantly reduce glutamate-induced α-syn secretion. Also, treatment with ATP-binding cassette (ABC) transporter inhibitor, probenecid, suppresses glutamate-induced α-syn secretion, and reduces α-syn secretion in exosome-enriched extracellular vesicle (EV) and non-EV fractions.
Conclusions: Collectively, the data indicate that neuronal activity drives autophagy-based secretion of α-syn in intracellular Ca2+ concentration- and amphisome formation-dependent manners, and this secretory pathway involves an ABC transporter for targeting α-syn into exosomes.

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P0942 / #2579

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

ROBUST AND VERSATILE ARRAYED LIBRARIES FOR HUMAN GENOME-WIDE CRISPR ACTIVATION, DELETION AND SILENCING

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Aims: Genome-wide CRISPR phenotypic screens are clarifying many fundamental biological phenomena. Pooled CRISPR guide RNA (sgRNA) libraries are powerful tools for identifying lethality phenotypes and, to some extent, modifiers of cell-surface markers. Arrayed CRISPR libraries extend the territory of CRISPR to cell-nonautonomous, biochemical, and morphological genetic screens. Yet, very limited resources for arrayed CRISPR screens are available.
Methods: Here we devise APPEAL (Automated liquid-phase Plasmid assEmbly And cLoning) for massively parallel liquid-phase plasmid cloning and generate two human genome-wide arrayed libraries termed T.spiezzo (CRISPRo, 19'820 plasmids) and T.gonfio (CRISPRa/CRISPRoff, 22'326 plasmids). APPEAL assembles 4 sgRNAs (driven by four different promoters) into a single lentiviral vector, and eliminates the necessity for colony-picking, enabling the automation of high-throughput liquid-phase cloning of libraries in a cost-effective manner. Our sgRNA design algorithm considers common DNA polymorphisms and selects highly specific and non-overlapping sgRNAs to maximize the synergistic activity and versatility of the libraries.
Results: This 4sgRNA-vector achieves maximal gene-perturbation efficacy while retaining high lentiviral titters. Sequencing of the library confers that ~90% of the plasmid population of each well contained ≥3 intact sgRNAs. Deletion, activation and epigenetic silencing experiments showed efficacy of 75-99%, up to 10,000x and 76-92%, respectively. Furthermore, in a proof-of-concept arrayed screen using T.gonfio sublibrary targeting human transcription factor (1,634 plasmids), several interesting genes, for the first time, were identified could restore the activity of the L444P mutation in lysosome enzyme beta-glucocerebrosidase (GCase), which is the most common risk factor for Parkinson disease and Gaucher diseases. Currently, we are extending the screen for modifiers of GCase at genome scale.
Conclusions: Our T.spiezzo and T.gonfio libraries present the next-generation efficacy and versatility and provide a powerful resource for the individual perturbation of each human protein-coding gene.

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P0943 / #1909

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

LRRK2 MUTATIONS AND PARKINSON'S DISEASE ARE ASSOCIATED WITH ALTERED INFLAMMATION PROFILES IN BLOOD AND CSF

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Aims: Parkinson's disease (PD) can result from LRRK2 gene mutations (LRRK2+). Growing evidence points to immune dysregulation in LRRK2+ subjects. The objective was to profile and compare a set of inflammatory cytokines, chemokines, and growth factors found in LRRK2+ and PD to those observed in LRRK2- and unaffected controls (UC), respectively.
Methods: A total of 129 CSF and 684 serum samples from LRRK2-/UC, LRRK2-/PD+, LRRK2+/UC, and LRRK2+/PD+ from four cohorts available in the LRRK2 Cohort Consortium were used to profile 65 analytes by Luminex assay. A multivariable robust linear model was used to associate analyte levels with LRRK2+/LRRK2- and PD/UC while adjusting for age, sex, and cohort.
Results: SDF-1 alpha*, TNF-RII*, MIP-1 beta, MCP-1, MIF, and IP-10 were elevated ($p<0.05$, $*p<0.05$ after adjusting for multiple comparisons) in LRRK2+ serum (n=438) compared to the serum of LRRK2- subjects (n=213). LRRK2+ CSF (n=63) had reduced BAFF, CD40L, MIP-3 alpha, and NGF beta levels ($p<0.05$) compared to those of the LRRK2- group (n=66). PD serum (n=242) had reduced levels of SCF ($p<0.05$) compared to those of UC (n=409). PD CSF (n=58) had decreased levels of MMP-1, MIF, and SDF-1 alpha ($p<0.05$) compared to those of UC (n=71).
Conclusions: LRRK2 mutations and PD status are associated with altered profiles of soluble immune regulators in serum and CSF. An elevation of pro-inflammatory cytokines in LRRK2+ serum is demonstrated. Further studies are needed to determine whether and how these altered soluble immune regulators may be mechanistically involved in PD.

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P0944 / #219

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

PATHOGENICITY OF I1371V VARIANT OF LRRK2 TO 6-HYDROXYDOPAMINE STRESS IN DOPAMINERGIC NEURONS DERIVED FROM LRRK2 I1371V PD PATIENT IPSCS

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Aims: To evaluate the pathogenicity of I1371V variant of LRRK2 in dopaminergic neurons in reference to the endogenous toxin 6-hydroxydopamine.
Methods: iPSCs of LRRK2 I1371V PD-patient & healthy control were used along with SH-SY5Y cells transfected LRRK2 I1371V. LRRK2 kinase effect on the cells was detected with the detection of phosphorylated LRRK2 in DA neurons. DA neurons were differentiated from iPSCs and characterized by mRNA and protein level. Functional studies of intracellular Ca^{2+} response, vesicular dopamine release was measured through live-cell fluorescence imaging. 6-OHDA stress on DA neurons and LRRK2 I1371V transfected SH-SY5Y cells was determined through cell survival MTT assay and ROS generation through fluorescent probe H_2DCF.DA and measured using spectrophotometry. Neurite blebbing and collapse was measured using neurite detection kit and labelled with cell survival fluorescent dye. Apoptosis of TH neurons was detected by co-labelling TH with Annexin V and measuring through FACS.
Results: DA neurons carrying LRRK2 I1371V mutation and SH-SY5Y cells overexpressing LRRK2 I1371V distinctly showed lesser cell survival, higher ROS generation and higher neurite collapse and blebbing upon 6-OHDA stress. Significant functional impairment in intracellular Ca^{2+} response upon KCl stimulation and its corresponding vesicular dopamine release was observed. PD DA neurons showed distinct α-synuclein pathology such as higher α-synuclein oligomer and phosphorylated α-synuclein expression.
Conclusions: The DA neurons derived from LRRK2 I1371V PD patient iPSCs and SH-SY5Y cells transfected with LRRK2 I1371V showed higher vulnerability to 6-OHDA stress as measured through cell survival, ROS generation and neurite detection assay. The PD DA neurons replicated PD pathology distinctly such as α-synuclein pathology and impaired intracellular Ca^{2+} response upon physiological stimulus. Therefore, LRRK2 mutation at I1371V is pathogenic to dopaminergic neurons.

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P0945 / #527

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

CATHEPSINS B AND D MAY REGULATE GLUCOCEREBROSIDASE ACTIVITY IN OPPOSING DIRECTIONS

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UCL, Institute Of Neurology, London, United Kingdom

Aims: Mutations in *GBA* are the greatest numerical risk factor for Parkinson's disease (PD). *GBA* encodes the lysosomal hydrolase, beta-glucocerebrosidase (GCase), and reduced GCase activity is associated with increased alpha-synuclein aggregation. GCase activity is not only impaired in PD-*GBA* individuals, but also in sporadic PD patients. It is thought that a lysosomal network, comprised of progranulin (*GRN*), prosaposin (*PSAP*), and cathepsins B (*CTSB*) and D (*CTSD*), may regulate GCase activity. We aimed to investigate the relationships underpinning this network to identify endogenous regulators of GCase activity, with the hope of revealing novel therapeutic targets.
Methods: In SH-SY5Y cells, we used siRNA technology to genetically knockdown (KD) *GRN*, *PSAP*, *CTSB*, and *CTSD*, and measured GCase protein expression and activity. In live SH-SY5Y cells, and wildtype (WT) iPSC-derived neurons, we pharmacologically inhibited cathepsins B and D, and measured live-cell GCase activity with the PFB-FDGlu probe. Using a novel protocol, we generated midbrain dopaminergic (mDA) neurons from healthy and *GBA* mutant (p.N370S heterozygous and homozygous) human iPSC lines. We assayed these cells for changes in the expressions and activities of the lysosomal network components.
Results: Upon siRNA KD in SH-SY5Ys, we saw a trend towards a reduction in GCase expression and a significant decrease in GCase activity upon *PSAP* KD. In live SH-SY5Ys, we saw a significant increase in GCase activity upon cathepsin B inhibition, and a trend towards an increase in iPSC-derived neurons. Conversely, we observed a trend towards a reduction in GCase activity upon cathepsin D inhibition.
Conclusions: Our data suggest that cathepsins B and D may have opposing effects on GCase activity in neuronal cell models. This finding would be novel and implicates the cathepsins as therapeutic targets in PD, warranting the need for further investigation.

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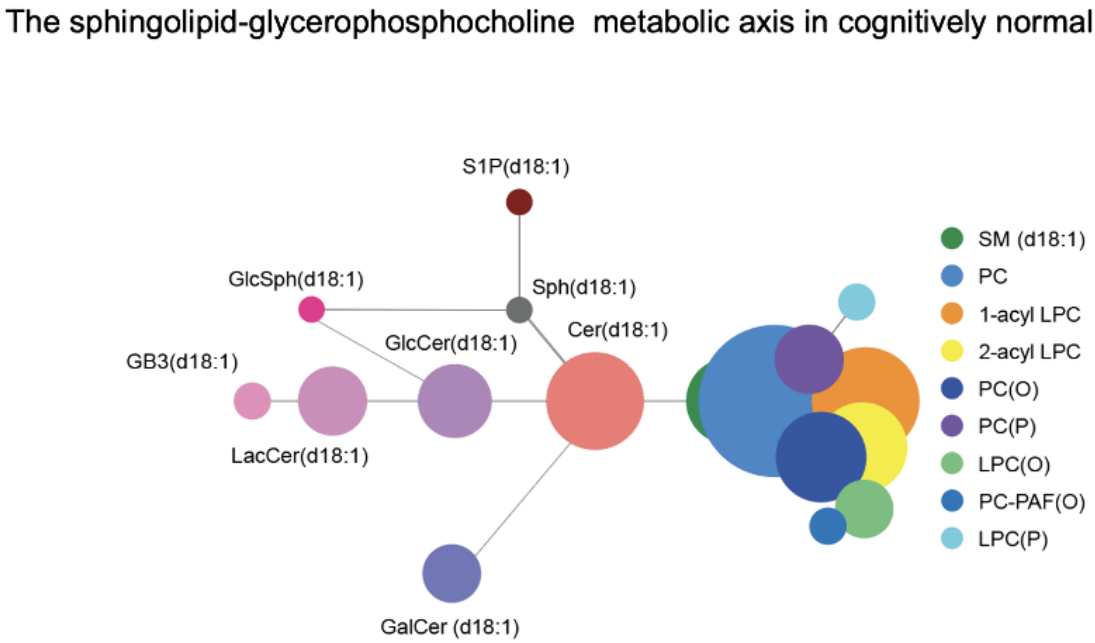
P0946 / #1891

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

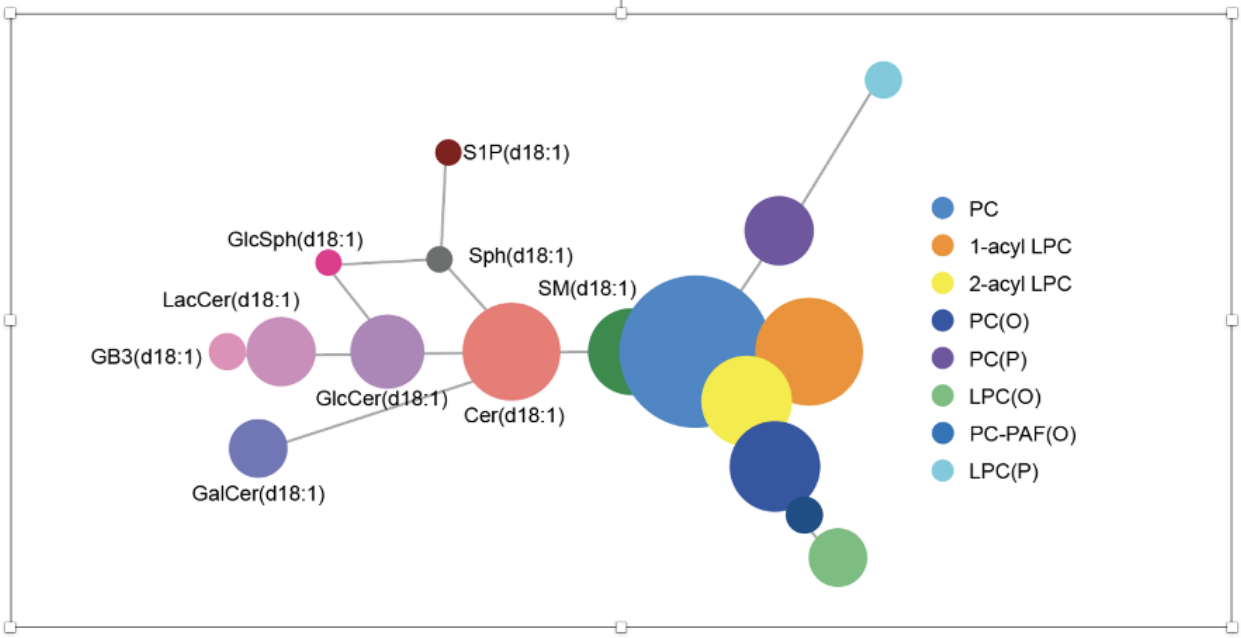
CONSTELLATION NETWORK MAPS: AN INNOVATIVE R-PACKAGE FOR MAPPING LIPID NETWORK DISRUPTIONS IN DEMENTIA WITH LEWY BODIES APPLICABLE TO ALL DEMENTIAS

Emily Hashimoto-Roth[1], Miroslava Cuperlovic-Culf[2], Steffany Bennett[1]
[1]Neural Regeneration Laboratory, Ottawa Institute of Systems Biology, University of Ottawa, Department Of Biochemistry, Microbiology, And Immunology And Department Of Chemistry, Ottawa, Canada, [2]National Research Council, Canada, Digital Technologies, Ottawa, Canada

Aims: Objectives: Systems biology is attempting to bridge different information spaces, including genomics, proteomics, lipidomics, imaging etc., with the expectation that their combination will highlight important biological features not otherwise apparent when analyzed in isolation. For example, we are currently studying neurodegenerative diseases by combining lipidomics and enzymatic assays to map the temporal changes in lipid metabolic disruption that occur during the transition from pre-symptomatic to symptomatic disease states. We require a means of visualizing these network level disruptions.
Methods: Methods: We have developed a new visualization tool, coded in R, that easily visualizes changes in lipid abundance, product to precursor conversion using distance correlation as a proxy measure for kinetics, and statistical changes in lipid abundance between groups and over time.
Results: Results: We present Constellation and its application to lipidomic network visualization, comparing lipidomic changes in metabolism between cognitively normal controls and patients with Dementia with Lewy Bodies as an example.



The sphingolipid-glycerophosphocholine metabolic axis is altered in DLB patients



Conclusions: Conclusions: Constellation is easily implementable and provides node and edge user input with complete documentation. It will be freely available at AD/PD at www.complimet.ca.

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P0947 / #679

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

THE CHROMATIN REMODELLING NSL COMPLEX: A MOLECULAR BRIDGE BETWEEN FAMILIAL AND SPORADIC PD?

Katie Kelly[1], Claudia Manzoni[2], Helene Plun-Favreau[1], Patrick Lewis[3]
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Aims: Development of a disease-modulating therapeutic option for PD remains a research priority. While linkage-based studies have illuminated dysregulated PINK1-mitophagy, clearance of damaged mitochondria, as a key driver of familial PD (fPD), the majority (95%) of PD cases are sporadic. A recently developed mitophagy screening assay of common PD risk gene candidates, derived from genome-wide association studies (GWAS), has functionally implicated the Non-Specific Lethal (NSL) complex in the regulation of PINK1-mitophagy. We have harnessed bioinformatics techniques to unpick the relevance of the NSL complex, for which a role in chromatin remodelling is well defined, to both sporadic and fPD progression.
Methods: We have modelled the cellular interactome of the NSL complex, mining 3 repositories: PINOT, HIPPIE and MIST, for curated, literature-derived protein-protein interaction (PPI) data. We have taken a multi-layered approach, following two distinct pipelines: **i)** Building the 'mitochondrial' interactome, applying PD gene-set enrichment analysis (GSEA) to explore the relevance of the NSL mitochondrial interactome to PD. **ii)** Building the PD-oriented interactome, and applying functional enrichment analysis. We have used the g:Profiler tool, g:GOSt, to uncover biological pathways underpinning the NSL /PD association.
Results: The mitochondrial interactome of the NSL complex is significantly enriched for PD gene proteins, including *LRRK2* and *VPS35*, associated with Mendelian PD. Conversely, the PD-associated interactome is enriched for mitochondrial processes; *"mitochondrial cell death*", *"mitochondrial protein localization",* "*membrane protein localization"* and *"mitochondrial transport"*. Our data suggests NSL complex members OGT and WDR5 are key drivers of the increased PD risk associated with these mitochondrial processes.
Conclusions: We propose that the NSL complex bridges familial and sporadic PD, with the association underpinned by a set of mitochondrial processes, strengthening a role for mitochondrial quality control in both familial and sporadic disease.

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P0948 / #490

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

SHEDDING LIGHT ON PARKINSON'S DISEASE GWAS GENES

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Aims: Over the past two decades, the discovery of dozens of new Parkinson's Disease (PD) genes has provided a tremendous opportunity to better understand how PD develops. However, the discovery rate of new genes has far outpaced our progress in understanding their roles in PD. Indeed, the research community has focused on a few of the "*popular*" PD genes (SNCA, PKRN, LRRK2, GBA), while the rest remain understudied. We refer to this set of *under-explored* genes as the "*PD Dark Genome*". We feel that with the advent of new technologies such as genome editing and the ability to differentiate human stem cells into different types of brain cells, the time is ripe to start disentangling how these *lesser-studied* genes contribute to PD. Our goal is to characterize *lesser-studied* PD genes in human stem cell-derived differentiated brain cells by systematically investigating them **1)** in cellular assays reflecting known PD pathways and **2)** in discovery genomic assays to uncover new PD mechanisms. These assays will yield biological signature for each profiled gene and determine if they are indeed associated with PD, and if so, understand their role in PD pathogenesis.
Methods: Using iPSC-derived DA neurons from the control cell line and 4 monogenic and PD risk gene KI/KOs (GBA KO, SNCA A53T, PINK1 KO and PRKN KO), we gathered a set of reference data.
Results: The results obtained assayed dopaminergic differentiation and maturation using immunofluorescence profiling, alpha-synuclein accumulation, and mitochondrial and lysosomal dysfunction. We also gathered scRNAseq and TMT proteomics data.
Conclusions: These results will serve as an experimental toolkit and pipeline to 1) explore the biology of GWAS genes responsible for PD risk, and 2) elucidate their role in PD pathogenesis and how they contribute to known or novel PD pathways.

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P0949 / #2161

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

META-ANALYSIS OF TRANSCRIPTIONAL REGULATORY NETWORKS FOR LIPID METABOLISM IN PARKINSON'S DISEASE PATIENTS HARBORING GLUCOCEREBROSIDASE MUTATION (GBA-PD)

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Aims: Mutations in the *GBA* gene, encoding for lysosomal enzyme glucocerebrosidases, confers increased risk to Parkinson's Disease, yet the molecular mechanism is unclear. Furthermore, not all carriers of *GBA* mutations develop PD. In this study, we aimed to identify the missing associations between transcriptional regulatory networks of lipid metabolism and PD, which could be the determining factor for developing this disease.
Methods: This study correlate results from publicly available large-scale transcriptomic dataset following our recently published meta-analysis workflow[1]. Transcriptomic datasets of GBA-PD patients with N370S mutation were obtained from NCBI GEO database. Differentially expressed genes (DEGs) were identified using a combination of DEGseq and multiple testing correction. All transcription factors (TF) and their target genes (TG), related to lipid metabolism were investigated by using GeneHancer, KEGG database and pathway enrichment analysis, to reconstruct a differentially regulated networks (DRNs). Finally, expression quantitative trait loci - single nucleotide polymorphisms (eQTL-SNPs) analysis was done to link genetic variants which affect the observed gene expression in GBA-PD patients. [1] Okamoto, L *et al* (2022). *Neurosci Res* 175:82-97
Results: Six transcriptomic datasets which met our criteria were included in this study. The regulation of the lipid metabolism genes in these datasets was found to be mostly due to TF which bind to enhancers. Hierarchical clustering analysis of the TF-TG pairs revealed common regulatory modules shared by multiple datasets. The functionality classes of these modules were traced to identify possible associations to GBA-PD progression. Finally, using eQTL-SNPs analysis, we found several common genetic characteristics of GBA-PD DRNs, shared by the datasets used in this study.
Conclusions: The presented study identified genetic signatures related to lipid metabolism which highlight possible determinant factors for GBA-PD progression.

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P0950 / #1860

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

CAUSAL LIPID NETWORK PROGRESSION TOWARDS PARKINSON'S DISEASE THROUGH MACHINE LEARNING AND NETWORK ANALYSIS

Miroslava Cuperlovic-Culf[1,2], Anuradha Surendra[1], Thao Nguyen[2], Irina Alecu[2], Roberto Ortega[3], Rachel Saunders-Pullman[3], Steffany Bennett[2]
[1]National Research Council, Canada, Digital Technologies, Ottawa, Canada, [2]University of Ottawa, Neural Regeneration Laboratory, Ottawa Institute Of Systems Biology, Department Of Biochemistry, Microbiology, And Immunology, Ottawa, Canada, [3]Mount Sinai Beth Israel Medical Center, Department Of Neurology, New York, United States of America

Aims: Major role of lipids in the development and progression of Lewy Body diseases is increasingly recognized with presented importance of the perturbation of lipids in the disease onset and an established presence of lipid core in Lewy Bodies. Quantitative lipidomics provides data that can aid in unbiased determination of the role of lipid metabolic network at different disease stages. However, lipid network determination remains a major challenge due to sparse experimental coverage, variety of different functional relationships between lipid molecules and only sporadically described reaction network.
Methods: Distance correlation is used for the development of undirected network of lipidome that provides a base for the application of Gaussian Process Regression (GPR) for derivation of directed, causal lipid network of PD. Dependence of each lipid on all the other members of lipidome is seen as a regression problem where the importance of a lipid in the prediction of the target lipid in GPR models is an indication of a putative regulatory link while comparison of prediction loss in different interaction directions is used to establish causalities.
Results: Derived are plasma lipid networks for PD and control groups separated by sex. Comparative analysis between groups have shown major functional changes in lipid interactions indicating the most important overall lipid changes as well as major lipid-to-lipid alterations. Modeling of trajectory from directed networks in control to PD state is used to determine possible combination of metabolic targets that can transform lipid network from control to PD state and multi-targeted route back into control state proposing a novel approach for PD target selection and testing.
Conclusions: Novel approaches are developed to derive PD networks and investigate multi-targeted approach for whole lipid network state change towards healthy state.

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P0951 / #1484

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

CHARACTERIZATION OF CELL CULTURE-DERIVED NEUROMELANIN GRANULE-LIKE STRUCTURES AS A POTENTIAL MODEL FOR PARKINSON'S DISEASE-RELATED RESEARCH

Britta Eggers[1,2], Maximilian Wulf[1,2], Ronja Kopton[1,2], Katalin Barkovits[1,2], Sarah Stahlke[3], Carsten Theiss[3], Katrin Marcus[1,2]
[1]Ruhr University Bochum, Medical Faculty, Medizinisches Proteom-center, Bochum, Germany, [2]Ruhr University Bochum, Center for Protein Diagnostics (ProDi), Medical Proteome Analysis, Bochum, Germany, [3]Ruhr University Bochum, Department Of Cytology, Institute Of Anatomy, Bochum, Germany

Aims: Neuromelanin (NM) is a blackish-brown pigment present in dopaminergic neurons in the substantia nigra (SN) pars compacta, where NM is stored in membrane-enclosed neuromelanin granules (NMGs). The study of the molecular composition of NMGs is of great importance because the selective loss of NMG-containing dopaminergic neurons in the SN leads to cardinal symptoms in Parkinson's disease (PD). However, since NMGs are not present in laboratory animals, research relies on and is limited to human post mortem brain tissue. To gain insights into NM as well as NMGs at the molecular level, we used a genetically modified human neuronal cell line that expresses the enzyme tyrosinase and thereby produces NMG-like pigments. Using a multi-method approach, we initially aimed to assess the comparability of cell culture NMGs and human NMGs in order to further investigate the origin, genesis and NM/NMG-associated mechanisms in the cell model.
Methods: We combined electron microscopy, lipidomics and proteomics to characterize the morphological structure, the molecular composition and the mechanism of generation of cell culture NMGs and combined these results with those obtained from human NMGs.
Results: The morphological analysis underlined an evident similarity between both structures. First proteomic analyses verified a comparable proteomic composition between both NMG species. Further, we identified a distinct influence of cell culture NMGs on healthy neuronal cells, by upregulation of vesicle transport-associated proteins, lysosomal proteins and proteins involved in oxidative stress response.
Conclusions: Our results demonstrate a promising comparability of cell culture-derived NMG-like structures with human NMGs in SN tissue at the structural and protein level and provide the basis for further functional studies.

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P0952 / #547

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

MASTER REGULATION OF PARKINSON'S DISEASE GENES BY HISTONE ACETYLATING NSL COMPLEX

Amy Hicks[1], Regina Reynolds[2], Ben O'Callaghan[1], Sonia Garcia Ruiz[2], Ana Luisa Gil Martinez[1], Juan Botia[3], Helene Plun-Favreau[1], Mina Ryten[2]
[1]UCL Queens Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom, [2]UCL Great Ormond Street Institute of Child Health, Genetics And Genomics Department, London, United Kingdom, [3]University of Murcia, Department Of Information And Communication Engineering, Murcia, Spain

Aims: Genetic variants conferring risk for Parkinson's disease (PD) have been highlighted through GWAS, yet exploration of their specific disease mechanisms is lacking. Two PD candidate genes, *KAT8* and *KANSL1*, identified through GWAS and a PINK1-mitophagy screen, encode part of the histone acetylating non-specific lethal (NSL) complex. This complex localises to the nucleus, where it has an established role in transcriptional activation, and to mitochondria, where a role in mitochondrial transcription has been explored. Here we sought to identify whether the NSL complex potentially acts as a master regulator of multiple PD-associated genes and pathways in human brain.
Methods: Using publicly available transcriptomic data provided by Genotype-Tissue Expression Consortium, we investigated correlations in the expression of NSL and PD-associated genes in both primary gene co-expression networks (GCNs) and secondary GCNs that accounted for cell type-specific signatures. Reverse engineering of gene regulatory networks was used to predict regulons of the NSL complex. Resulting gene sets were tested for PD heritability using stratified linkage disequilibrium score regression and validated as NSL complex targets in vitro using a QuantiGene multiplex assay.
Results: We found significant clustering of NSL genes with PD-associated genes in frontal cortex primary GCN modules. Primary and secondary GCN modules containing these genes were enriched for predominantly neuronal cell types. NSL complex regulons were nominally enriched for PD heritability and significantly enriched for biological pathways genetically linked to the disease. When examined in neuroblastoma cells, 41% of prioritised genes displayed significant changes in mRNA expression following NSL complex perturbation.
Conclusions: Overall, these findings reveal a potentially wider role for the NSL complex in regulating multiple genes and pathways implicated in PD.

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P0953 / #1710

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

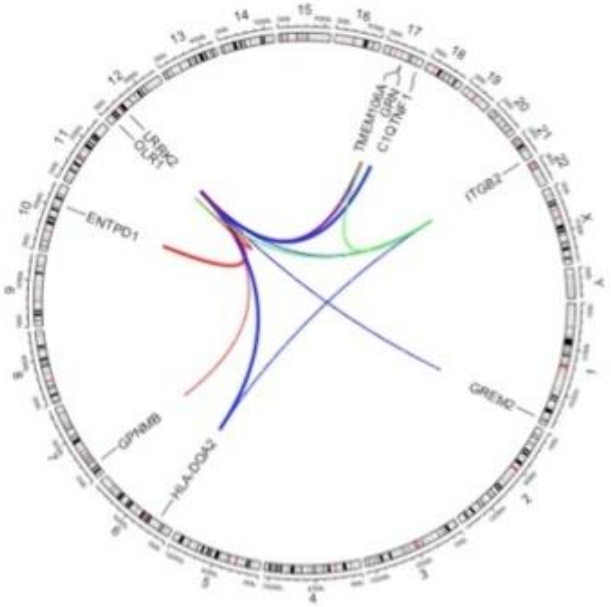
CEREBROSPINAL FLUID PROTEOMIC SIGNATURE OF SPORADIC AND GENETICALLY-DEFINED PARKINSON'S DISEASE

Mei-Yu Lai[1], Bruno Benitez[2]
[1]Beth Israel Deaconess Medical Center, Neurology, Boston, United States of America, [2]Beth Israel Deaconess Medical Center/Harvard Medical Center, Neurology, Boston, United States of America

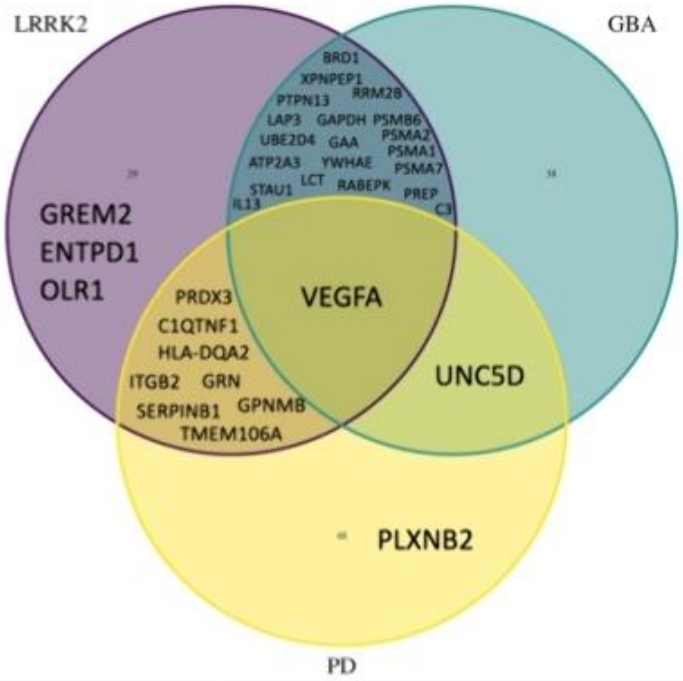
Aims: We integrated genome-wide genotyping data and cerebrospinal fluid (CSF) proteomic data to identify protein quantitative trait loci (pQTLs) in samples with Parkinson's disease (PD). We used clinical (movement and cognitive tests), neuroimaging, and CSF phosphorylated-tau, total-tau, alpha-synuclein, and amyloid-beta levels to uncover PD proteomic signatures.
Methods: We used data from the Parkinson's Progression Markers Initiative (PPMI) cohort (N = 1158); 683 individuals passed quality control for pQTL analysis. Differentially expressed proteins in LRRK2+, GBA1+, or sporadic PD (sPD) were curated using F-test, adjusting for sex, age, and principal components 1-4. Weighted correlation network analysis (WGCNA) and least absolute shrinkage and selection operator (LASSO) algorithm were used to explore modules of proteins associated with CSF biomarkers and clinical and neuroimaging data.
Results: We found trans-pQTL for TMEM106A, ITGB2, ENTPD1, OLR1, GRN, GPNMB, GREM2, C1QTNF1, and HLA-DQA2 in the LRRK2 locus. We identified subgroups of proteins associated with mutation carriers in LRRK2 (n=709) and GBA1 (n=505), or sPD (n=97), which are linked to the proteasome, spinocerebellar ataxia, and the Rap1 signaling pathways. The WGCNA revealed two modules of proteins associated with higher levels of CSF biomarkers in PD patients. We did not find modules associated with cognitive (MoCA), movement (UPDRS-III) tests, or volumetric measures of caudate, striatum, or putamen. We found 117 proteins that distinguish genetically-defined PD from sPD with an area-under-ROC-curves (AUC) =0.94. We identified 158 proteins that differentiate PD from controls with an AUC=0.86 outperforming CSF biomarkers but underperforming UPDRS-III (AUC=0.993) and putamen (AUC=0.983).
Conclusions: Our proteome-genome approach suggests LRRK2 as a pleiotropic genetic modifier. Genetically defined PD subgroups are associated with distinct proteomic signatures. Protein modules correlated to CSF biomarkers and differentiated PD from

controls.

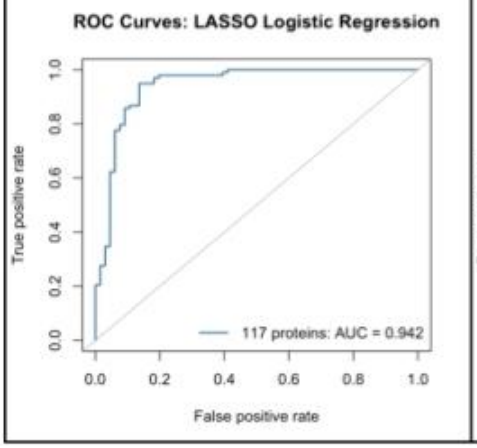
(a) The circos plot of LRRK2-locus associated with 9 unique CSF proteins.



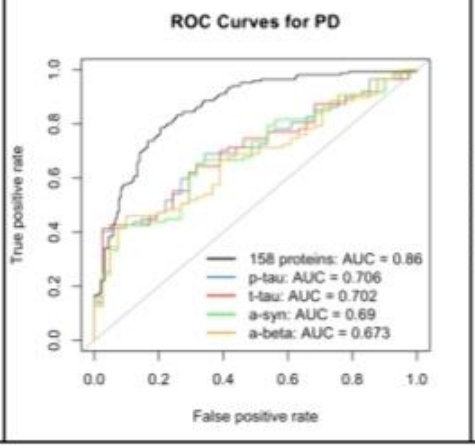
(b) The Venn diagram for 709, 505, and 97 proteins differently expressed in LRRK+, GBA1+, and sPD, respectively.



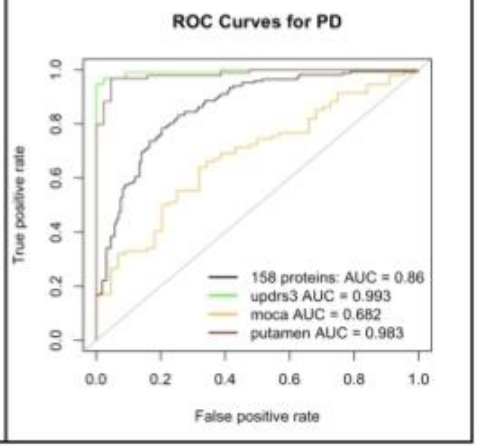
(c) The ROC curves for idiopathiic PD prediction.



(d) The ROC curves for PD prediction with CSF biomarkers.



(e) The ROC curves for PD prediction with clinical data.



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P0954 / #1622

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

DEVELOPMENT OF COMPUTER-BASED APPROACHES FOR THE DIAGNOSIS AND TREATMENT OF NEURODEGENERATIVE DISEASES

Letizia Messa[1], Pietro Pinoli[1], Federica Rey[2], Gianvincenzo Zuccotti[2], Stephana Carelli[2], Cristina Cereda[3], Stefano Ceri[1]
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Aims: In recent years, high-throughput techniques have been used to produce genetic and transcriptomic data of Parkinson's Disease (PD) patients to investigate their transcriptional deregulation, but data interpretation is hard due to the lack of validation and data integration. In this context, we used computer-based approaches to analyze and interpret large and complex transcriptomic data towards the identification of new potential innovative biomarkers in PD.
Methods: Public transcriptomic datasets were explored in GEO repository. Raw FASTQ files were downloaded and reprocessed using a common pipeline to obtain comparable data. Differential expression analysis was performed with DESeq2 R while functional enrichment analysis with g:Profiler and GSEA.
Results: Among the available datasets we considered 5 obtained from brain samples. The differential expression analysis returned 670 deregulated genes. The functional enrichment analysis showed that differentially expressed genes are enriched in pathways related to neurodegenerative specific processes. Since the disease pathology may be different between brain areas, we also performed the analysis for specific brain tissues, returning 1502 differentially expressed genes when considering the substantia nigra, 3034 in the subthalamic nucleus, 86 in the putamen, 348 in the medial temporal gyrus, 1619 in the prefrontal cortex and 14 in the amygdala.
Conclusions: We highlighted a global transcriptional deregulation in the brain, highlighting a different degree of gene expression alteration in different brain PD-affected areas. We will use computer-based approaches, such as machine learning, to identify PD specific signatures in PD-prodromal patients.

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P0955 / #1673

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

AN ANALYTICAL AND BIOINFORMATIC PIPELINE FOR PROFILING GLYCOSPHINGOLIPIDS AND STERYL GLYCOSIDES IN PLASMA AND CEREBROSPINAL FLUID OF PARKINSON'S DISEASE PATIENTS.

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Aims: Most allelic risk variants that confer risk of Parkinson's Disease (PD) converge on sphingolipid metabolism yet have modest, individual effect sizes, requiring multiple genetic hits to enhance susceptibility. These data suggest a common sphingolipid pathology exacerbated by genetics. The central genetic regulator is glucosylceramidase (*GBA1*). GBA1 encodes GCase, the enzyme responsible for removing the glucose headgroup from glucosylceramides. GCases also catalyze transglucosyl and, surprisingly, transgalactosyl reactions generating glucosyl and galactosyl cholesterols. Here, we describe an integrative, mass-spectrometry and machine-learning-based pipeline to profile and interrogate glycolipid metabolism directly in biofluids from PD patients biofluids to map these networks.
Methods: Disruptions in glycosphingolipid metabolism were assessed using a combination of analytical and bioinformatics methods. Firstly, nanobore liquid chromatography-electrospray ionization-tandem mass spectrometry (nLC-MS/MS) was utilized. Specifically, we combined the highly selective and sensitive quantification characteristics of multiple-reaction-monitoring (MRM) method with the structurally informative fragmentation of enhanced-product-ion (EPI) scan. Secondly, we coupled nLC-MS/MS to differential mobility spectrometry (DMS) to distinctly separate cerebroside isomers. Finally, we applied hybrid mechanistic and machine learning models to our analytical assessment to further infer mechanistic information linking lipid metabolism and PD.
Results: Our pipeline first profiles levels of individual cerebrosides (Hexosylceramides), globosides (GB3), gangliosides (GD1b, GD2, GD3), and steryl glycosides (Hexosylcholesterol) with structural validation in patients' plasma and cerebrospinal fluid. Next DMS-MS/MS is employed to quantify different cerebroside and steryl glycoside isomers, β-Glucosylceramides, β-Galactosylceramides, β-Glucosylcholesterols and β-Galactosylcholesterols. We further describe the bioinformatic strategies that resulted identification of enzymatic determinants of secondary lipid metabolism disruption in PD patients.
Conclusions: The presented pipeline is efficacious and applicable for clinical assessment of circulating glycosphingolipids in PD's patients and helps to shed insights to the underlying molecular mechanism of PD.

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P0956 / #1371

POSTERS: C06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

SINGLE CELL TRANSCRIPTOMIC AND EPIGENOMIC PROFILING OF THE DOPAMINERGIC SYSTEM

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Aims: Parkinson's Disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and to a lesser extent in the ventral tegmental area (VTA). There is a gap in knowledge in the molecular mechanisms underlying this difference in vulnerability. Our aim is to combine transcriptomic and epigenomic single nuclei sequencing to understand the molecular basis underlying PD vulnerability. A secondary goal is to determine the defects in other cell types.
Methods: We used 10x Chromium single nuclei RNA sequencing to generate a transcriptomic atlas of the mouse VTA, which we validated using smFISH techniques. Two epigenomic techniques are used to generate an epigenomic atlas of histone modifications in the mouse/human VTA and SNpc, using antibody tethering of either protein-A-micrococcal nuclease (sortChIC) or protein-A-Tn5 transposase (CUT&Tag).
Results: Our data shows a large diversity of neuronal subsets (44 populations) in the mouse VTA, with the most diversity found in GABAergic and combinatorial neurons. Of interest, we identified a new, large subset of neurons lacking specific neurotransmitter markers. Once complete, histone modification atlases will provide a comprehensive understanding of how gene expression is epigenetically regulated in the adult human and mouse VTA/SNpc in different cell types. We will computationally integrate our datasets with the literature to identify transcriptomic and epigenomic signatures of the VTA/SNpc.
Conclusions: Epigenetic factors underlying PD vulnerability have been previously indicated, but an exact pattern of histone modification in the VTA/SNpc is missing. Our research will give insight into histone marks and their regulatory function of PD vulnerable genes and cell types. This will aid in the research in preventing cell death and since histone modifications are reversible, generate new targets for PD treatment.

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P0957 / #1684

POSTERS: C06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

EXPLORING SELECTIVE NEURONAL VULNERABILITY IN ALZHEIMER'S AND PARKINSON'S DISEASE USING IPSC DERIVED CORTICAL AND DOPAMINERGIC NEURONS AND ALPHA SYNUCLEIN FIBRILS

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Aims: Alzheimer's and Parkinson's disease feature progressive neurodegeneration associated with the accumulation of protein aggregates in a remarkably regionally selective manner. The cortical neurons that are relatively vulnerable in Alzheimer's Disease (AD) are only affected late in Parkinson's Disease (PD), whereas midbrain dopaminergic neurons exhibit striking vulnerability in PD, but are relatively spared in AD. Rodent and human *post mortem* studies have posited a role for cell autonomous mechanisms driving this, but having a live human cell model that can replicate the phenomenon of selective neuronal vulnerability can help to better determine common and contrasting disease mechanisms and identify therapeutic targets.
Methods: Here, we used induced pluripotent stem cell (iPSC) derived neurons as they offer a rare opportunity to examine cell autonomous vulnerability in live human cells. iPSCs from patients with AD-related presenilin-1 mutations (n=3), PD-related leucine rich repeat kinase 2 mutations (G2019S n=3, R1441C n=3), and isogenic corrected (n=3) and healthy controls (n=4) have been differentiated into both cortical neurons and midbrain dopaminergic neurons to enable comparison of vulnerability phenotypes in different neuronal subtypes from the same patient.
Results: AD cortical neurons insulted with alpha-synuclein pre-formed fibrils (PFFs) have impaired neurite outgrowth, reduced synaptic density, and extensive aggregate formation. Meanwhile, PFF insulted PD cortical neurons exhibit normal neurite outgrowth and relatively little aggregation, whereas PD dopamine neurons readily produce aggregates.
Conclusions: These preliminary results show relative vulnerability of AD and resilience of PD cortical neurons to alpha synuclein aggregates for the first time. This suggests the selective vulnerability to proteinopathy exhibited in these diseases may be replicated by the iPSC neuronal model, and additionally supports the notion that cell intrinsic factors may partly determine this vulnerability.

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P0958 / #401

POSTERS: C06.H. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

ALTERATIONS IN THE EXPRESSION OF PAX6 WITH PARKINSON'S ASSOCIATED PROTEINS IN MICE BRAIN

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Aims: To study the histological changes in cell types of cerebral cortex and striatum of control and MPTP treated mice and further investigate the expression of Pax6 with Parkin, α-synuclein, S100*β*, p53, GFAP, Iba1 and NGN2 in these brain regions.
Methods: The AKR strain of mice (*Mus Musculus*) was used for the experiments,maintained as per the IAEC guidelines.Nissl's staining was performed to observe the structural changes in neurons in different brain regions of control and MPTP treated mice(20mg/kg, subcutaneous). The expression of Pax6 with different proteins (Parkin, α-synuclein, S100*β*, p53, GFAP, Iba1 and NGN2) was observed by co-localization in striatum and cerebral cortex.
Results: The neuronal change in cellular architectureof different cell typesand decrease in their numberwere seen in the substantial nigra (SNc) of striatum (DV, sylvious) and layers of cerebral cortex; molecular layer (MoLr), external granular layer (ExGl), pyramidal layer or external plexiform layers (PyLr/ExPl), inner granular layer (InGl), ganglionic layer (GaLr), multiform layer (MuLr)] inMPTP induced Parkinson's model of mice brain. Further, decline in the expression of Pax6, parkin, and NGN2 and increased expression of α-synuclein, S100*β*, p53, GFAP, Iba1 was observed.
Conclusions: The findings suggest Pax6 which is conventionally considered to be developmental protein but is also associated with progression of Parkinson disease in MPTP induced mice brain. The change in expression of other proteins in different brain regions may be related to dysfunction of different brain functions (axonal path finding, motor control, neuronal cell survival) in PD.

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P0959 / #1693

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

EVIDENCE FOR PRODROMAL NEUROINFLAMMATION IN A RODENT MODEL OF ALPHA-SYNUCLEINOPATHY

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Aims: Toxic aggregation of alpha-synuclein is a key feature of alpha-synucleinopathies, including dementia with Lewy bodies and Parkinson's disease dementia. Early neuroinflammation, mitochondrial dysfunction, and neuronal excitability changes could all be hallmarks of the progression of alpha-synucleinopathy in patients. In addition, transgenic mice expressing human alpha-synuclein exhibit hippocampal and neocortical network hyperexcitability. The current study investigated the early changes in the CA3 region of the hippocampus of mice aged 2-4 months expressing human mutant (hA30P) alpha-synuclein. We focused on evidence of neuroinflammation, quantifying changes in astrocytic and microglial activation.
Methods: We used immunofluorescence (IF) to detect GFAP, a marker for reactive astrocytes, and Iba-1, a marker for reactive microglia in horizontal frozen sections containing hippocampus from paraformaldehyde fixed brains of male hA30P and age-matched C57BL/6 wild type (WT) mice. Sections were imaged using a Nikon NiE microscope and densitometric analysis carried out using FIJI software.
Results: IF results showed a highly significant increase in the percentage area of sections of CA3 occupied by GFAP+ astrocytes in all layers of the hippocampus ($p<0.0001$; WT = 47 sections/8 mice and hA30P = 54 sections/8 mice). There was also a significant difference in percentage area occupied by Iba-1+ microglia ($p<0.05$, WT = 38 sections/7 mice and hA30P = 53 sections/8 mice). We observed morphological changes in astrocytes and microglia consistent with neuroinflammation. There was an interesting laminar difference in the distribution of astrocytes and microglia. The major population of Iba-1+ microglia occupied the *stratum pyramidale* of CA3, in contrast to GFAP+ astrocytes, which were most prevalent in oriens and radiatum strata.
Conclusions: These results suggest there is an early neuro-inflammation in young hA30P mice. Future work will determine whether metformin, an anti-hyperglycemic drug with known anti-inflammatory effects, has a neuroprotective role in hA30P mice.

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P0960 / #1687

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

DEVELOPMENT OF MOUSE MODELS FOR A-SYNUCLEINOPATHY

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Aims: Parkinson's disease (PD) is a devastating neurodegenerative disorder, affecting ~10 million individuals worldwide. Its genetic connection to the SNCA gene encoding for α-synuclein (aSyn) and aSyn's localization to Lewy pathology, a hallmark of idiopathic PD, places PD alongside other α-synucleinopathies. Disease progression in PD is inexorable, yet no effective therapies currently exist. Since aggregation and spreading of misfolded aSyn are hypothesized to be crucially involved in disease progression, prevention or clearance of aSyn aggregation is a promising disease-modifying strategy. To support the development of such therapies, we implemented mouse models of PD that resemble aSyn pathology seen in patients.
Methods: The mouse models involve the intrastriatal injection of aSyn preformed fibrils (PFFs) that trigger endogenous aSyn to misfold and accumulate into hyperphosphorylated inclusions.
Results: Intrastriatal inoculation of PFFs into wild-type mice led to aSyn pathology with hyperphosphorylated aSyn deposits observed in the injection site and in the substantia nigra, cortex and amygdala within 30 days post-injecion (dpi). At 90dpi deposits had substantially diminished, which coincided with the loss of tyrosine-hydroxylase-positive neurons. For the development of therapies targeting intracellular human aSyn, there is a need for mouse models that express human aSyn, so we also assessed aSyn pathology following intrastriatal PFF injection in these mice. However, so far, induction of aSyn pathology in these animals is less efficient compared to wild-type mice.
Conclusions: Here we present the induction of aSyn aggregation in wild-type mice and mice expressing human aSyn following intrastriatal PFF injection, and show the difference between both models.

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P0961 / #1117

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

INVESTIGATING CHANGES IN INTERNEURONS AND PERINEURONAL NETS IN A RODENT MODEL OF ALPHA-SYNUCLEINOPATHY

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Aims: Dementia with Lewy Bodies (DLB) is characterized by the accumulation of aggregated insoluble α-synuclein (α-syn) protein. DLB patients exhibit impaired higher cognitive functions which involve the prefrontal cortex (PFC). Parvalbumin-expressing interneurons, which are critical for normal cognitive function, are surrounded by a protective extracellular matrix – the perineuronal nets (PNNs). Recent evidence suggests changes in both PV cells and the PNN could play an important role in neurodegeneration. Using transgenic mice that express human mutant (hA30P) a-syn we are investigating the impact of α-syn pathology on PV interneurons and the PNN in the PFC at different disease stages in A30P compared to control mice.
Methods: We used frozen coronal sections containing PFC from paraformaldehyde fixed brains of male hA30P and age-matched C57BL/6 wild type (WT) mice. PNNs were labelled with fluorescently tagged Wisteria floribunda lectin and interneurons revealed by immunofluorescent labelling for PV. Sections were imaged using fluorescence and confocal microscope and analysis was achieved using FIJI software.
Results: Our preliminary results show that the majority of PV-expressing interneurons in the mPFC are surrounded by a PNN in both wild type and hA30P mice. However, there are a small proportion (~10%) of PV interneurons without any perineuronal net. Furthermore, some PNNs are associated with non-PV cells. The extent to which the presence of abnormal alpha-synuclein effects different interneurons classes is currently being assessed. Furthermore, we are investigating whether there are changes in the PNN in the PFC of hA30P mice with age and disease progression.
Conclusions: The majority of PV cells in the PFC in A30P and control mice are associated with a PNN. On-going studies will determine whether the PNN could provide protection against alpha-syn-mediated neurodegeneration.

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P0962 / #1350

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

CHARACTERIZATION OF THE HA53TTG A-SYNUCLEIN MOUSE MODEL OF PARKINSON'S DISEASE

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Aims: Aggregation of α-synuclein (α-syn) plays a crucial role in Parkinson's disease and other synucleinopathies. Point mutations in α-syn have been identified in rare forms of familial PD and are reported to accelerate α-syn oligomerization and aggregation as well as age of symptom onset. Here, we characterized human α-syn transgenic mice with A53T mutation (hA53Ttg) biochemically and histologically.
Methods: hA53Ttg and non-transgenic (ntg) littermates at the age of 2, 4, 6, 10 months were analyzed. Brain hemispheres were immersion-fixed and sagittally cryosectioned. Multichannel immunofluorescence was performed for human α-syn, phospho-Ser129 α-syn, GFAP and Iba1. Labeling was quantified by image analysis in the cortex, hippocampus, striatum, and brainstem. The concentration of hα-syn and phospho-Ser129 α-syn was determined in different brain compartments using immunosorbent assays. Neurofilament-light chain (NF-L) was quantified in plasma and cerebrospinal fluid using ELISA.
Results: Human α-syn, phospho-Ser129 α-syn, and GFAP levels were higher in hA53Ttg mice compared to ntg mice. Greatly increased phospho-Ser129 α-syn, GFAP, and Iba1 levels were found in the brainstem of 10 months old hA53Ttg mice. Biochemical data also suggest higher concentrations of hα-syn and phospho-Ser129 α-syn in brain tissue of hA53Ttg animals. NF-L levels in plasma and CSF of 10 months old hA53Ttg mice were significantly increased compared to ntg littermates.
Conclusions: Our analyses revealed a severe α-syn pathology in the brainstem of 10 months old hA53Ttg mice accompanied by gliosis. Increased NF-L levels indicate axonal damage in the brain of 10 months old mice.

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P0963 / #1188

POSTERS: C07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

TARGETING AUTOPHAGY TO IDENTIFY NOVEL MODULATORS OF PARKINSON'S DISEASE USING MIDBRAIN ORGANOIDS

Javier Jarazo[1,2], Isabel Rosety[1,2], Catarina Serra-Almeida[1,3], Raquel Marques[1], Claudia Saraiva[1], Rohan Davis[4], Jens Schwamborn[1,2]
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Aims: Parkinson's disease (PD) is a neurodegenerative ailment caused by polygenetic factors that converge, among others, in the autophagy pathway. Genes known to cause PD when mutated, such as PINK1, Parkin, VPS35, LRRK2, and SNCA, play a role in autophagy. Natural compound libraries are a great source of new chemical molecules that could restore the altered phenotypes in patient derived cells. The objective of this project was to discover compounds that modify the autophagy pathway in the context of a genetic form of PD, which was further validated in midbrain organoids derived from patients with different genetic backgrounds.
Methods: Using genetically encoded pH sensors, we engineered healthy and patient iPSC lines to monitor autophagy for screening a library of natural compounds in a high-throughput phenotypic platform with automated high-content image analysis. Identified hits were further selected based on dose response curves. The effects of these compounds on the number of dopaminergic neurons, as well as others features, were assessed in 2D and 3D midbrain organoids.
Results: A library of 640 compounds, the majority of which have been obtained from Australian natural sources, such as fungi, plants, and marine invertebrates, was screened leading to the identification of 9 small molecule compounds that rescued autophagy alterations in cells derived from a patient having the D620N mutation in the VPS35 gene. Three compounds were selected, and further tested in 2D neurons and midbrain organoids derived from patients having mutations in the GBA, SNCA, and MIRO genes, improving the phenotypes observed in these cells.
Conclusions: Modifiers of the autophagy pathway activity are interesting candidates for further development as therapeutic molecules to target neurodegeneration in PD.

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POSTERS: C07.C. ANIMAL MODELS: NON-MAMALIAN MODELS

ΔHNS E. COLI CAN RESCUE PARKINSON'S DISEASE (PD)-LIKE PHENOTYPES IN C. ELEGANS: EVIDENCE FOR THE ROLE OF GUT MICROBE GENES ON PD

Min Gi Shin[1,2], Eun Jeong Lee[2]
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Aims: Parkinson's disease (PD) is a neurodegenerative disorder that affects predominately dopaminergic neurons in a specific area of the brain called substantia nigra. In addition to the degeneration of dopaminergic neurons, PD patients show motor dysfunction and increases in methylglyoxal (MG). MG is a reactive carbonyl species involved in the formation of advanced glycation end products, which are implicated in various pathologies, including neurodegenerative diseases. We hypothesized that *Δhns Escherichia coli (E. coli),* which was reported to extend lifespan of *Caenorhabditis elegans* (*C. elegans*) (Shin et al., 2020, PNAS), could ameliorate PD-like symptoms such as neurodegeneration of dopaminergic neurons, based on the several features of *Δhns E. coli*-fed *C. elegans*: 1) *Δhns E. coli* enhanced motility of *C. elegans*, 2) neuronal projection and synapse-related genes were up regulated in *Δhns E. coli*-fed *C. elegans*, and 3) *Δhns E. coli* produced much lower amounts of MG.
Methods: We used *C. elegans* mutant which can observe dopaminergic neurons with gfp. *bcat-1* RNAi was applied to degenerate dopaminergic neurons.
Results: To explore the possibility, we used RNAi-mediated knockdown of *C. elegans bcat-1* (branched-chain amino acid transferase 1), which can induce PD-like symptoms including degeneration of dopaminergic neurons and motility dysfunction in *C. elegans* (Yao et al., 2018, Nat Biotechnol). Indeed, we found that *Δhns E. coli* could rescue the degeneration of dopaminergic neurons and motility dysfunction induced by knockdown of *bcat-1* in *C. elegans*.
Conclusions: Our findings showed that modification of genes in *E. coli can* recover neurodegenerative phenotypes in the host, *C. elegans.* Therefore, the cure strategies aiming at genes of gut microbes can provide new insights for PD treatment.

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P0966 / #2729

POSTERS: C07.E. ANIMAL MODELS: OTHER

INDUCTION OF ALPHA-SYNUCLEIN PATHOLOGY IN THE RODENT BRAIN: PHENOTYPE IN THREE MODELS OF PARKINSON'S DISEASE

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Aims: Induction of α-synuclein pathology in the adult rodent brain is used to model Parkinson's disease in pre-clinical drug discovery. Our aim with this work was to compare the behavioral and biomarker phenotype in three rodent models in which α-synuclein pathology has been induced with viral vector-mediated overexpression or with pre-formed fibrils (PFF).
Methods: Alpha-synuclein pathology was induced by either AAV1/2-mediated overexpression of A53T α-synuclein in the rat and mouse substantia nigra, or by delivery of α-synuclein PFF into the mouse striatum. Analysis of the animals' fine motor and kinematic gait was performed during in-life using MotoRater (TSE Systems) together with an in-house developed analysis software. The main readouts consisted of endpoint evaluation of α-synuclein pathology and neurodegeneration in the nigrostriatal dopaminergic tract using immunohistochemistry and neurochemical assessment of striatal dopamine and dopamine metabolites.
Results: AAV1/2-mediated overexpression of A53T α-synuclein in both the rat and mouse substantia nigra lead to a mild but significant change in the animals' fine motor and kinematic gait performance. The change in motor performance was accompanied by a decrease in tissue dopamine. Although injection of PFFs lead to an increase in phosphorylated S129-α-synuclein throughout the mouse brain, including aggregation in the mouse substantia nigra, we were not able to detect a model phenotype in the fine motor and kinematic gait analysis.
Conclusions: The models displayed Parkinson's-like pathology, including phosphorylated α-synuclein and decreased levels of dopamine and dopamine metabolites in the striatum. Changes in the fine motor and kinematic gait of the animals were mild. When choosing the α-synuclein model for pre-clinical research projects, the mode-of-action of the therapy as well as the treatment window in the targeted readout(s) need to be taken into consideration.

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POSTERS: C07.E. ANIMAL MODELS: OTHER

EARLY SCREENING OF 6-OHDA STRIATAL LESIONS IN A RAT MODEL OF PARKINSON'S DISEASE USING MRI AND PET IMAGING

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Aims: Unilateral 6-hydroxydopamine (6-OHDA) lesioning of the nigrostriatal pathway is a widely used rodent model for Parkinson's disease (PD). 6-OHDA-induced destruction of dopaminergic cells results in robust and permanent changes in behavioral and biomarker readouts. However, for striatal 6-OHDA injections the lesion size and its location have a major effect on the dopaminergic cell loss and can drive variability between the animals resulting in a need for larger group sizes for efficacy testing.
Methods: In this study, male CD rats underwent 6-OHDA-induced unilateral striatal injury. One day post-lesion, the lesion volume and location were assessed with T_2-weighted MRI. Amphetamine-induced rotations and forelimb use asymmetry were evaluated to detect functional deficits at 2 days, 2 weeks, and 4 weeks after the lesion. Dopaminergic dysfunction was assessed with PET imaging using 3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine (^{18}F-FDOPA) at 3 weeks after the 6-OHDA lesion. Finally, at 5 weeks the animals underwent in vivo ^{1}H-magnetic resonance spectroscopy (MRS), followed by sampling for assessment of striatal dopamine with HPLC and nigral tyrosine hydroxylase (TH) -reactive cell counts with immunohistochemistry.
Results: As expected, a unilateral injection of 6-OHDA in rats lead to motor asymmetry and a robust decrease in striatal dopamine and TH-reactive cells in the substantia nigra. Early screening of the 6-OHDA lesion with MRI could be efficiently applied to distinguish successful and incomplete 6-OHDA lesions, verified with the other assays.
Conclusions: Based on our results, MRI scanning one day after the 6-OHDA injection can efficiently be used to screen for successful lesion development, with results correlating with the other traditional readouts. Early screening with MRI can thereby reduce the model variability and improve the data quality for efficacy testing in preclinical PD projects.

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P0968 / #1148

POSTERS: C07.E. ANIMAL MODELS: OTHER

NON-INVASIVE SYSTEMIC VIRAL DELIVERY OF HUMAN ALPHA-SYNUCLEIN MIMICS SELECTIVE AND PROGRESSIVE NEURONAL PATHOLOGY IN PARKINSON'S DISEASE

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Aims: Alpha-synuclein (α-syn) aggregation into proteinaceous intraneuronal inclusions, known as Lewy bodies, is one of the major neuropathological hallmarks of Parkinson's disease (PD) and related synucleinopathies. However, the exact role of α-syn inclusions in the pathogenesis of this diseases remains elusive. Currently, none of transgenic models exhibited significant early dopaminergic neuronal loss. An alternative approach using Adeno-associated viral (AAV) allowed for a local α-syn accumulation and a significant dopaminergic neuronal loss. However, the viral delivery requires specific equipment and technical training. New applications based on the use of a new generation of viruses have been reported to have a fast and less invasive method for protein expression in the brain. These applications use intravenous injections rather than stereotaxic AAV injections
Methods: We describe here a novel approach for a non-invasive systemic delivery of viral particles overexpressing human α-syn allowing for a large-scale overexpression in mouse brain. We cloned plasmid for human α-syn expression under ubiquitous CAG promotor to produce the recombinant AAV2 with specific capsid called "PHP.eB". Mice received retro-orbital injection of AAV-PHP.eB-CAG-human_α-syn. Examination of human α-syn overexpression in mouse brains was performed 2 weeks post-injection. Subsequently, α-syn overexpression impact was also assessed using behavioral tasks several months post-injection.
Results: Using this model, we report that the widespread human α-syn overexpression in mouse brains induced the selective dopaminergic neurons degeneration in the substantia nigra. This neuronal degeneration was associated with a progressive manifestation of PD-like motor impairment, without affecting cognitive performance.
Conclusions: Our data demonstrate that this non-invasive novel in vivo delivery of α-syn represents a viable strategy for modeling PD to study the selective vulnerability of the nigral dopaminergic neurons that can essentially help to decorticate the role of α-syn in PD pathogenesis.

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P0969 / #2269

POSTERS: C07.E. ANIMAL MODELS: OTHER

GBA P.E326K PARKINSON'S DISEASE AND DEMENTIA WITH LEWY BODY MOUSE MODEL

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Aims: Biallelic mutations in the Glucocerebrosidase (*GBA*) gene cause Gaucher's disease (GD), one of the most common lysosomal storage disorders. We and others have shown that specific mutations in *GBA*, in the heterozygous state, are a risk factor for Parkinson's disease (PD) and Dementia with Lewy bodies (DLB). Among the *GBA* variants associated with PD and DLB, the p.E326K allele is the most common risk factor. To further our understanding of the mechanistic link between this specific *GBA* variant and the development of PD and DLB, we have developed a *Gba* p.E326K mouse model.
Methods: A point mutation knockin mouse model, *Gba* p.E326K, was generated by genome editing using CRISPR-Cas9 technology. Behavioral phenotyping was performed at two time points. Motor function was assessed using the balance beam and catwalk test. Cognitive function was assessed using the novel object recognition (NOR) test. The Nanostring nCounter mouse neuropathology panel was used to perform a comprehensive assessment of neurodegenerative pathways and processes in different brain regions in the *Gba* p.E326K mouse model.
Results: Motor deficits were observed in the *Gba* p.E326K mouse model, with significant differences in a number of the parameters in the beam walk and catwalk tests, including catwalk BOS and beam walk velocity, as observed for other PD mouse models. Significant differences in learning and memory using the NOR test were not observed. Neuropathology data will be presented.
Conclusions: Current therapies being developed for *GBA* associated PD include glucosylceramide synthase inhibitors and the molecular chaperone, ambroxol hydrochloride. Development of a mouse model for the most common *GBA* variant associated with PD, the *GBA* p.E326K variant, and determining the disease mechanism will allow a personalized medicine approach and may open up new avenues for therapeutic development

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P0970 / #1286

POSTERS: C07.E. ANIMAL MODELS: OTHER

MOTOR AND NON-MOTOR SYMPTOMS IN AN ANIMAL MODEL OF PARKINSON'S DISEASE.

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Aims: To investigate the critical period of onset of non-motor symptoms during disease progression of PD using chronic MPTP mouse model.
Methods: We subcutaneously (s.c.) injected C57BL6 mice (3-4 months old) at a dose of 10 mg/kg body weight of MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride), daily for 60 days. Saline was injected (s.c.) as vehicle control group. MPTP induced behavioral alterations were assessed after 15 days and 45 days for non-motor and motor behavior, respectively. Using immunohistochemistry and western blot analysis methods, we assessed the loss of TH+ve (tyrosine hydroxylase) neurons in SNpc region, as well as α-Syn aggregation and phospho-S129 α-Syn inclusions in TH+ve neurons in SNpc region.
Results: We observed depressive and anxiety-like behavior during early time point, followed by motor symptoms at later stage after administration of low dose of MPTP. There was loss of TH+ve neurons in SNpc region, as well as α-Syn aggregation and phospho-S129 α-Syn inclusions in TH+ve neurons in SNpc region.
Conclusions: We have developed an animal model of PD with sub-chronic MPTP dosing, which exhibits progressive onset of non-motor and motor symptoms at early and later time course of MPTP injections, respectively. This model recapitulates the clinical observations during disease progression in PD patients. Further, the pathological analysis of brains from this animal model depicts key features reported in PD brains such as loss of dopamine producing neurons in SNpc and α-Syn protein aggregation.

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P0971 / #1328

POSTERS: C07.E. ANIMAL MODELS: OTHER

ACUTE AND CHRONIC ER-STRESS-INDUCED ANIMAL MODELS OF PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a neurodegenerative disease characterized by loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to impairments of motor and cognitive functions. Although the etiology is still not known, α-synuclein aggregation plays an important role in PD pathogenesis, which may be associated to some pathological processes such as endoplasmic reticulum (ER) stress. In the present study, we characterize and compare the behavioral hallmarks of ER stress-induced mouse models using different treatment protocols for the well-known ER stressor rotenone.
Methods: For the generation of a chronic model, 2 months old C57BL/6JRj mice are daily treated orally with rotenone (30 mg/kg) or vehicle (4 % CMC and 1.25 % chloroform) and subjected to the nesting behavior test, wire hanging test, and beam walk. For the generation of an acute model, 2 months old 57BL/6JRj mice are injected with rotenone at different concentrations directly into the striatum. All animals are subjected to the weekly cylinder test, D-amphetamine-induced rotation test and beam walk test for 4 weeks.
Results: Preliminary results suggest that after 2 months of daily rotenone treatment, mice show a reduced nesting behavior but no motor deficits. For the acute model, rotenone injection directly into the right striatum caused increased ipsilateral rotations when compared to control injected mice.
Conclusions: The present study will allow to characterize and compare different ER stress-induced PD mouse models, which will be valuable to test new PD drugs that are directed against increased ER stress.

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P0972 / #249

POSTERS: C07.E. ANIMAL MODELS: OTHER

ANALGESIC EFFECT OF SAFINAMIDE MESYLATE, TYPE-B MONOAMINE OXIDASE INHIBITOR AND SODIUM CHANNEL BLOCKER, ON THE CHRONIC NEUROPATHIC PAIN IN RATS

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Aims: Safinamide is a selective and reversible type-B monoamine oxidase inhibitor with voltage-gated sodium channel inhibitory effect. Safinamide is an anti-Parkinsonian drug with possible analgesic effect due to the dual action. We investigated the efficacy of safinamide for neuropathic pain in rats.
Methods: The left sciatic nerve was ligated to create the chronic constriction injury (CCI) rat model at Day 0. Pain assessments were conducted at Day 14 and 21. Stimulus-evoked pain was evaluated with pain threshold in von Frey test, being considered as mechanical allodynia, and non-stimulus evoked pain was assessed by weight bearing ratio of left to right hind paw in static weight bearing test. Areas under the curve (0-4hr post-dosing) of both measurements were calculated. Safinamide (15 and 45 mg/kg) were orally administered once a day for 8 days from Day 14 to 21. Safinamide (30 and 70 mg/kg) were administered once a day at Day 14.
Results: Stimulus-evoked pain and non-stimulus evoked pain could be detected in CCI rats. The stimulus-evoked pain was dose-dependently reversed by safinamide (30-70 mg/kg, p.o.) at Day 14. The non-stimulus evoked pain was also significantly reversed by safinamide (15-70 mg/kg, p.o.) at Day 14. Repeated administration of safinamide (15 and 45 mg/kg, p.o.) significantly improved both of pain at Day 21.
Conclusions: Safinamide improved neuropathic pain caused by CCI in rats. Since MAO-B inhibition is constant at the dose of this experiment, the dose-dependent nature of safinamide's effects suggests that its analgesic effects might be mediated by voltage-gated sodium channel inhibition.

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P0973 / #2187

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

EXTRAPYRAMIDAL SIGNS ARE LINKED TO TDP-43 BURDEN IN THE SUBSTANTIA NIGRA OF FTLD-TDP BRAIN DONORS

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Aims: Extrapyramidal symptoms (EPS) have been linked to neuronal degeneration in the substantia nigra (SN) in Parkinson's Disease. EPS are also a common cause of disability in frontotemporal dementia (FTD). In most FTD post-mortem studies, EPS have been linked to frontotemporal lobar degeneration with tau pathology (FTLD-tau), although they can also occur in FTLD with TDP-43 pathology (FTLD-TDP). The distribution of TDP-43 pathology in FTLD-TDP patients with EPS is largely unexplored. The aims of this study are to characterize EPS in a cohort of FTLD-TDP brain donors and to investigate the relationship between the TDP-43 burden in the SN and the presence of EPS.
Methods: From our cohort of FTLD-TDP patients (n=53), we included 13 donors who presented with EPS (FTLD-EPS+). and nine age-sex matched donors without EPS (FTLD-EPS-) for whom the SN was available. In these donors, the TDP-43 burden and the neuronal density in the SN were assessed with ImageJ and Qupath software. The results were compared between the two groups using T-test.
Results: We found that the TDP-43 burden in the SN was higher in FTLD-EPS+ (mean 3,43%, SD±2,7) compared to FTLD-EPS- (mean 1,21%, SD±0,67) (p=0,04). No significant difference in nigral neuronal density was found between the groups (p=0,09).
Conclusions: 17% of FTLD-TDP patients developed EPS, which present as symmetric akinetic-rigid parkinsonism or CBS. Given the absence of a significant nigral neuronal cell loss, TDP-43 induced neuronal dysfunction could be sufficient to cause EPS.

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P0974 / #678

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ALS-FTD-LINKED KNOCK-IN MUTATIONS IN TDP-43 RESULT IN MICROGLIAL ACTIVATION IN A HUMAN IPSC-DERIVED MODEL

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Aims: ALS and FTD exist on a clinicopathological and genetic spectrum (ALS-FTD) characterised by disturbances in TDP-43, a conserved DNA/RNA-binding protein. Our identification of TDP-43 mutations in ALS indicated a mechanistic role for TDP-43 in neurodegeneration. To elucidate genuine pathogenic roles of TDP-43 in ALS-FTD we created a TDP-43^{Q331K} knock-in mouse, which harbours only a single human-equivalent point mutation in the endogenous mouse *Tardbp* gene, thereby replicating the human genetic state as closely as possible. We showed this mouse displays ALS-FTD like phenotypes due to perturbed TDP-43 autoregulation. We also found that TDP-43^{Q331K} mouse brains display signatures of microglial activation at early stages of disease. Microglial TDP-43 has previously been found to regulate phagocytosis and synaptic pruning. We therefore aimed to study the effect of disease-linked mutations in TDP-43 on microglial function and activation.
Methods: Using CRISPR-Cas9 we generated human induced pluripotent stem cell (hiPSC) lines having homozygous mutations in TDP-43 (Q331K and M337V). We derived microglia-like cells from wild-type and mutant lines using published protocols. Using biochemical assays and high-content microscopy, we studied the expression of markers, cellular motility, and phagocytosis in wild-type and TDP-43 mutant microglia.
Results: TDP-43 mutant microglia show impaired TDP-43 autoregulation, as previously observed in the TDP-43^{Q331K} mouse model. Mutant microglia display an activated status compared to wild-type microglia, having larger cell bodies and increased lysosome content. They also show reduced motility and increased uptake of synthetic amyloid-β oligomers and synaptosomes. At the transcriptomic level, TDP-43 mutant microglia show reduction of the CX3CR1 fractalkine receptor, essential for neuron-microglia signalling.
Conclusions: Taken together, ALS-FTD-related mutations in TDP-43 result in signatures of microglial activation and altered function in a hiPSC model. Microglia may therefore be crucial in development of TDP-43-linked neurodegeneration.

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P0975 / #2235

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

SUPPRESSION OF A NOVEL RAN TRANSLATION REGULATOR REDUCES POLY-GA DPR EXPRESSION IN A CELLULAR MODEL OF C9ORF72 FTLD/ALS.

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Aims: A hexanucleotide expansion mutation in the first intron of *C9orf72* gene is the most frequent genetic cause of both frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). This repeat sequence is transcribed and translated into dipeptide repeat (DPR) proteins via repeat-associated non-AUG (RAN) translation. DPR accumulates in the brain of *C9orf72* FTLD/ALS patients, and DPR is thought to be neurotoxic. Therefore, downregulation of DPR expression level via inhibition of RAN translation may have therapeutic potential. In this study, we tested the effect of a potential regulator of *C9orf72* RAN translation, herein referred to as TR1.
Methods: We used HeLa cells expressing 80 repeats of GGGGCC as a disease model.
Results: Knockdown of TR1 decreased the expression level of poly-GA DPR. Conversely, overexpression of TR1 increased poly-GA expression level without increasing of the repeat RNA. Moreover, inactivation of TR1 by site-directed mutagenesis reduced poly-GA expression. Puromycin incorporation assay revealed that TR1 preferentially upregulates poly-GA DPR through RAN translation over global translation labeled by puromycin.
Conclusions: TR1 reduction or inhibition of its activity reduces poly-GA expression level. Thus, TR1 could be a therapeutic target for *C9orf72* FTLD/ALS.

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P0976 / #917

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

EFFECTS OF C9ORF72 HEXANUCLEOTIDE REPEAT EXPANSION ON THE FUNCTION OF FTD PATIENT-DERIVED IPSC-MICROGLIA

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Aims: The most common genetic cause underlying frontotemporal dementia (FTD) is the *C9orf72* hexanucleotide repeat expansion (HRE). Activation of microglia in FTD patient brains has been observed, but the exact mechanisms of how the *C9orf72* HRE affects human microglia function is not currently known. Interestingly, *C9orf72* is highly expressed in microglia and, thus, the effects of the *C9orf72* HRE on microglia function in FTD should be examined.
Methods: Human induced pluripotent stem cell (iPSC)-derived microglia from healthy controls, sporadic FTD patients or FTD patients carrying the *C9orf72* HRE were used to assess potential functional changes in microglia. Global RNA-sequencing was conducted to reveal gene expression changes in all the iPSC-microglia groups. In the functional studies, lipopolysaccharide (LPS) treatment was used to assess the effects of a pro-inflammatory stimulus on iPSC-microglia. Lipid droplet staining, immunofluorescence imaging and Western blotting were used to study intracellular lipid droplet formation and the levels of endosomal-lysosomal proteins. In addition, number and morphology of endo-lysosomal vesicles were examined. Seahorse XF Cell Mito Stress Test was used to study energy metabolism of the iPSC-microglia.
Results: RNA-sequencing followed by targeted gene expression and pathway analyses highlighted alterations in pathways related to phagocytosis, inflammatory response, energy metabolism, and endosomal-lysosomal pathway in FTD patient-derived iPSC-microglia. Preliminary data from lipid droplet staining suggest a decreased response of the *C9orf72* HRE-carrying microglia to the LPS treatment. Furthermore, measurement of mitochondrial ATP production suggested possible defects in both C9orf72 HRE-carrying and sporadic FTD patient-derived iPSC-microglia as compared to healthy controls.
Conclusions: The current early results point towards possible functional changes in microglia carrying the FTD-associated *C9orf72* HRE.

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P0977 / #2148

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

HNRNP K WHITE MATTER PATHOLOGY IN NEURODEGENERATIVE DISEASES

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Aims: Background: Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a class of RNA binding proteins that play important roles in the regulation of mRNA processing and metabolism. HnRNP K is the most widely distributed and expressed hnRNP in the brain, which plays a key role in transcriptional regulation. In a recent study by our lab, hnRNP K cytoplasmic mislocalisation was found to be associated with frontotemporal lobar degeneration (FTLD), leading to aberrant downstream splicing events. We also observed intense hnRNP K staining in the white matter of cases with neuronal cytoplasmic mislocalisation. **Objectives:** We extended the study of hnRNP K pathological deposits in white matter in multiple brain regions to other neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD).
Methods: Brain samples from different neurodegenerative disease cases (and healthy age-matched controls) were subjected to hnRNP K immunohistochemistry. The hnRNP K staining in white matter was analysed by QuPath and ImageJ quantification. The presence of hnRNP K within the white matter was compared between the different neurodegenerative diseases (AD, PD, FTLD) and control groups.
Results: suggested that higher hnRNP K staining intensity was observed in the white matter of neurodegenerative diseases. We have extended these findings further to additional pathological cases from brains with PD, AD and FTLD, compared to age-matched healthy controls.
Conclusions: Different types of neurodegenerative diseases may be associated with hnRNP K mislocalisation in a subset of cortical neurons, leading to alterations in downstream splicing events. The mislocalisation of hnRNP K from the nucleus to the cytoplasm and along axons in the white matter highlight that hnRNP K may have a broader role in different neurodegenerative processes.

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P0978 / #1996

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ARGININE-RICH DIPEPTIDE REPEAT PROTEINS INHIBIT THE ACTIVITY OF THE RNA EXOSOME COMPLEX AND PROMOTE THE ACCUMULATION OF C9ORF72 EXPANDED HEXANUCLEOTIDE REPEAT RNA

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Aims: A hexanucleotide repeat expansions in the C9orf72 gene cause frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Repeat RNA accumulates within RNA foci and is also translated into toxic dipeptide repeat proteins (DPR). The RNA exosome complex is a multimeric 3' exoribonuclease involved in degradation of cellular defective RNA during RNA quality control. We examined whether the expression of poly-(Gly-Arg: GR) or poly-(Pro-Arg: PR) DPRs affect the RNA degrading actiity of the RNA exosome complex.
Methods: A cellular model of C9orf72 repeat expansion was used. Codon optimized versions of poly-GR, poly-PR N-terminally fused with GFP or control GFP were expressed with or without C9orf72 GGGGCCx80 repeat expression plasmids. RNA expressions were quantified with RT-qPCR.
Results: Cells expressing toxic poly-GR or poly-PR proteins accumulate 3' extended small nucleolar RNA 48 and 68 precursors, which are physiological substrates of EXOSC10, an nucleolar-enriched catalytic component of the RNA exosome complex. Moreover, poly-GR and poly-PR expressions promote the accumulation of co-expressed C9orf72 GGGGCC repeat RNA. These results indicate that arginine-rich DPR proteins impair the intrinsic activity of the RNA exosome complex and thus promotes the accumulation of the repeat RNA.
Conclusions: Arginine-rich DPR-mediated impairment of the RNA exosome complex compromises repeat RNA metabolism and may thus exacerbate C9orf72-FTLD/ALS.

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P0979 / #667

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

LEGUMAIN (LGMN) - A POSSIBLE LINK BETWEEN PROGRANULIN (PGRN) DEFICIENCY AND FRONTOTEMPORAL DEMENTIA (FTD)

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Aims: Mutations in the granulin (*GRN*) gene are causative for a subtype of FTD with TDP-43-positive inclusions. *GRN* haploinsufficiency in patients results in cytoplasmic mislocalization, enhanced phosphorylation, proteolytic processing and aggregation of TDP-43. Recent findings from our laboratory indicate that PGRN deficiency in mouse models, iPSC derived human microglia and in FTD patients leads to enhanced activity of legumain (LGMN), a protease known to proteolytically process TDP-43 and other aggregating proteins in neurodegenerative diseases. To further study the role of LGMN in FTD *in vivo*, we either overexpressed or deplete LGMN in a PGRN deficient mouse.
Methods: To investigate a potential involvement of LGMN in FTD pathology, we generated *Grn-/-* & *Lgmn* +/- mice with the goal to rescue *Grn-/-* phenotypes. We also overexpressed hLGMN in brain of *Grn-/-* and *wt* mice using an adenoviral delivery system. Disease associated pathology was analysed with a focus on motor deficits, lysosomal activity and TDP-43 pathology.
Results: Initial results suggest that overexpression of LGMN leads to motor deficits and strongly affects the activity and expression levels of lysosomal proteases, especially cathepsin B, in a gene dose dependent manner. Moreover, LGMN overexpression caused increased processing of TDP-43 and accumulation of phosphorylated TDP-43. Mice overexpressing LGMN also exhibit a strong micro- and astrogliosis.
Conclusions: The increased activity of lysosomal proteases, processing and accumulation of TDP-43 as well as aberrant proliferation of microglia and astrocytes after LGMN overexpression indicate, that LGMN might be one of the main drivers of lysosomal dysfunction and TDP-43 pathology in FTD and could link PGRN deficiency to TDP-43 pathology.

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P0980 / #631

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

CELLULAR IN VITRO MODELS FOR STUDYING TDP43 PATHOLOGY IN ALS

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Aims: Amyotrophic lateral sclerosis (ALS) is a disease characterized by progressive motor neuron degeneration. One of the mechanisms of pathology on the cellular level in ALS is the deposition of TAR DNA-binding 43 protein (TDP-43) into cytoplasmic and intranuclear inclusions. *Objectives* To model the pathomechanisms of TDP-43 and other ALS-relevant genes, we developed multiple cell-based *in vitro* model systems and evaluated TDP-43 overexpression.

Methods: *Methods* As motor neurons (MN) are most affected in ALS, we established a scalable differentiation protocol to generate MN from human induced pluripotent stem cells (iPSCs) using neural induction and regional patterning conditions. Several fluorescently tagged TDP-43 genetic constructs, in wild type as well as in a mutant version were designed and evaluated in MNs alongside immortalized cell lines.
Results: *Results* Our differentiation protocol demonstrated that the motor neuron progenitors (MNPs) generated can be expanded and cryopreserved, allowing a faster generation of neurons. Furthermore, mRNA analysis demonstrated that neurons differentiated from MNPs derived from multiple different iPSC donor lines expressed comparable levels of MN markers. Prolonged overexpression of TDP-43 proved to be toxic in our cell models, with varying intensity. Interestingly, prolonged overexpression of TDP-43 constructs was better tolerated in MN than in cell lines. To control overexpression toxicity, inducible expression strategies were evaluated in the iPSC – derived models and cell line-based models. These resulting stable cell lines and inducible overexpression strategies are currently being optimized as a possible ALS disease model.
Conclusions: *Conclusion* Collectively, our observations suggest that these stable cell lines could serve as an ALS disease model.

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P0981 / #1130

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

IMPLICATIONS OF TAR DNA-BINDING PROTEIN 43 IN ALZHEIMER'S DISEASE-RELATED BLOOD-BRAIN BARRIER DYSFUNCTION

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Aims: The inclusions of phosphorylated TAR DNA-binding protein 43 (p-TDP-43) have been found in hippocampi of 57% of Alzheimer's disease (AD) patients, with disease progression being increased in these individuals. The inclusions are foremost found in neurons, but TDP-43 grains have also been found in the end-feet of blood-brain barrier (BBB)-forming astrocytes. Moreover, overexpression of TDP-43 has been shown to increase BBB permeability, a finding interesting from a perspective that BBB dysfunction affects the clearance of amyloid beta (Aβ). In the current study, we further explore the link between p-TDP-43 and BBB dysfunction in AD.
Methods: The localization of p-TDP-43 in brain sections of AD patients and APP-transgenic mice of increasing ages were analyzed using immunohistochemistry. The effect of oligomeric Aβ42 and islet amyloid polypeptide (IAPP) on the cellular localization of p-TDP-43 and aquaporin 4 (AQP4) (which is crucial for Aβ clearance) in cultured astrocytes were analyzed using immunocytochemistry. The p-TDP-43 levels in lysates of stimulated astrocytes were analyzed using ELISA.
Results: Grains of p-TDP-43 were associated with perivascular astrocytic end-feet in hippocampi of human AD and APP transgenic mice brain. The presence of p-TDP-43 grains increased with the progression of Aβ plaque formation in mice. Furthermore, Aβ42 and IAPP induced TDP-43 mislocation from the nucleus to the cytosol and reduced the presence of AQP4 in the membranes of cultured astrocytes. The Aβ increased (not significantly), while IAPP reduced, the levels of p-TDP-43 in cultured astrocytes.
Conclusions: Our results suggest that AD pathology is associated with p-TDP-43 inclusions in astrocytic end-feet and that these inclusions are a result of amyloid peptide-induced TDP-43 mislocalization and phosphorylation leading to a loss of Aβ clearing by AQP4 at astrocytic membranes.

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P0982 / #2099

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ENHANCED LEGUMAIN ACTIVITY IN PROGRANULIN-DEFICIENT HUMAN IPSC-DERIVED MICROGLIA IS LINKED TO PATHOLOGICAL TDP-43 PROCESSING IN HUMAN IPSC-DERIVED NEURONS

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Aims: One of the main genetic risk factors for TDP-43-associated frontotemporal lobar degeneration (FTLD-TDP), where TDP-43 inclusions are found mostly in neurons, are loss-of-function mutations in *GRN*. Progranulin (PGRN) is a secreted growth factor-like protein that is primarily expressed by microglia in the brain. It is transported to lysosomes and then processed into granulin peptides. Loss of PGRN results in lysosomal dysfunction and hyperactivation in microglia. The link between PGRN loss-of-function, lysosomal dysfunction, and TDP-43 pathology is unknown. We found that PGRN slows maturation of the lysosomal protease legumain (LGMN), which is involved in pathological processing of TDP-43.
Methods: We generated a GRN knockout (KO) human induced pluripotent stem cell line (iPSC). The WT and GRN KO iPSCs were further differentiated into neurons and microglia using standard procedures.
Results: In monocultured WT and GRN KO neurons, we detect low levels of the inactive LGMN proform but observed high levels of LGMN expression and activity in monocultured microglia, which is increased in GRN KO microglia. When WT neurons are co-cultured with WT or GRN KO microglia, an increase in LGMN expression and activity is observed in comparison to monocultures, with the most increase seen in the GRN KO microglia co-culture. The co-culture of GRN KO microglia and WT neurons also shows a significant increase in pathological TDP-43 processing. The co-culture transduced with AAV-CSTF inhibited LGMN maturation and activity selectively in the neurons. The treatment successfully decreased legumain maturation and activity, as well as TDP-43 processing back to WT co-culture levels, indicating that pathological processing of TDP-43 by LGMN occurs predominantly in neurons.
Conclusions: These findings suggest a cross-talk between microglia and neurons, which leads to proteolytically active neuronal LGMN, which mediates pathological processing of TDP-43.

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P0983 / #2104

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

PROXIMITY LABELLING PROTEOMICS IDENTIFIED A NOVEL MOLECULE IN THE C9ORF72 REPEAT RNA DEGRADATION PATHWAY IN FTLD/ALS.

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Aims: Neurodegeneration in *C9orf72*-frontotemporal lobar degeneration (FTLD)/amyotrophic lateral sclerosis (ALS) is assumed to be caused by the toxicities of transcribed G_4C_2 repeat RNA itself and/or its repeat-associated non-AUG (RAN) translation products, dipeptide repeat protein (DPR). We previously reported that hnRNPA3 suppressed the accumulation of repeat RNA and DPR through binding to G_4C_2 repeat RNA. It is likely that hnRNPA3 promotes the degradation of the repeat RNA; however, hnRNPA3 itself is not structurally expected to have RNA degrading activity. Here, we aimed to identify repeat RNA degradation-associated proteins which interact with hnRNPA3.
Methods: In the presence or absence of G_4C_2 repeat RNA, we performed APEX2 proximity labelling to biotinylate and purify the proximal interactors of hnRNPA3-APEX2 in HeLa cells. Biotinylated proteins were then identified by LC-MS/MS. To test their effects on repeat RNA accumulation, siRNA-mediated knockdown screenings were performed. Further validation was conducted on endogenous *C9orf72* repeat RNA using fibroblasts derived from *C9orf72* expansion mutation carriers.
Results: As a result of APEX2 proteomics including LC-MS/MS and Gene Ontology analysis, we identified nine RNA-binding proteins (GO: 0003723) as candidate proximal interactors which might involve in the hnRNPA3-mediated repeat RNA degradation pathway. The secondary screening identified siRNA-mediated reduction of one of the candidate RNA-binding proteins (RDF1, tentative name), as well as hnRNPA3, increased the accumulation of repeat RNA in HeLa cells. In addition, *In Situ* Hybridization revealed that the siRNA-mediated reduction of RDF1 also promoted the accumulation of repeat RNA foci in repeat expression HeLa cells and in carrier-derived fibroblasts.
Conclusions: With proximity labelling proteomics, we identified a novel molecule which might play a role in the hnRNPA3-mediated degradation pathway of the toxic *C9orf72* repeat RNA. Our results have the potential to develop novel therapies for *C9orf72*-FTLD/ALS.

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P0985 / #2681

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

THE MONOCLONAL TDP-43 ANTIBODY AGAINST THE OLIGOMERIC TDP-43 MITIGATES NEUROPATHOLOGY

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Aims: The cytoplasmic mislocalization and aggregation of the TAR DNA-binding protein 43 (TDP-43) are the histopathological hallmark of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTLD). Studies show the TDP-43 oligomers antibody revealed that TDP-43 oligomers presented in the forebrain of the FTLD transgenic mice as well as FTLD-TDP patients. Interestingly, the ALS-linked TDP-43 mutant (TDP-43^{Q331K}) mice model shows the impairment of motor performance as early as 3 months without the formation of cytoplasmic inclusion nor loss of TDP-43. Those studies emerge antibody therapeutic approaches to prevent the neuropathology in the transgenic mice model. Therefore, we study the target and therapeutic efficacy of TDP-43 oligomer antibody in the transgenic mice model.
Methods: To study the efficacy of the antibody, we delivered TDP-43 oligomer antibody on the TDP-43^{Q331K} mice by i.v. injection weekly for 1mg/kg and IgG2a injection was served as an antibody control. The animal motor performance was evaluated by rotarod for a month after injection.
Results: Interestingly, we observed TDP-43 oligomers in the spinal neurons. We also demonstrated TDP-43 oligomer antibody injection ameliorate the motor performance deficits and mitigate the reduction of spinal neurons. We found that antibody treatment increases the astrogliosis with A2 neuroprotective phenotypes.
Conclusions: These results suggest astrocytes may play a role on the antibody treatment.

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P0986 / #1985

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

TRODUSQUEMINE: A PROMISING THERAPEUTIC MOLECULE FOR TDP-43 PROTEINOPATHIES

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Aims: A number of neurodegenerative conditions, such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD), are associated with a common histopathology within neurons of the central nervous system, consisting in the deposition of cytosolic inclusions of TAR DNA-binding protein 43 (TDP-43). In the last years, the natural aminosterol trodusquemine showed significant protective effects against the pathological aggregation and toxicity of α-synuclein and amyloid β peptide. Our studies with trodusquemine were aimed to probe its ability to modulate the liquid-liquid phase separation (LLPS) and aggregation of human full-length TDP-43 *in vitro* and in cultured cells, as well as to prevent its cytotoxicity toward motor neurons.
Methods: We evaluated the effect of trodusquemine in modulating TDP-43 phase separation through the Fluorescence Recovery After Photobleaching (FRAP) technique; we also assessed its ability to prevent TDP-43 neurotoxicity both in neuronal cells and in a *C. elegans* model, taking advantage of the high-resolution power of Stimulated Emission Depletion (STED) microscopy.
Results: We showed that trodusquemine can slightly modulate TDP-43 LLPS and aggregation both *in vitro* and in cultured cells. We also revealed that trodusquemine prevents the mislocalisation of overexpressed human wild-type full-length TDP-43 in motor neurons; in particular, this natural aminosterol decreases the cytoplasmic TDP-43 accumulation promoting its re-localization in the nucleus, and rescues TDP-43 neurotoxicity. Consistently, we observed a significant decrease of inclusion formation and a very significantly improved motility in TDP-1 worms exposed to trodusquemine, with respect to worms in the absence of the aminosterol.
Conclusions: This study provides evidence that trodusquemine can prevent the pathological effects induced by TPD-43, putting forwards its potential as a new therapeutic candidate in TDP-43 proteinopathies.

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P0987 / #2393

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

FUNCTIONAL PHENOTYPIC SCREENING MODEL FOR FRONTOTEMPORAL DEMENTIA WITH HUMAN IPSC-DERIVED GLUTAMATERGIC NEURONS WITH A MAPT MUTATION

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Aims: Frontotemporal Dementia (FTD) is a dementia that shares mechanisms with other neurodegenerative diseases. Amyotrophic lateral sclerosis, where the C9orf72 mutation is a known familial ALS mutation, is also accompanied by FTD. FTD is a severe disease with high relevance that receives less public attention than Alzheimer's disease. Its disease mechanisms are not fully understood, therefore, phenotypic disease models are desirable for the development of new therapies. The disease occurs in familial and sporadic forms, fFTD and sFTD. Known fFTD forms have mutations in the MAPT gene among others.
Methods: Human-induced pluripotent stem cells (iPSC) with MAPT mutations can be differentiated toward glutamatergic neurons. They are canonical disease models that reflect phenotypic disease symptoms. In our hands, iPSC-derived glutamatergic neurons with the MAPT mutation P301S/P301S could be cultivated on microelectrode array plates for more than 30 days. No difference in survivability between diseased and wild-type cells was observed.
Results: First electrophysiological activity can be observed after 7 days and lasts for more than 5 weeks. After 14 days in vitro, a reliable hyperexcitation of the disease glutamatergic neurons compared to the wild-type genetically matched control neurons can be observed. Hyperexcitation is consistent with the clinical experience of this disease. Riluzole at 2 µM applied on day 14 in vitro with medium change caused a reliable reduction of hyperexcitation after 14 days in vitro.
Conclusions: The assays could serve as a new screening method for potential FTD drugs.

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P0988 / #2533

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

APPLICATION POINTS OF COMPLEX NEUROMUSCULAR ULTRASOUND IN ALS

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Aims: Highlighting the clinical and translational benefits of neuromuscular ultrasound (NMUS) for assessing the condition of patients with ALS.
Methods: A review of recommendations from literature sources focused on indications for NMUS based on their significance for the diagnosis and management of patients.
Results: a. Detection of fasciculations as a specific differential diagnostic feature. Fasciculations are part of the diagnostic criteria of ALS (according to Awaji criteria), are a biomarker of the disorder. Ultrasound is a dynamic method and therefore is able to visualize normal muscle movements and a continuous pattern of fasciculations.
The number of fasciculations occurring in 60 seconds can also provide important prognostic information about the rate of disease progression. The pattern of fasciculations prevailing in the upper extremities and proximal muscle groups is more specific for the diagnosis of ALS than multifocal motor neuropathy (MMN).
b.Evaluation of the index of bifurcation of the hand using the ratio of the echointensivity of the tenor and hypotenor muscles. The difference in atrophy between the medial and lateral arm muscles is most pronounced in ALS.
c. Estimation of the diameter and cross-sectional area of motor nerves.
In differentiation from MMN, in which nerve enlargement is more common. Patients with ALS have a smaller peripheral nerve size.
d. Diaphragmatic monitoring. The relationship between the dynamic thickness of the diaphragm and respiratory function (violation of the vital capacity of the lungs) in patients with ALS has a positive correlation. It indicates atrophy and impaired contractility of the diaphragm in patients with hypoventilation. Ultrasound of the diaphragm can be performed at the patient's bedside and in patients sitting in a wheelchair.
Conclusions: The preparation of doctors require additional NMUS training to work with similar patients.

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P0989 / #2686

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

ASSOCIATION OF NOVEL CSF BIOMARKER CANDIDATES WITH CORTICAL THICKNESS IN GENETIC FRONTOTEMPORAL DEMENTIA

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Aims: We have previously described a set of 14 proteins that could distinguish symptomatic mutation carriers from controls (Bergström et al. Mol Neurodegener. 2021; 16(1):79). The aim of this study was to explore the relationship between the previously identified CSF biomarker candidates and cortical thickness in presymptomatic and symptomatic mutation carriers.
Methods: We have analysed T1 MRI scans alongside concurrent CSF samples from 202 individuals from the GENFI cohort, including symptomatic mutation carriers, presymptomatic mutation carriers and non-carrier controls. Cortical thickness was estimated with FreeSurfer 7.1.1, and CSF protein levels were measured via a multiplexed antibody-based suspension bead array. The correlations between regional cortical thickness and protein levels were calculated via linear regression.
Results: Altered levels of NEFM, AQP4, APOA1, PTPRN2, CTSS, SERPINA3, C4, AMPH, SPP1 and CD14 were all correlated with increased atrophy of at least one cortical region. They also showed a significant negative correlation with mean cortical thickness. NPTX2, VGF, APOE4 and SEC63 did not show any significant correlations. We also tested if regional cortical thickness was influenced by any interactions between protein levels and which gene was mutated. Mutations in *GRN* showed significant interactions with AQP4, PTPRN2 and CD14 while *C9orf72* expansions interacted with CTSS, SERPINA3 and C4 protein levels.
Conclusions: To conclude, the proposed fluid biomarker candidates continue to show promise and continued studies will further elucidate their relationship to cortical atrophy in genetic FTD.

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P0990 / #2350

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

ACCURACY OF DIAGNOSTIC CRITERIA FOR PRODROMAL FRONTOTEMPORAL DEMENTIA

Alberto Benussi[1], Mario Grassi[2], Silvana Archetti[3], Roberto Gasparotti[4], Antonella Alberici[5], Arabella Bouzigues[6], Lucy Russell[6], David Cash[7], Emily Todd[6], Rhian Convery[6], Imogen Swift[6], Aitana Sogorb Esteve[8], Carolin Heller[6], John Van Swieten[9], Lize Jiskoot[9], Harro Seelaar[9], Raquel Sanchez-Valle[10], Fermin Moreno[11], Robert Laforce[12], Caroline Graff[13], Matthis Synofzik[14], Daniela Galimberti[15], James Rowe[16], Mario Masellis[17], Carmela Tartaglia[18], Elizabeth Finger[19], Rik Vandenberghe[20], Alexandre De Mendonça[21], Fabrizio Tagliavini[22], Chris Butler[23], Isabel Santana[24], Alexander Gerhard[25], Isabelle Le Ber[26], Florence Pasquier[27], Simon Ducharme[28], Johannes Levin[29], Adrian Danek[29], Sandro Sorbi[30], Markus Otto[31], Alessandro Padovani[1], Jonathan Rohrer[6], Barbara Borroni[32]
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Aims: The Genetic Frontotemporal Initiative (GENFI) Staging Group has recently proposed clinical criteria for the diagnosis of prodromal FTD, termed mild cognitive and/or behavioral and/or motor impairment (MCBMI). The objective of the present study was to validate the proposed set of research criteria for MCBMI-FTD.
Methods: 435 participants were consecutively enrolled from the GENFI study, 125 of whom were carriers of an FTD pathogenic mutation (165 *C9orf72*, 178 *GRN*, 84 *MAPT*, 8 *TBK1*) in the MCBMI phase (*i.e.*, with a CDR plus NACC FTLD of 0.5), while 310 were familial non-carriers. Clinical criteria were defined as: gradual and progressive cognitive and/or behavioural and/or motor changes compared to prior functioning with preserved independence in functional abilities of daily living, occurring along with one or more of the following features: objective evidence of a dysexecutive syndrome, occurring in isolation or associated with other cognitive changes, such as impaired social cognition; language deficit; behavioural changes: apathy, disinhibition, loss of empathy, compulsive behaviour, and change in appetite; signs and symptoms of parkinsonism or motor neuron disease. Clinical features were evaluated in all participants and a subgroup underwent blood NfL and GFAP measurements. ROC curves were applied, and specificity and sensitivity analyses were performed.
Results: Clinical criteria correctly classified carriers vs non carriers with an AUC of 0.77, $p<0.001$, while the addition of

symptoms of anxiety and depression non-significantly increased the AUC to 0.79, $p<0.001$. Blood NfL and GFAP measurements significantly increased the AUC to 0.83, $p<0.001$, with a sensitivity of 71.2% and a specificity of 77.9%. **Conclusions:** The proposed MCBMI criteria showed near excellent classification accuracy for identifying the prodromal stage of FTD. The addition of biological markers further improves diagnostic accuracy.

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P0991 / #1021

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

NEUROFILAMENT LIGHT OLIGOMERS IN NEURODEGENERATIVE DISEASES: DETECTION BY HOMOGENEOUS IMMUNOASSAY IN CEREBROSPINAL FLUID

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Aims: Objectives: Neurofilament light (NFL) is a widely used biomarker for neurodegeneration, with many well-established protocols capable of detecting it in body fluids. Nevertheless, the precise molecular nature of this widely used biomarker remains unknown and standardized protocols do not distinguish between aggregation states of this protein. Based on this, the objective of this study was to develop a homogeneous ELISA capable of detecting NFL oligomers.
Methods: The homogeneous ELISA was based on a previously developed assay (Gaetani et al., 2018), but in this case using the same capture and detector in-house antibody (NFL21). This assay was tested on samples from behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), semantic dementia (SD), Alzheimer´s disease (AD) and healthy controls. NFL was also characterized by high performance liquid chromatography (HPLC) after size exclusion chromatography (SEC) of cerebrospinal fluid (CSF), as well as in the in-house calibrator used.
Results: Samples were run randomized under the same conditions and the results showed a significant increase in oligomeric NFL concentration in PNFA ($p<0.0001$) and SD ($p<0.05$) compared with controls. PNFA NFL was also significantly increased compared with bvFTD ($p<0.001$) and AD ($p<0.01$). However, bvFTD, AD and controls did not show any statistically significant differences. SEC-HPLC on in-house calibrator showed a peak in NFL signal in the fraction compatible with a full-length dimer (135 kDa). Yet, for CSF, the peak was found in a fraction corresponding to lower molecular weight (approx. 53 kDa), raising the possibility that dimers can be formed of truncated NFL.
Conclusions: The newly developed homogeneous ELISA provides insights into the presence of NFL oligomers in CSF, however further studies are needed for better characterization of NFL aggregation states in neurodegenerative disorders.

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P0992 / #1436

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

AMYGDALA ATROPHY SCALE TO IDENTIFY LATE PATIENTS: PRELIMINARY VALIDATION

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Aims: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by TDP-43 deposition mainly in the amygdala and medial temporal lobes. In these patients, brain atrophy is also found in a pattern that corresponds to the regions of TDP-43 deposition. However, while the medial temporal lobe atrophy scale (MTA) is well known and clinically validated, a scale to assess amygdala atrophy has not been developed yet and could help identifying LATE patients together with the MTA assessment.
Methods: 60 patients were randomly selected from the Geneva Memory Center cohort with the following criteria: (i) availability of structural MRI; (ii) MTA-neurodegeneration positivity based on Rhodius Meester age-weighted criteria. Amygdala atrophy was evaluated on a 3-point scale (0=no atrophy; 1=mild atrophy; 2=severe atrophy) by two independent expert neuroradiologists. Inter-rater reliability was measured by Cohen's Kappa (K).
Results: The two raters agreed on 68% of the cases. Weighted K was 0.71 (confidence interval, 0.56-0.86), indicating a substantial agreement between raters.
Conclusions: The amgydala scale, combined with MTA assessment, could be a cost-effective tool for early in-vivo detection of LATE patients in a memory clinic setting. A further validation with three independent raters will be performed together with clinical validation of clinical, neuropsychological, and additional biomarkers data.

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P0993 / #683

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

NEUROTRANSMITTER PATTERN IMPAIRMENT IN PRODROMAL FRONTOTEMPORAL DEMENTIA: A GENFI STUDY

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Aims: Detailed knowledge of neurotransmitters impairment in early stages of Frontotemporal dementia (FTD) holds the potential to identify new tailored therapeutic targets. JuSpace toolbox allows for cross-modal correlation of MRI-based measures with nuclear imaging derived estimates covering various neurotransmitter systems.
Methods: We applied JuSpace toolbox to the GENFI cohort, considering 84 mutation carriers with prodromal FTD (i.e., CDR® plus NACC FTLD= 0.5, 33 *C9orf72,* 33 *GRN,* and 18 *MAPT*), 77 mutation carriers with symptomatic FTD (CDR® plus NACC FTLD>0.5, 39 *C9orf72,* 24 *GRN,* and 14 *MAPT*) and 276 mutation-negative controls (HC). We tested if spatial patterns of grey matter volume alterations (as compared to HC) were correlated with specific neurotransmitter systems. Bonferroni correction for multiple comparisons was applied.
Results: As compared to HC, voxel-based brain changes in prodromal FTD due to *C9orf72* mutations were significantly associated with spatial distribution of dopamine (p=0.02) and acetylcholine (p=0.02) pathways, while in prodromal FTD due to *MAPT* mutations to dopamine (p=0.01) and serotonin (p=0.01) pathways. No significant changes were detected in

prodromal FTD due to *GRN* mutations. In symptomatic FTD, widespread neurotransmitters pattern impairment was reported across all mutations.

Conclusions: This study suggests that JuSpace is a helpful tool to indirectly assess neurotransmitter deficits in FTD. This approach may provide novel insight into disease mechanisms and therapeutic approaches in different monogenic FTD subtypes.

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P0994 / #979

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

OPTIMIZATION OF AFFINITY, SELECTIVITY AND PHARMACOKINETIC PROFILE OF TDP-43 PET LIGANDS

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Aims: TDP-43 proteinopathy is common in patients with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) and is present as co-pathology in other neurodegenerative diseases further complicating the diagnosis. Selective and sensitive fluid or imaging biomarkers of TDP-43 pathology are currently not available. Direct detection of TDP-43 aggregates by positron emission tomography (PET) holds promise for a more accurate diagnosis, patient stratification and assessment of therapeutic efficacy in clinical trials.
Methods: Initial screening of ACI's proprietary Morphomer® library was followed by an iterative medicinal chemistry optimization program using TDP-43 aggregates from human diseased brain samples. Radiobinding and autoradiography experiments on FTLD-TDP brain samples were used to evaluate binding affinity and target engagement**.** These techniques were also employed to assess selectivity using brain material from Alzheimer's (AD) and Parkinson's disease (PD) cases. CNS pharmacokinetic (PK) profile was established in mice, and brain uptake, distribution and washout were also assessed for selected 18F radiolabeled compounds in non-human primates.
Results: Rational drug design and medicinal chemistry optimization enabled the identification of several chemical series showing improved binding affinity to aggregated TDP-43. This translated into a substantial improvement in target engagement observed by autoradiography in FTLD-TDP brain sections compared to earlier designs. Selectivity over amyloid beta, alpha-synuclein and Tau was observed for selected compounds. Optimization of the scaffold further improved brain uptake whilst preserving the optimal binding and selectivity profile.
Conclusions: From the initial chemical series reported previously, further investigation has led to the discovery of substantially improved new analogs and a new series. With additional rounds of medical chemistry efforts, a molecule will soon be selected for evaluation as the first TDP-43 PET tracer in patients with TDP-43 proteinopathies.

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P0995 / #2168

POSTERS: D04. IMAGING, BIOMARKERS, DIAGNOSTICS

ALPHA-SYNUCLEIN SPECIES EXHIBIT REGIONAL DIFFERENCES BETWEEN DLB AND PDD AND CORRELATE WITH HYPER-PHOSPHORYLATED TAU PATHOLOGY

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Aims: To identify whether there are diffeences in leverls of C-terminally truncated α-syn (CT truncated α-syn) between Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), and to explore their association with clinical and pathological features.
Methods: Monoclonal antibodies were generated against putatively pathogenic CT truncated α-syn species and evaluated using different biochemical assessments methods and *in vitro* α-syn aggregation cell models. The antibodies were employed to explore whether subjects with PDD or DLB carry different burdens/species of CT truncated α-syn aggregates in human *post-mortem* brain tissues.
Results: The mouse monoclonal antibody cmAb4**,** recognized aggregates of full-length (FL) and CT truncated α-syn in slot blot analysis ELISA assay. Levels of CT truncated α-syn aggregates captured by cmAb4 antibody correlated with tau pathology in the amygdala, insula and temporal cortex in PDD and DLB subjects. The burden of CT truncated α-syn aggregates captured by cmAb4 antibody showed regional differences in accumulation, with a higher burden in amygdala than substantia nigra of DLB and higher in substantia nigra than amygdala of PDD.
Conclusions: Our findings suggest that CT truncated α-syn aggregates captured by cmAb4 antibody correlate with Alzheimer-type co-pathology in Lewy body dementia, showing regional differences in abundance between DLB and PDD cases. These findings highlight the pressing need to better understand the diversity of α-syn forms in the human brain and their relationship to clinical and pathology variables.

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P0996 / #2534

POSTERS: D05. GENETICS, EPIDEMIOLOGY

ESTIMATED PREVALENCE OF AMYOTROPHIC LATERAL SCLEROSIS IN THE REPUBLIC OF KAZAKHSTAN

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Aims: The main purpose of this study is an analytical calculation of the prevalence of ALS in the Republic of Kazakhstan as a whole.
Methods: The risk of developing amyotrophic lateral sclerosis (ALS) varies depending on continents and ethnic groups. Kazakhstan is an Asian country with a multiethnic composition (mainly Kazakhs, Slavs). An assessment of the size of the regional distribution of the population of ALS patients, including those of genetic origin, is necessary to understand the burden of the disease, to provide state support in treatment. A search was conducted for patients with ALS in the capital Astana (population 1,328,535 people) and 5 regional cities comparable in total (1,366,384 people) according to the medical documentation of polyclinics. As of September 1, 2022, the population of Kazakhstan is 19,666,840 people.
Results: The combined prevalence rates (per 100,000 people) were 1.6 for the capital and 0.6 for regional cities. Moreover, there is a significant heterogeneity of prevalence from 0 to 0.97 in individual cities. The estimated prevalence of ALS in the Republic of Kazakhstan is 1.1 per 100,000 populations.
Conclusions: Possible explanations for the regional spread of data are insufficient accurate diagnosis, lack of knowledge of doctors. These data emphasize the need to study the main mechanisms and innovations in healthcare systems for the management of complex patients with orphan diseases.

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P0997 / #2122

POSTERS: D05. GENETICS, EPIDEMIOLOGY

C9ORF72 REPEAT LENGTH MIGHT INFLUENCE CLINICAL SUB-PHENOTYPES IN DEMENTIA PATIENTS

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Aims: *C9orf72* repeat expansions have been observed in a wide variety of neurodegenerative disorders. The cut-off between normal and pathogenic alleles is not well established as repeat sizing methods are often semi-quantitative. However, intermediate alleles might influence disease prevalence and phenotype, as seen for other repeat expansion disorders. We aimed to further delineate the prevalence of small, intermediate and expanded *C9orf72* alleles and elucidate their potential influence on the disease phenotype.
Methods: DNA derived from patients (n=1804) and healthy individuals (n=643) was obtained from multiple collectives in Austria. Genotyping was performed using a two-step PCR assay followed by Southern blotting.
Results: 3.4% of clinically diagnosed frontotemporal dementia (FTD; n=5/147) cases and 0.8% of clinically diagnosed Alzheimer's disease (AD; n=5/602) cases were carriers of a pathological *C9orf72* repeat expansion. A significantly earlier disease onset was detected in expansion carriers compared to non-carriers in the FTD and AD cohorts (median 50 years, range 39-64 vs. median 64 years, range 36-92, p=0.018 and median 63 years, range 54-71 vs. median 74 years, range 45-92, p=0.006, respectively). *C9orf72* intermediate alleles were significantly associated with cerebellar symptoms (p=0.0004) and sensory deficits in the dementia cohort (p=0.01).
Conclusions: Compared to other causal mutations, *C9orf72* repeat expansions occur in a considerable proportion of patients with clinically early onset FTD and AD. Furthermore, *C9orf72* intermediate repeats might modify the phenotypic expression in dementia.

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P0998 / #2089

POSTERS: D06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

IDENTIFICATION AND LOCALIZATION OF TDP-43 SPECIES IN A YEAST MODEL FOR ALS/FTD

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Aims: TDP-43 is an aggregation-prone RNA-binding protein associated with neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and limbic-predominant age-related TDP-43 encephalopathy (LATE). Yeast is an established model for analyzing evolutionary conserved mechanisms underlying TDP-43 proteinopathies. Here, we aim to characterise TDP-43 species in yeast cells expressing human TDP-43.
Methods: Expressing TDP-43-EGFP in wild-type yeast cells as well as cells lacking known protein interaction partners of TDP-43, we aim to analyse the different protein populations present in these cells. Therefore, we perform subcellular fractioning assays in combination with membrane association studies: cells are lysed by high pressure rupture and extracts are submitted to differential centrifugation, solubilization assays and semi-native as well as denaturing electrophoresis. TDP-43 species are identified by Western blotting.
Results: We observe different TDP-43 species in cytoplasmic and membrane-enriched cellular fractions. Aside from oligomeric forms of TDP-43, full length molecules prevail throughout the cells. In some fractions, differential effects on degradation patterns are observed.
Conclusions: Taken together, our data suggests that the majority of TDP-43 is present in full length forms, organized in a wool ball like conformation and associated with membranes. Minor amounts are present as SDS-resistant oligomers and degradation products. This pattern can be affected by other proteins such as Dhh1/DDX6.

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P0999 / #2429

POSTERS: D06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

MODELLING NEURODEGENERATION USING A HUMAN ISOGENIC SYSTEM: A NEXT GENERATION APPROACH TO STUDY FRONTOTEMPORAL DEMENTIA AND AMYOTROPHIC LATERAL SCLEROSIS

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Aims: Development of therapies to treat neurodegenerative diseases is hampered because less than 10% of findings derived from preclinical animal models can be translated to humans. Patient-derived induced pluripotent stem cells (iPSCs) enable generation of in vitro models that can recapitulate human disease phenotypes. However, conventional human iPSC differentiation protocols are often lengthy, inconsistent, and difficult to scale. The lack of genetically matched controls for patient-derived models further complicates the investigation of disease phenotypes. bit.bio has developed opti-ox™, a robust iPSC reprogramming technology that overcomes these limitations and enables generation of mature cell types and isogenic disease models. Our objective was to generate disease models for frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) for use with isogenic, wild type ioGlutamatergic Neurons to improve screening specificity and accelerate drug discovery for these neurodegenerative disorders.
Methods: We used CRISPR/Cas-9 gene editing to introduce the disease-relevant mutation M337V in the TARDBP gene, encoding TDP-43, and the mutations P301S or N279K in the MAPT gene, encoding Tau. During the pathogenesis of FTD and ALS, mutant TDP-43 and Tau proteins are prone to misfolding, aggregation and mislocalisation, and have been reported to affect a range of neuronal subtypes, including cortical glutamatergic neurons.
Results: Characterisation of the FTD and ALS disease models showed that the expression profiles of TDP-43, Tau, and pan-neuronal and glutamatergic markers are highly similar to the ioGlutamatergic Neurons. We demonstrate characterisation of these disease models and the genetically matched control to show the differences in their transcriptome, neuronal activity and proteinopathy.
Conclusions: Using opti-ox technology to produce hiPSC-derived isogenic disease models provides physiologically-relevant, robust, standardised tools for neurodegenerative research and drug discovery.

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P1000 / #1828

POSTERS: D06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

MODULATION OF TDP-43 SPECIES BY THE DEAD-BOX HELICASE DHH1/DDX6 IN A YEAST MODEL FOR ALS/FTD

Julia Tischer, Israfil Yalcin, Regina Dahlhaus, Ralf Braun
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Aims: TDP-43 is an aggregation-prone RNA-binding protein associated with neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and limbic-predominant age-related TDP-43 encephalopathy (LATE). Applying a genome-wide screen in a yeast model for human TDP-43 proteinopathies, we identified yeast proteins interacting with human TDP-43. Among them, the evolutionary conserved cytoplasmic DEAD-box helicase Dhh1/DDX6 was detected, which is involved in P body and stress granule formation. Here, we aim to validate the role of Dhh1/DDX6 in TDP-43 aggregation in yeast.
Methods: We aim to express TDP-43-EGFP fusion proteins in wild-type yeast cells, yeast cells lacking Dhh1, yeast cells overexpressing Dhh1 or a loss-of-function variant of this protein. We aim to follow aggregate-like TDP-43-EGFP foci in yeast cells using epifluorescence microscopy, determine the level of TDP-43-EGFP in yeast cell extracts. Finally, we aim to measure TDP-43-triggered cytotoxicity in these cells measuring growth with a spot dilution assay.
Results: We observed that cells lacking Dhh1 show increased levels of TDP-43 aggregate-like foci, whereas the cytotoxicity based on growth assays appears to be unaffected. Currently, we are validating these initial findings in cells with increased levels of functional and non-functional Dhh1.
Conclusions: Dhh1 potentially shifts TDP-43 species into aggregate-like structures without affecting TDP-43 cytotoxicity.

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P1001 / #545

POSTERS: D06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

A COMBINED TDP43-TAU CELLULAR MODEL FOR THE UNDERSTANDING OF LATE-NC PROTEINOPATHY

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Aims: The development of a cellular assay aimed to study TDP43 and hyperphosphorylated Tau protein combination to elucidate new pathways of molecular signaling in LATE disease and pathological synergy between these two targets.
Methods: U2OS cell line stably expressing induced TDP43- tGFP was transfected with a triple mutant TAU (G272V, P301L and DK280) tagged with FP650 fluorescent protein. Cells were treated with 300 mM sodium arsenite during 90´, dyed with 0.5 mg/ml Hoechst the last 30´of the sodium arsenite treatment. 1 mM ISRIB and 30 mM LiCl were used as TDP-43 and Tau controls, respectively. Fluorescent images were acquired in the Cell insight CX7 high content equipment.
Results: Cellular model characterization. The image analysis provides the number of TDP-43 granules and Tau bundles per cell. The addition of 300 mM sodium arsenite during 90´ increased the TDP-43 aggregates number 2.9-fold. The treatment with 30 mM LiCl increased the number of bundles 2.08-fold. **HCS analysis.** A screening of 1200-compound library was performed with the TDP43_Tau-TM cell line. Cells were treated with each compound at 10 µM. Under these conditions 16 positive compounds were detected for TDP43 and 8 for TAU. Z' = 0.67 ± 0.1. **Dose-response Assay.** 3 compounds were found to be positive for both proteins but only compound I2240 (Niclosamide) performed a dose response curve. Cells were treated with 8 decreasing concentrations starting with 10 µM.
Conclusions: - This cellular model allows the evaluation of compounds that may present synergies in neuroprotection through their effect on both cellular targets. - In the search for synergistic compounds for the TDP-43 and Tau targets, 3 possible candidates have been found. Only compound I2240 (Niclosamide) shows a neuroprotective effect against both targets in a dose-dependent manner.

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P1002 / #2172

POSTERS: D07. ANIMAL MODELS

ROLE OF HEAT SHOCK PROTEIN-22 (HSP-22) IN ALZHEIMER'S DISEASE NEURODEGENERATION

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Aims: The study aims to identify expression alteration in proteins with specific reference to heat shock proteins that can serve as potential biomarkers for AD.The study aims to identify expression alteration in proteins with specific reference to heat shock proteins that can serve as potential biomarkers for AD.
Methods: In this study animal models of AD were prepared via co-administration of $AlCl_3$ and D-galactose in male albino wistar rats. The behavioral analysis for assessing memory and anxiety was performed using Open Field Test, Morris Water Maze Test and Elevated Plus Maze Test in control and test animals. Animal decapitation and blood sample collection was done followed by behavioral test. The serum separated from blood was quantified by Bradford method followed by expression profiling using SDS_PAGE and validation by western blotting.
Results: SDS-PAGE analysis revealed differential expression of several proteins one of them being Heat Shock Protein with increased expression in AD animal models detected through western blotting. The present study concludes that pathological consequences associated with Alzheimer's disease are not only because of an individual protein but maybe a combinatorial effect of altered expression of several proteins.
Conclusions: Further understanding of protein expression through two-dimensional electrophoresis and electro-blotting could give detail insight of the disease.

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P1003 / #437

POSTERS: D07. ANIMAL MODELS

INTERFERON SIGNALLING AS POTENTIAL THERAPEUTIC TARGETS IN AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEMENTIA – A SYSTEMATIC REVIEW AND META-ANALYSIS OF ANIMAL STUDIES.

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[1]University of Aberdeen, The Institute Of Medical Sciences, Aberdeen, United Kingdom, [2]University of Edinburgh, Centre For Clinical Brain Sciences, Edinburgh, United Kingdom, [3]University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: Amyotrophic lateral sclerosis frontotemporal spectrum disorders (ALS-FTSD) exhibit heterogeneous features of immune system dysfunction such as excessive inflammation, inefficient immune response, and autoimmunity, with recent studies identifing interferon signalling as a key player in this dysfunction. Given that interferon dysregulation may contribute to disease heterogeneity and pathogenesis, we set out to perform a systematic review and meta-analysis of the preclinical literature to enhance our understanding of the role of interferon signalling pathways in ALS-FTSD.
Methods: We performed a comprehensive review of the ALS-FTSD preclinical literature to compile a list of, (i) interventions affecting interferon signalling pathways, and (ii) specific interferon signalling pathway targets that may be manipulated for therapeutic benefit in patients with ALS-FTSD. We assessed the literature for the effects of interferon signalling manipulation in studies comparing models of ALS-FTSD to controls, with the primary outcome measure being survival, and secondary outcome measures including histological, biochemical, and behavioural metrics.
Results: PubMed, Medline and EMBASE searches yielded 5,167 studies. Following the removal of duplicates, 4,323 papers remained, of which 4209 were excluded during the screening process. Full texts were retrieved for 114 studies from which suitable data were extracted. We report that mouse studies dominate (all but 4 studies utilised murine models). The SOD1-G93A mouse model was employed in almost 60% of all studies, over six times the number of studies than the next most utilised model (TDP-43). Successful therapeutic interventions were identified amongst a range of interventions (e.g. drug, genetic) targeting interferon signalling.
Conclusions: Taken together, these data better our understanding of the contribution of inflammation and interferon signalling to ALS-FTSD pathogenesis, as well as highlight targets for further preclinical and clinical studies that aim to improve personalised therapies for people with ALS-FTSD.

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P1004 / #1473

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

MICROVASCULAR PATHOLOGY IN THE SPINAL CORD OF SEVERE SPINAL MUSCULAR ATROPHY PATIENTS

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Aims: Spinal muscular atrophy (SMA) is an inherited childhood form of motor neurone disease and a leading cause of infant disability. In addition to characteristic neuromuscular pathology, depletion of cell-ubiquitous survival motor neurone protein also manifests in extensive non-neuronal pathology, particularly of the cardiovascular system. Vascular abnormalities, both intrinsic and extrinsic, are widespread. Vascular supply to the spinal cord is essential for development and function, and reports of reduced microcirculation in SMA models is associated with functional hypoxia throughout the central nervous system.
Methods: Applying gold-standard stereological techniques, we developed a robust and reliable methodology to quantify spinal cord microcirculation on sections stained for endothelial cells (von Willebrand Factor). In a post-mortem cohort of Type I SMA patients and age-matched controls, we investigated anatomical and physiological parameters of microvascular density and oxygen diffusion distances. Immunohistochemistry for cell division (Ki67) was also carried out. Post-mortem samples were obtained from Johns Hopkins University, NIH Neurobiobank and BRAIN-UK.
Results: SMA patient spinal cord showed increased microvascular density in four key regions of interest assessed: the ventral and dorsal horns of the grey matter, and the lateral corticospinal (motor) and medial lemniscus (sensory) white matter tracts. Proliferating endothelial cells were also observed, suggestive of angiogenesis in the SMA spinal cord.
Conclusions: Together with recent reports of ongoing endothelial injury in SMA patients, these results suggest postnatal angiogenesis and ongoing endothelial repair response mechanisms. These data highlight a microvascular pathology in the spinal cord of SMA patients which is likely to impact the neuronal environment. Hypoxia is a recognised signal for angiogenesis, but also a trigger for motor neuron degeneration. Microvascular defects therefore have the potential to influence or exacerbate SMA neuropathology.

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P1005 / #2002

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

LOW SERUM HDL-CHOLESTEROL IS ASSOCIATED WITH INCREASED RISK OF THE SUBCORTICAL SMALL VESSEL TYPE OF DEMENTIA

Elin Axelsson Andrén[1], Dewa Safi[1], Anders Wallin[2], Johan Svensson[1]
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Aims: There are conflicting results whether serum lipid pattern is related to the amount of white matter hyperintensities (WMHs) on magnetic resonance imaging. Little is known of the associations with the risk of the subcortical small vessel type of dementia (SSVD), in which WMHs are a prominent manifestation. The aim of this study was to determine if lipid levels were associated with the risk of SSVD, Alzheimer's disease (AD), or mixed dementia (combined AD and SSVD) at a single memory clinic.
Methods: This is a prospective study of 329 patients with subjective or objective mild cognitive impairment. The statistical analyses included Cox proportional hazards regression analysis.
Results: During the follow-up (mean 4.1 years), 80 patients converted to dementia [SSVD, n=15 (5%); AD, n=39 (12%); mixed dementia, n=26 (8%)]. There were no associations between serum lipid levels and the risk of AD or mixed dementia after adjustment for covariates. Serum high-density lipoprotein cholesterol (HDL) was inversely associated with the risk of SSVD, whereas triglycerides (TG), low-density lipoprotein cholesterol (LDL)/HDL ratio, and TG/HDL ratio were positively associated with the risk of SSVD. In further analyses, the lowest HDL tertile was associated with a seven-fold increase in the risk of SSVD, and the highest tertile of TG/HDL ratio was associated with a three-fold increase in SSVD risk after full adjustment for covariates.
Conclusions: Low serum HDL and high serum TG/HDL ratio were associated with increased risk of SSVD. Furthermore, the lack of associations with the risk of AD or mixed dementia support that SSVD is a specific disease entity.

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P1006 / #1925

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ASSOCIATION BETWEEN COGNITIVE DECLINE AND CARDIOVASCULAR MORTALITY MODIFIED BY GENDER

Sri Banerjee
Walden University, Public Health, Leola, United States of America

Aims: Dementia is a significant public health problem which leads to poor health outcomes. Inflammatory biomarkers have been found to be important in signaling cardiovascular disease. In this study, we determined whether the longitudinal evidence supports the need to use biomarkers like C-reactive protein (CRP) as poor prognostic indicators for cognitive decline, especially in individuals with congestive heart failure (CHF).
Methods: We used population-based cohort study of 1999-2002 National Health and Nutrition Examination Surveys with mortality data obtained through 2015. Adults aged 60 years or older were assessed for cognitive skills using Digit Symbol Substitution Test (DSST). Outcomes of CVD-mortality were evaluated using Cox regression at gender levels.
Results: Percent of deaths from low cognitive function among the population (N=1123) were higher among Hispanic Americans (12.0%) than Caucasians (9.4%). The mean follow-up was 13.1 years. For all-cause mortality, the overall unadjusted hazard ratio (HR) of low cognitive function was 1.59 (95% confidence interval [CI], 1.11-2.27, $p < 0.01$). Adjusted HR was elevated, 15.31 (CI 4.67-50.15, $p < 0.001$), was slightly elevated females among low cognitive function but closer to 1.0 (1.36 CI 0.74-2.51, $p < 0.31$) among males and low cognitive function, after controlling for medical (hypertension and CKD) and demographic risk factors (age and poverty-income-ratio).
Conclusions: Our research shows that low cognitive function leads to higher cardiovascular mortality, especially among females. Improved identification of dementia, increased surveillance efforts, and addressing issues with health equity are needed to improve survival.

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P1007 / #1927

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

EFFECT MODIFICATION OF HYPERTENSION IN COGNITIVE-RELATED MORTALITY FROM INDIVIDUALS WITH DIABETES

Sri Banerjee
Walden University, Public Health, Leola, United States of America

Aims: Dementia is associated with many age-related disease conditions . Diabetes also is a chronic disease that also affects cognition. In this study, we determined whether the longitudinal evidence supports the need to understand hypertension better along with diabetes in order to better characterize overall mortality.
Methods: In the National Health and Nutrition Survey, we used population-based cohort study of 1999-2002 National Health and Nutrition Examination Surveys with mortality data obtained through 2015. Adults aged 20 years or older with diabetes were assessed for cognitive skills using Digit Symbol Substitution Test (DSST). Outcomes of all-cause mortality were evaluated using Cox regression.
Results: We had a mean follow-up of 10.1 years. Percent of deaths from low cognitive function among the population (N=2,982) was high. For all-cause mortality, the overall unadjusted hazard ratio (HR) of low cognitive dysfunction had a hazard ratio of 2.35 (95% confidence interval [CI], 1.74-3.18, p = 0.001). Adjusted HR was elevated, 1.53 (CI 1.02-2.29, p < 0.001), among individuals with hypertension and low cognitive function but closer to 1.41 (CI 0.81-2.46, p = 0.219) among individuals without hypertension with low cognitive function, after controlling for medical (stroke and chronic kidney disease) and demographic risk factors (age, gender, poverty-income-ratio, and education).
Conclusions: Our research shows that when an individual has diabetes, there are more likely to have higher mortality from cognitive dysfunction with hypertension than those individuals without hypertension if the individual has diabetes. Our research shows that low cognitive function leads to higher mortality. In addition, diabetes individually can directly cause increased overall mortalityImproved identification of dementia, increased surveillance efforts, and addressing issues with health equity are needed to improve survival.

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P1008 / #1850

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ON CEREBRAL MICROVASCULAR 'RASPBERRIES': REGIONAL DISTRIBUTION AND ASSOCIATIONS WITH CEREBROVASCULAR PATHOLOGY

Henric Ek Olofsson, Elisabet Englund, Mattias Haglund
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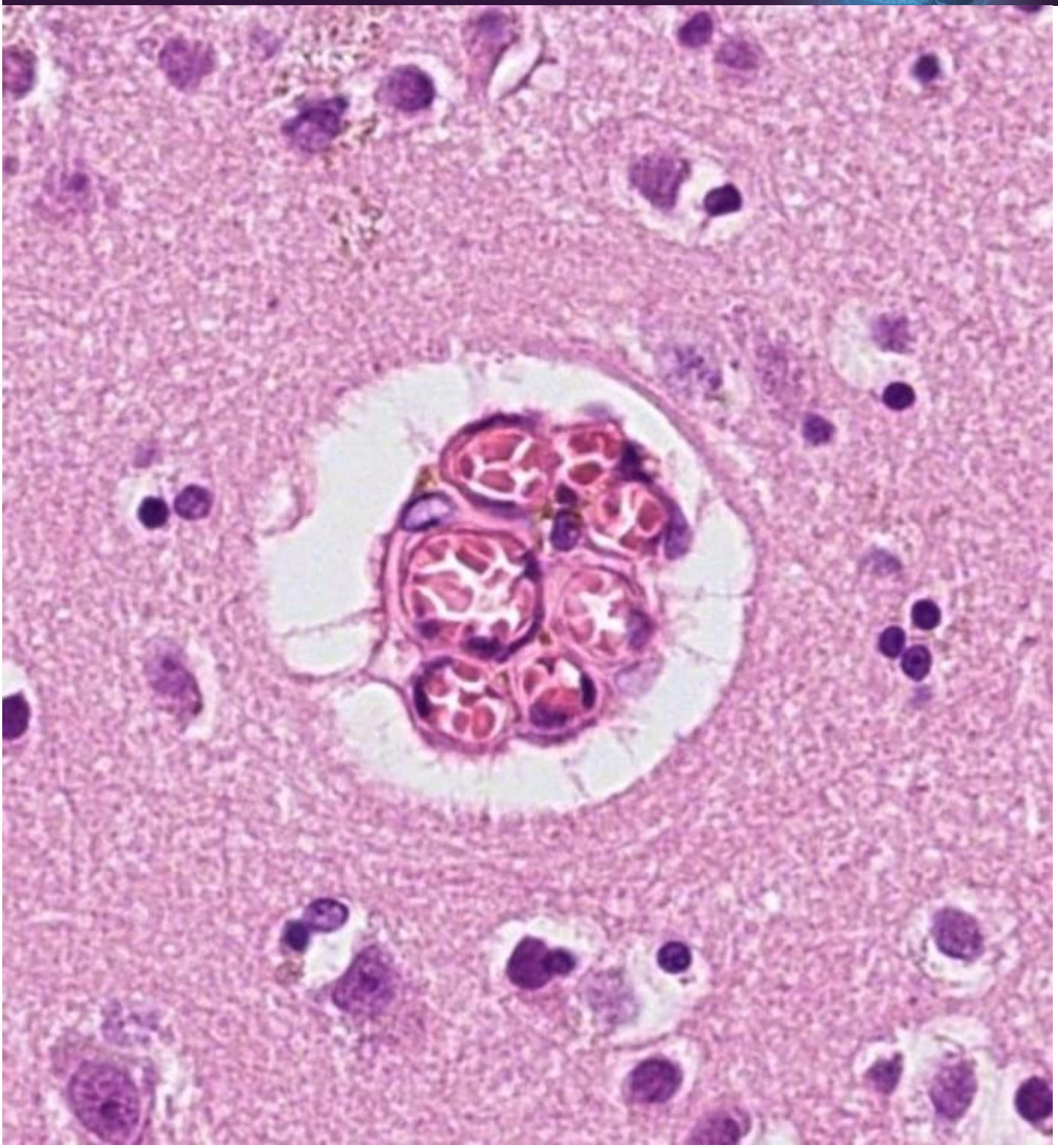
Aims: The aim of this ongoing PhD project in neuropathology is to examine a cerebral microvascular formation termed 'raspberry' (Figure 1). The aim is currently addressed by describing the distribution of raspberries throughout the brain as well as their association with clinical and pathological
findings.



Methods: Our research is based on material from diagnostic neuropathological autopsies performed at our lab. Raspberries are quantified on haematoxylin-eosin-stained tissue sections of the brain and correlated with other autopsy findings as well as clinical data collected from medical records.

Results: Raspberries are more frequent in neuropathologically verified cases of major vascular cognitive impairment compared to other diagnoses (1). We observed a smaller, statistically inconclusive difference in raspberry frequency when comparing cases of Alzheimer's disease and frontotemporal lobar degeneration to control cases. Raspberries were associated with atherosclerosis of the basal cerebral arteries but did not show an association with small vessel disease,

including amyloid angiopathy, in a cohort of limited size (2). Raspberries have mainly been found in cortical and subcortical grey matter but are rare in white matter and in cerebellum.

Conclusions: Raspberries are associated with markers and consequences of cerebrovascular disease, although the direction of this association is unknown. We hypothesise that the pathogenesis of raspberries is related to ischaemia and will test this hypothesis further through immunohistochemical studies. 1. Ek Olofsson H, Englund E. A cortical microvascular structure in vascular dementia, Alzheimer's disease, frontotemporal lobar degeneration and nondemented controls: a sign of angiogenesis due to brain ischaemia? Neuropathol Appl Neurobiol. 2019;45(6):557-69. 2. Ek Olofsson H, Haglund M, Englund E. Are cortical microvascular raspberries caused by cerebral hypoperfusion? An exploratory pathological study. Cerebral Circulation - Cognition and Behavior. 2021;2:100026.

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P1009 / #1388

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

LOCALIZATION OF PAS GRANULES IN BRAIN AREAS OF SAMP8 MICE.

Clara Romera[1], Marta Riba[1,2,3], Raquel Alsina[1], Carme Pelegrí[2,3,4], Jordi Vilaplana[1,2,3], Jaume Del Valle[1,2,3]
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Aims: Corpora amylacea (CA) of human brain are polyglucosan aggregates that gather waste products of different origins. Their presence is increased with age and in neurodegenerative diseases. These CA are released to the cerebrospinal fluid (CSF), and follow an exit route from the brain to the lymphatic system, where they would be eliminated. In several mouse strains, degenerative granular structures, frequently referred to as "PAS granules" due to their positive staining with periodic acid-Schiff (PAS), have been identified and postulated to be analogous to human CA. Provided PAS granules also appear with aging, the senescence-accelerated mouse prone 8 (SAMP8) strain of mice is a good model to study these granules. In this study, we aimed to define the precise localization of PAS granules in the mouse brain of SAMP8 animals, in order to determine if these granules, as CA, are located in areas that function as a brain exit doors to the CSF.
Methods: PAS staining and immunohistochemistry techniques have been used to recognize PAS granules. In addition, confocal microscopy and 3-D reconstruction have been used to precisely locate PAS granules.
Results: We found that PAS granules are specifically located in the perivascular space (associated to the walls of large blood vessels), in the ventricular zones (in the lateral and the central ventricles) and in subpial areas (within the meninges).
Conclusions: This is the first study that demonstrates that PAS granules are located in areas that function as a brain exit doors to the CSF. It also suggest that PAS granules may exit the brain through similar routes than CA, and supports the fact that these granules are the murine equivalent of human CA.

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P1010 / #1694

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

VASCULAR DEMENTIA AND VASCULAR PARKINSONISM ARE ASSOCIATED WITH AN INCREASED RISK OF DEATH OR VASCULAR EVENTS.

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Military Institute of Medicine, Clinic Of Neurology, Warsaw, Poland

Aims: Introduction: The natural course of vascular parkinsonism (VaP) and dementia (VaD) due to cerebral small vessel disease (SVD) is not well known. **The aim** of this single-center study was to evaluate the long-term risk of vascular events, death and dependency in patients with VaP or VaD and to compare it with patients without cerebrovascular disease but with high atherothrombotic risk.
Methods: Material and methods: 87 consecutive, independent patients with MRI features of SVD and with recently diagnosed VaD (n = 50) and VaP (n = 28) and 55 controls (CG) with high 10-year risk of total cardiovascular disease (SCORE ≥ 5%) were followed for 24 months.
Results: Results: Patients with SVD had lower prevalence of CAD compared with the CG (20.5% vs. 40%; p = 0.02) but similar prevalence of vascular risk factors including mean age (73.7 ±7.3 vs. 72 ±5.9 years, p = 0.09). 31% of SVD patients (34% of VaD vs. 25% of VaP, p = 0.45) experienced vascular events or died vs 6% of CG (p < 0.01). After adjustments for confounders patients with VaP (HR 7.5; 95% CI: 1.6-33) and VaD (HR 8.7; 95% CI: 2.1-35) had higher risk of vascular events or death and death or dependency (HR 3.9; 95% CI: 0.83-18.8; HR 4.7, 95% CI: 1.1-19.7). Significantly (p = 0.03) more patients with VaD deteriorated in MMSE during follow-up (n = 24; 53%) compared to VaP (25%), half of patients with VaP (n = 11; 48%) transited between Hoehn-Yahr stages during the study (mean: 3.4 ±0.7).
Conclusions: Conclusions: Patients with VaP or VaD due to SVD had significantly higher risk of vascular events, death and dependency compared to controls with high cardiovascular risk and without cerebrovascular disease.

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P1011 / #455

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

DEMOGRAPHIC FACTORS AND MEDICAL CONDITIONS ASSOCIATED WITH SUBJECTIVE COGNITIVE DECLINE IN THE BRAIN HEALTH REGISTRY

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[1]University of California San Francisco, Radiology, San Francisco, United States of America, [2]University of California San Francisco, Epidemiology & Biostatistics, San Francisco, United States of America, [3]Northern California Institute for Research and Education, Va Advanced Imaging Research Center, San Francisco, United States of America, [4]University of California San Francisco (UCSF), Psychiatry, San Francisco, United States of America

Aims: Demographic factors and medical comorbidities frequently correlate with age-related cognitive decline and Alzheimer's disease. However, the role is not well understood in subjective cognitive decline (SCD). The objective of this work is to identify demographic and medical factors associated with SCD within the Brain Health Registry (BHR) cohort.
Methods: Participants aged 55+ (N= 35,529) in the BHR self-reported SCD, medical comorbidities, depressive symptoms (Geriatric Depression Scale), BMI, family history of Alzheimer's, years of education and gender. All assessments were completed online. SCD was measured by the Everyday Cognition Scale (ECog), an assessment of change in capability to perform everyday tasks. Using linear regression, we tested the hypotheses that (1) presence of cardiovascular-related conditions (BMI, stroke and high blood pressure) are associated with higher ECog scores, and (2) the association is stronger in females. We also explored differences in ECog amongst ethnocultural groups.
Results: Higher ECog was associated with self-reported high blood pressure (coefficient = 0.03, $p = 0.03$), diabetes (coefficient = 0.07, $p = 0.01$), stroke (coefficient = 0.15, $p < 0.001$) and heart disease (coefficient = 0.05, $p = 0.03$). The associations between ECog and high blood pressure and cholesterol were significantly stronger for females than males (interaction coefficient = 0.05, $p = 0.04$). There were no significant associations between ethnocultural identity and ECog.
Conclusions: Self-report cardiovascular conditions were associated with SCD in an older adult cohort, and associations were stronger in females. This highlights the importance of accounting for medical conditions and demographic factors when assessing older adults for SCD.

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P1012 / #827

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ENDOTHELIAL NITRIC OXIDE SYNTHASE DEFICIENCY REDUCES PERLECAN EXPRESSION IN THE BRAIN OF A MOUSE MODEL OF VASCULAR DEMENTIA

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Aims: Perlecan (HSPG2) is a prominent component of the vascular basement membrane and regulates stability of the blood-brain barrier (BBB). BBB integrity is compromised in stroke, and perlecan hypomorphs sustain more BBB damage and neuronal cell death than wild-type animals in models of acute ischemic stroke. Whether loss of perlecan contributes to the development of chronic ischemic conditions such as vascular dementia (VaD) remains unexplored. Using the endothelial nitric oxide synthase (eNOS)-deficient mouse that models VaD through cerebral small vessel disease and gradually worsening brain ischemia, we sought to understand whether alterations in perlecan were associated with the development of VaD symptoms.
Methods: Whole-brain lysates were prepared for quantitative PCR and immunoblotting, and target mRNA and protein levels were normalized to those of GAPDH. Error bars correspond to the standard error of the mean, and differences were assessed using unpaired, two-tailed t-tests.
Results: We found that 12-month-old eNOS+/- mice had reduced levels of perlecan relative to age-matched controls. Additionally, we found that integrin alpha 5, a receptor through which perlecan exerts its neuroprotective and angiogenic effects, was decreased. In contrast, 3-month-old eNOS+/- mice, which do not yet display overt signs of neurodegeneration, did not show a reduction in perlecan, or integrin alpha 5.
Conclusions: As perlecan knockout mice also express less eNOS and have significant neurologic dysfunction, these observations suggest that the absence or gradual loss of perlecan expression coincides with neurocognitive symptoms associated with acute (stroke) or chronic (VaD) cerebral ischemia. Furthermore, as treatment with perlecan c-terminal domain V (DV) is neuroprotective and pro-angiogenic in acute cerebral ischemia, our preliminary data suggest that DV could also be neuroprotective and pro-angiogenic in the eNOS +/- chronic ischemia model of VaD worthy of further study.

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P1013 / #637

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

NX210C DRUG CANDIDATE PEPTIDE STRENGTHENS THE BLOOD-BRAIN BARRIER

Sighild Lemarchant[1], Chris Greene[2], Leslie Renouard[1], Yann Godfrin[1], Matthew Campbell[2]
[1]Axoltis Pharma, -, Lyon, France, [2]Trinity College Dublin, Smurfit Institute Of Genetics, Dublin, Ireland

Aims: Most of CNS diseases or injuries imply blood-brain barrier (BBB) alterations that contribute to disease progression and functional impairments. Here, we screened the effect of a subcommissural organ-spondin-derived peptide (NX210c), known to promote recovery in several neurological disorders, on BBB integrity.
Methods: Mouse brain endothelial bEnd.3 cells were treated with NX210c (0, 1, 10, 100 µM) for up to 72h. BBB integrity was evaluated using transendothelial electrical resistance (TEER) and FITC-40kDa Dextran transwell permeability assays. The expression of tight junction proteins (claudin-5, ZO-1 and occludin) was measured by RT-qPCR, western-blot and/or immunocytochemistry.
Results: The TEER of endothelial cell monolayers was increased in presence of NX210c from 24h post-exposure and maintained for up to 72h (+31% at 100 µM). In addition, NX210c decreased by half the permeability of endothelial cell monolayers to the FITC-Dextran after 24h or 72h of treatment (-50% at 100 µM). NX210c did not modulate tight junction mRNA levels, nor claudin-5 and ZO-1 protein levels. regardless of the concentrations and times of exposure used. However, a transient increase in occludin levels was found in NX210c-exposed cultures after 24h of treatment (+ 37% at 100 µM). Claudin-5 levels at cell surface were increased after 24h with NX210c at 10 and 100 µM (+23 % and +43%, respectively). This effect was maintained for at least 72h at 100 µM (+19%).
Conclusions: We are currently deciphering the mechanism of action behind the modulatory effect of NX210c on claudin-5 and subsequent strengthening of the BBB. In parallel, we are evaluating the effect of NX210c on BBB leakage in vivo. By repairing damaged CNS barriers, NX210c may represent an innovative drug candidate for the treatment of a large broad of neurological disorders.

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P1014 / #666

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

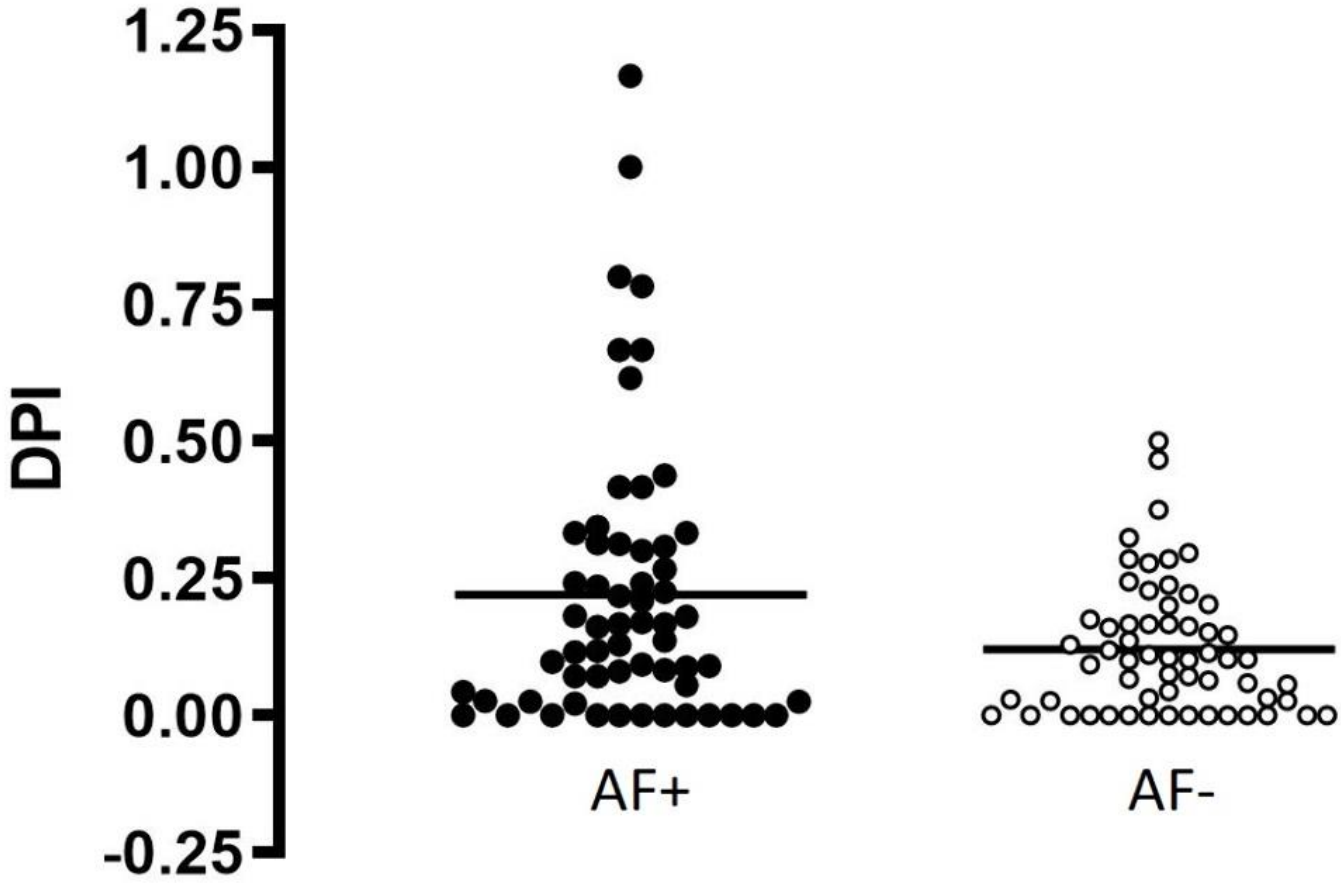
DISEASE PROGRESSION INDEX IN COGNITIVELY IMPAIRED PATIENTS WITH ATRIAL FIBRILLATION: AN OBSERVATIONAL STUDY

Benedetta Storti, Giulia Negro, Federico Emanuele Pozzi, Ildebrando Appollonio, Lucio Tremolizzo
San Gerardo Hospital, Neurology Unit, Monza, Italy

Aims: To establish the correlation between dementia and atrial fibrillation (AF) and quantify the negative impact of AF on the progression of cognitive impairment. To verify the cognitive protective effect of anticoagulant therapy and to report any possible difference in effect between vitamin K antagonists (VKA) and new oral anticoagulants (NOACs).
Methods: Sixty (n=60) patients with AF were identified from May 2014 and May 2021 at the outpatient memory clinic in San Gerardo Hospital, Monza. We used a matched pair design: every subject affected by AF (AF+) was paired with a similar subject not affected by AF (AF-). The matching variables chosen were sex, age, years of education and baseline MMSE score. To test the speed of cognitive decline we designed a disease progression index (DPI) consisting in the ratio of MMSE points lost over the observation time interval. The MMSE drop over time was compared between AF+ and AF-. The DPI of AF+ patients were also analyzed according to the anticoagulant treatment
taken.

$$\frac{MMSE(T0)-MMSE(Tx)}{(Tx)-(T0)}$$

Results: DPI was about twofold higher in AF+ patients with respect to AF- ones (0.22 ± 0.03 vs 0.12 ± 0.01, p=0.007). Covariate analysis including age, MMSE-T0, education, follow-up time, CHA2DS2-VASc, and HAS-BLED scores did not substantially change the results. AF+ patients subdivided according to anticoagulation treatment did not show any significant difference in
DPI.



Conclusions: A two-fold faster cognitive impairment is present in patients with AF. When further sub-classified according to NOAC vs VKA, patients with AF did not show any difference. Nevertheless, considering the relatively slow loss of MMSE points observed in our population, we could hypothesize that the antithrombotic therapy, taken by 66% (n=80), could at least participate in slowing down the cognitive decay.

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P1015 / #2673

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

THE RELATIONSHIP BETWEEN CHOLESTEROL, MEDICATION, AND PVS ALTERNATION

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Aims: Perivascular space (PVS) has been reported to be a potential biomarker for cerebral small vessel disease. High cholesterol is a high-risk factor for cerebrovascular disease and is associated with cognitive decline affecting the brain. Previous research has also shown that abnormal cholesterol levels in the blood may impair cognitive performance by reducing cerebral blood flow in the brain. There are many types of medication to treat cholesterol, some of which cross the blood-brain barrier (BBB). Statins, cholesterol-lowering drug that crosses the BBB may affect cognitive function. However, the relationship between cholesterol levels and PVS and the effect of cholesterol drugs on PVS remain unknown. Here, we investigated whether cholesterol causes detectable changes in PVS volume fraction (VF) in ADNI3 cohort.
Methods: There are 514 participants included in this study from ADNI3. PVS in 68 white matter sub-regions (created by Freesurfer Desikan-Killiany atlas) were segmented automatically. We then used linear gamma regression to assess if PVS volume fraction is associated with cholesterol level, correcting for age, sex, BMI, medication, and diagnosis.
Results: PVS-VF in left hemisphere isthmus cingulate was found to be significantly associated with total cholesterol level (t=-2.31, p=0.021). PVS-VF in right hemisphere isthmus cingulate (-2.13, p=0.034), caudal anterior cingulate (t=-2.45, p=0.015), caudal middle frontal (t=-2.15, p=0.032), supramarginal (t=-2.28, p=0.023), and insula (t=-2.06, p=0.040) regions were found to be significantly associated with total cholesterol level. But, none of the regions survived the multiple comparison correction.
Conclusions: We found that there is the tendency of association between total cholesterol levels and PVS-VF. In further, we will investigate whether cholesterol medications that pass the BBB affect PVS differently.

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P1016 / #2046

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

INFLUENCE OF CAROTID FUNCTION PARAMETERS ON ETIOLOGY OF COGNITIVE IMPAIRMENT

Greta García Escobar[1], Albert Puig-Pijoan[1,2,3], Joan Jiménez-Balado[1], Aida Fernández-Lebrero[1,2,3,4], Irene Navalpotro-Gómez[1,2,3,4], Jose Contador[1,2,4], Rosa María Manero-Borràs[1,2], Víctor Puente-Periz[1,2], Marc Suárez-Calvet[1,2,5,6], Oriol Grau-Rivera[1,2,5,6], Jaume Roquer[1,2], Jordi García-Ojalvo[3,7], Ángel Ois[1,2,3]
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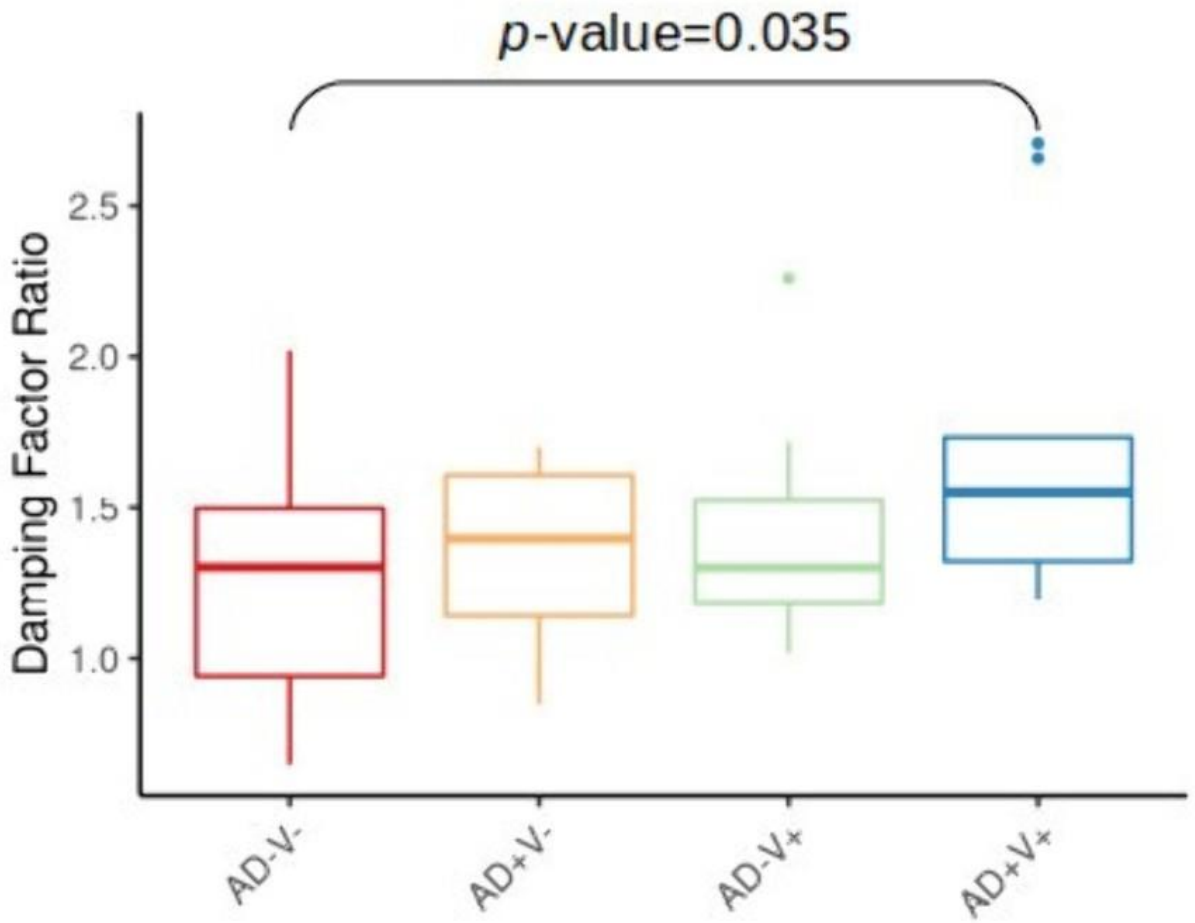
Aims: The main purpose of this study was to explore the relationship between ultrasonographic data and Alzheimer's disease and cerebrovascular disease as pathophysiological mechanisms of cognitive impairment (CI) in a memory clinic sample.
Methods: Fifty patients having mild (n=32, 36%) or moderate (n=18, 64%) CI were recruited from the BIODEGMAR cohort at Hospital del Mar (Barcelona) from June 2021 to January 2022. We labeled patients as Alzheimers Disease (AD+ according to their CSF Ab42/p-tau ratio) or cerebrovascular etiologies (V+: Fazekas' score higher than 1 or presence of infarcts). We also collected several markers of carotid hemodynamic data from ultrasonographic exploration: carotid flow, distensibility, intima-media thickness [IMT] and the damping factor (DF) as the ratio between distal and proximal pulsatility. We compared these parameters according to CI groups as well as their interaction (AD-V-; AD+V- ; AD-V+; AD+V+).
Results: Average age of the sample was 72.9 (±5.08) and 62% were female, 26 (52.0%) and 17 (34.0%) subjects were positive on AD and vascular markers, respectively. Considering both etiologies, there were 16 (32%) patients with AD-V-, 17 (34%) AD+V-, 8 (16%) AD-V+ and 9 (18%) AD+V+.Patients with vascular CI presented a lower damping (*p*=.05). Interestingly, when we further compared damping levels against the interaction between both groups, these differences were driven by those patients having AD+V+ as compared to AD-V- (*p*-value=.035). On the other hand, there was no association between CI etiologies and carotid flow, distensibility or IMT.



Conclusions: Patients with AD+V+ had an increased DF as compared to AD-V-, suggesting a role of arterial stiffness in mixed etiologies of CI.

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P1017 / #1169

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

ASSOCIATIONS BETWEEN WHITE MATTER LESIONS, CSF NEUROINFLAMMATORY BIOMARKERS, ANDCOGNITIVE DECLINE OVER TIME

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Aims: Small vessel disease and neuroinflammation occur in Alzheimer's disease (AD), and other neurodegenerative diseases. It is unclear if these processes are related or independent mechanisms in AD, especially in the early stages of disease. We therefore investigated the association between white matter lesions (WML; the most common manifestation of small vessel disease), CSF biomarkers of neuroinflammation and their effects on longitudinal cognition in a non-demented population.
Methods: 495 cognitively unimpaired (CU) elderly and 247 patients with mild cognitive impairment (MCI) from the Swedish BioFINDER study were included. WML volumes were determined at baseline. CSF was analyzed for interleukin (IL)–6, IL-7, IL-8, IL-15, IL-16, interferon-γ–induced protein 10, monocyte chemoattractant protein 1 (MCP-1), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular adhesion molecule 1 (sVCAM1)), placental growth factor (PlGF), soluble fms-related tyrosine kinase 1, vascular endothelial growth factors (VEGF-A, VEFG-D), and Aβ42 and Aβ40. Cognition was determined at baseline and followed-up over six years using MMSE and CDR measurements.
Results: Greater baseline WML volume was associated with longitudinal decline in MMSE in CU (β=-0.11, p=0.001), and MCI (β=-0.19, p=0.028). No associations were found between neuroinflammatory markers and longitudinal MMSE. Associations between more WML and higher longitudinal CDR score (worse cognition) were seen in CU (β=0.01,p=0.004), and MCI (β=0.03, p=0.012). In CU, associations were seen between higher IL-8 (β=0.01, p=0.001), MCP-1 (β=0.01, p=0.001), sICAM-1 (β=0.01, p=0.005), sVCAM-1 (β=0.01, p=0.001), VEGF-A (β=0.01, p=0.024), and increased longitudinal global CDR (worse cognition). Associations for both, biomarkers and WML, with longitudinal CDR in CU remained significant, when adjusting for the other modality.
Conclusions: Longitudinal analyses of cognition showed partly independent effects of CSF inflammatory markers and WML on longitudinal cognition, especially in people without cognitive impairment at baseline.

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P1018 / #2248

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

ASSOCIATION BETWEEN CEREBRAL MICROINFARCTS, CEREBRAL AMYLOID ANGIOPATHY INCIDENTALLY DETECTED ON MRI AND COGNITIVE DECLINE IN MEMORY CLINIC PATIENTS.

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Aims: Cerebral amyloid angiopathy (CAA) is known to be highly coexisted with Alzheimer's dementia (AD) pathology and has been related to the pathogenesis of small artery disease as well as microhemorrhage. In addition, it also causes vascular cognitive impairment (CAA-VCI; Greenberg SM, 2004). We investigated an association between cerebrovascular disorders and CAA that incidentally detected on MRI in the initial visit to a memory clinic and cognitive impairment.
Methods: We examined 53 patients (53% females, mean age 79.7±6.3) who showed abnormal findings on initial MRI (1.5T MRI-DWI, T2* and/or SWI), among 1,315 patients who visited to our memory clinic during 3 years. Clinical data including with or without incidental microinfarcts and microbleeds, vascular risk factors, neuropsychological tests and the degree in addition to the type of dementia were evaluated.
Results: Abnormal findings on initial MRI included 42 cases of cerebral infarction, 4 cases of cerebral hemorrhage, 6 cases of chronic subdural hematoma, and 1 case of brain tumor. Hypertension was found in 43 cases. Microbleeds were observed in 29 cases. CAA including cases with cortical superficial siderosis, was detected clearly and more extensively on 3T MRI-SWI. CAA-VCI was suspected in 19 cases (35.8%), including AD comorbidity with hippocampal/temporal lobe atrophy. Neuropsychological exams in CAA-VCI showed a tendency to decline of executive function and/or visuospatial ability.
Conclusions: It has been reported CAA is highly coexisted with AD pathology. It is necessary, however, to take a presence of VCI into consideration when we perform a clinical practice of elderly patients.

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P1019 / #2447

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

BROADENING THE CLINICAL SPECTRUM OF CADASIL: ACUTE ENCEPHALOPATHY AS AN UNUSUAL PRESENTATION

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Aims: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) constitutes the most common monogenic form of stroke. It is characterized by migraine with aura, lacunar infarcts, and cognitive impairment. We describe a patient with an acute encephalopathic presentation of the disease.
Methods: A 59-year-old woman with generalized tonic-clonic seizures (GTCS) and reduced consciousness, but no headache or fever, was admitted to intensive care. Brain CT showed hypodense lesions in subcortical white matter of temporal and frontal lobes. CSF examination was normal. A diagnosis of possible herpes simplex encephalitis was made and treated with acyclovir and levetiracetam. She was discharged after two weeks with her memory and attention slightly impaired. Later on, her 40-year-old son sought medical attention due to right leg weakness; at age 32 he had suffered GTCS.
Results: Brain MRI of the son and his mother evidenced extensive high signal affecting the deep and subcortical white matter of temporal and frontal lobes, thalamus, and mesencephalon-pons. Genotyping identified both members as carriers of the heterozygous mutation c.328C>T (P.R110C) in the NOTCH3 gene, as well as two of three son´s siblings (two had stroke, and one, migraine with aura) and two mother´s siblings (one with history of stroke and epilepsy). The mother developed an acute step-wise decline in cognition, recurrent stroke and seizures and died nine years later.
Conclusions: CADASIL should be considered in the differential diagnosis of acute unexplained encephalopathies, especially in case MRI white matter changes, previous migraine with aura, or a family history of stroke and dementia. The encephalopathy is self-limiting but may recur.

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P1020 / #2461

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

BLOOD-BRAIN BARRIER PERMEABILITY AND CEREBROVASCULAR BURDEN IN A MEMORY UNIT COHORT

Albert Puig-Pijoan[1,2,3], Joan Jiménez-Balado[3], Aida Fernández-Lebrero[1,2,3,4], Greta García Escobar[3], Irene Navalpotro-Gómez[1,2,3,4], Jose Contador[1,3,4], Rosa María Manero-Borràs[1], Víctor Puente-Periz[1,3], Marc Suárez-Calvet[1,3,5,6], Oriol Grau-Rivera[1,3,5,6], Jaume Roquer[1,3], Jordi García-Ojalvo[2,7], Ángel Ois[1,2,3]
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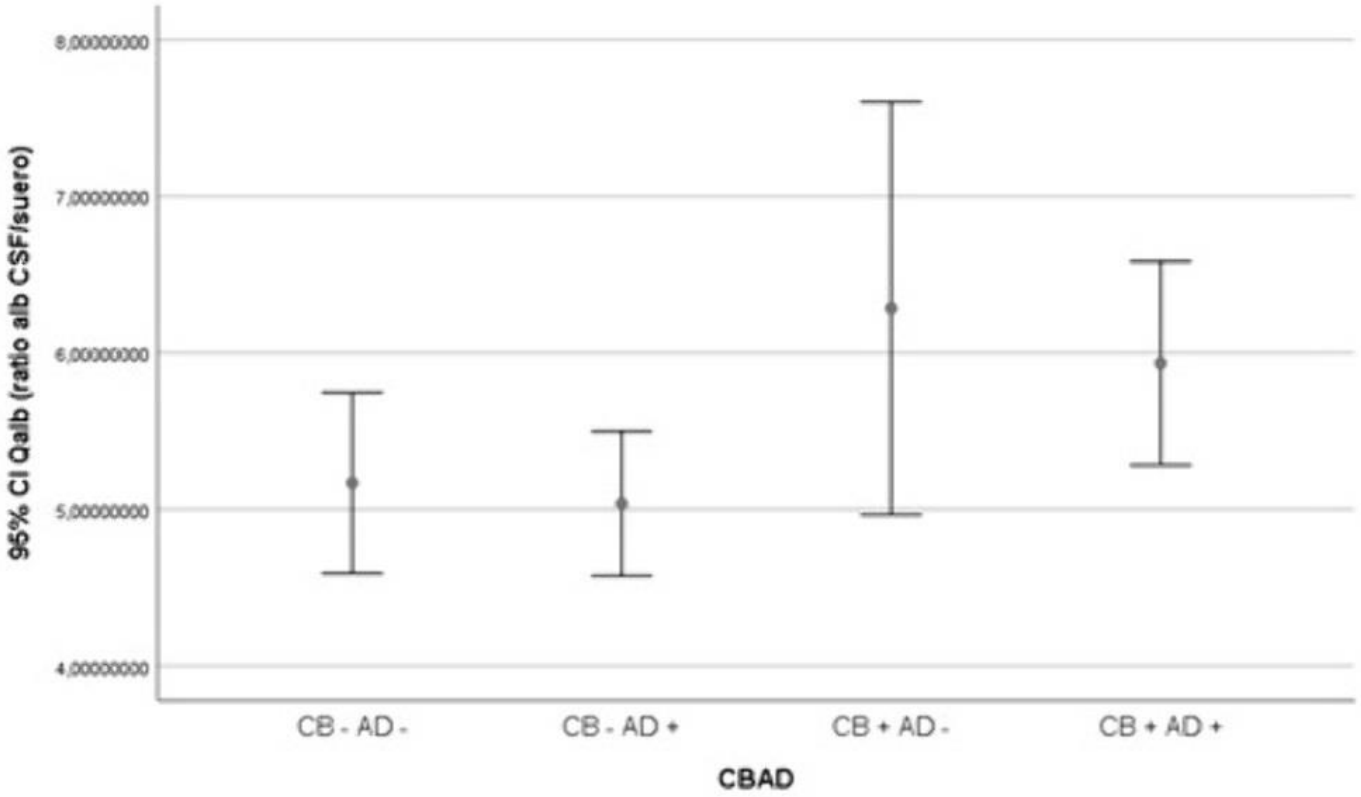
Aims: Blood–brain barrier dysfunction (BBBd) has been proposed as one of the underlying pathophysiological mechanisms of cognitive impairment (CI). However, the relationship between BBBd, Alzheimer's disease (AD) and cerebrovascular burden (CB) remains poorly understood. Our aim was to investigate associations between BBB permeability (BBBp) with AD and CB in a memory unit cohort.
Methods: A total of 268 individuals with subjective cognitive complaints (n=21, 7.8%), mild cognitive impairment (n=102, 38.1%) or dementia (n=145, 54.1%) were recruited from the BIODEGMAR cohort at Hospital del Mar (Barcelona) from 2017 to 2022. Study protocol included neuropsychological assessment, blood sampling, lumbar puncture and brain MRI. BBBp was measured by CSF/serum albumin ratio (Qalb). Participants were biologically-defined as AD+/- according to their CSF Aβ42/p-tau ratio, regardless of the syndromic diagnosis. CB+ was defined as Fazekas scale >1 or presence of brain infarcts. We categorized participants into four groups: CB-AD- (n=65, 24.3%); CB-AD+ (n=107, 39.9%); CB+AD- (n= 29, 10.8%) and CB+AD+ (n=67, 25%). Statistical analysis were performed with no parametric tests.
Results: Mean age was 72.4 (±5.77 years, range: 51-84), 151 were female (56.3%). Median Qalb was 4.73 mg/g (q1-q3:3.54-6.67, range: 1.52-17.8). Qalb was associated with male sex (p<0.001), diabetes mellitus (p=0.040) and CB (5.11 vs. 4.39; p=0.009). A marginal association with hypercholesterolemia (p=0.075) was found. No associations were found between Qalb and age (p=0.78), hypertension (p=0.59), biologically-defined AD (4.75 vs. 4.66; p=0.98) or CI severity (p=0.74). Diferences between the four groups were found (p<0.001), being the CB+AD- group the one with higher Qalb (see figure
1).



Conclusions: Our results show an association of BBBp with male sex, cardiovascular risk factors and CB in individuals with cognitive decline, while no association with biologically-defined AD or CI severity was found.

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P1021 / #640

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

VASCULAR AND INFLAMMATORY PLASMA BIOMARKERS ASSOCIATE WITH HUMAN POST-MORTEM SMALL VESSEL PATHOLOGIES

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Aims: Cerebral small-vessel disease (SVD) results from damaging of the small arteries, arterioles, and capillaries of the brain, and is a common pathology in the aging brain contributing to vascular contributions to cognitive impairment and dementia (VCID). Pathologically, SVD can present as arteriolosclerosis and microinfarctions. Identifying SVD in an individual is limited to MRI where white matter hyperintensities (WMH) are indicators of SVD. In this study, we evaluate the relationships between vascular and inflammatory plasma biomarkers with global levels of SVD pathology in human post-mortem tissue.
Methods: Plasma and brain tissue samples were obtained from an autopsy cohort at the University of Kentucky Alzheimer's Disease Research Center (UK-ADRC). Only cases that had a banked plasma sample within two years of death were selected. Plasma samples from participants were analyzed using Quanterix Simoa assays to determine levels of AD, inflammatory, and vascular plasma biomarkers, with patients being grouped into quartiles for each biomarker based on our entire population of plasma biomarkers samples. Pathological evaluation was performed by the Neuropathology Core of the UK-ADRC.
Results: Global arteriolosclerosis severity was examined using a scale of none, mild, moderate, or severe. PlGF was found to have associations with severity of arteriolosclerosis. MMP9 and TNFa also had relationships with arteriolosclerosis. These effects were also seen when we compared patients who had microinfarctions to those without. We also found that plasma PlGF has significant associations with WMH volumes assessed by MRI.
Conclusions: Plasma PlGF, MMP9 and TNFa have associations with global SVD pathology, suggesting utility for biomarkers of SVD-VCID. Future studies will examine the longitudinal changes in these biomarkers to determine their sensitivity for progression of SVD.

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P1022 / #812

POSTERS: E04. IMAGING, BIOMARKERS, DIAGNOSTICS

PARENCHYMAL CSF FRACTION IS BETTER ASSOCIATED WITH AGE AND DTI-ALPS COMPARED THAN THE PERIVASCULAR SPACE BURDEN

Liangdong Zhou, Thanh Nguyen, Gloria Chiang, Tracy Butler, Ke Xi, Lidia Glodzik, Mony De Leon, Yi Li
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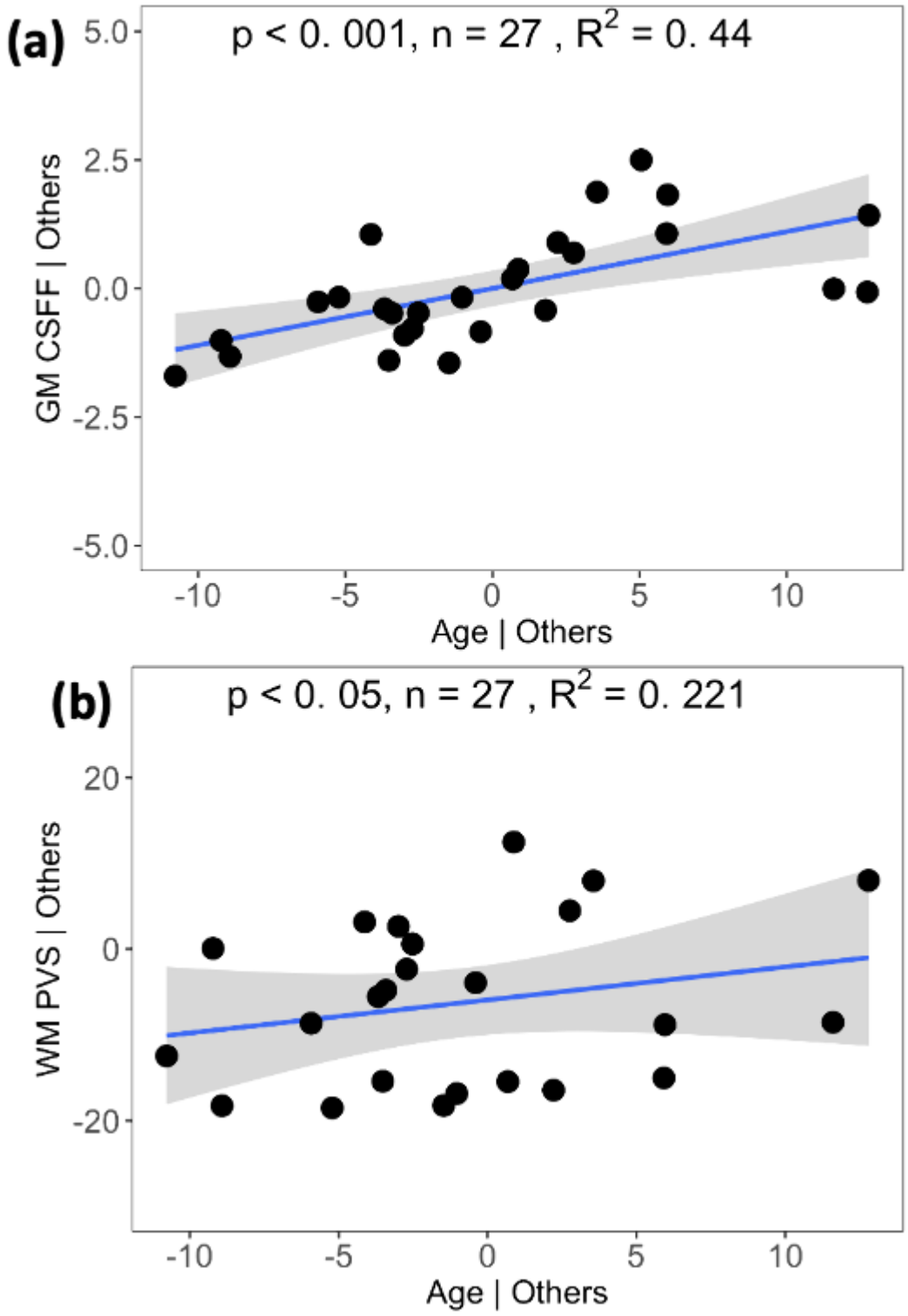
Aims: The glymphatic system, which is affected by aging and neurodegenerative diseases, plays a critical role in maintaining brain homeostasis. Perivascular spaces (PVS) are a key component of glymphatic clearance and enlarged PVS can be detected on T2W MRI. The previously developed DTI-ALPS index is a measure of diffusivity of CSF along PVS and reflects glymphatic function. (Taoka, 2017) We developed an imaging biomarker, brain parenchymal CSF fraction(CSFF), as an alternate method to assess glymphatic clearance. (L. Zhou, 2022). This study compares CSFF against PVS volume in detecting age-associated changes in glymphatic clearance.
Methods: We acquired T1W (ROI segmentation), T2W (PVS segmentation), multi-echo FAST-T2 (CSFF), SWI (veinous PVS), and DTI (ALPS) data on a 3T MR scanner in twenty-seven cognitively normal subjects (age: mean=68.1, std=6.2.) We associated age with CSFF and PVS load separately with DTI-ALPS and gender as covariates using two multivariate regression models: **CSFF (or PVS) = $\beta 0+\beta_1$*Age+β_2*ALPS+β_3*Gender.** These models aim to evaluate the effects of normal aging and DTI-based glymphatic function on CSFF and PVS.
Results: Figure-1 shows that the combination of age and DTI-ALPS can better explain the variation CSFF than PVS (R^2=0.44 vs 0.22). The partial correlation test indicates that the age correlates to CSFF (r=0.61, p<0.001) more than the PVS load (r=0.43, p=0.03) after controlling for the ALPS and



gender.

Conclusions: Conventional PVS volume measurement is insensitive to micro-scale PVS in the brain parenchyma, which is invisible on conventional MRI and may reflect glymphatic dysfunction at the early stage. CSFF could be a more sensitive and accurate marker of CSF/glymphatic flow alterations. A multimodal imaging protocol including both DTI and FAST-T2 could provide a non-invasive and comprehensive framework for evaluating glymphatic/CSF flow and clearance in humans.

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P1023 / #2443

POSTERS: E05. GENETICS, EPIDEMIOLOGY

INSIGHTS FROM HETEROZYGOUS HTRA1-RELATED CEREBRAL SMALL VESSEL DISEASE: PINPOINTING A MILDER FORM OF CARASIL?

Raquel Manso Calderón, María Dolores Sevillano García
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Aims: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is caused by homozygous mutations in HTRA1 gene. Recently, several heterozygous mutations in HTRA1 have also been associated with a milder form of CARASIL; we analyse the genetic and clinical characteristics of a new case.
Methods: A 57-year-old woman with progressive memory deterioration and mood disorder since the age of 54, small-step gait, and urinary incontinence. She also reported a history of migraine and smoking; but denied other cardiovascular risk factors, lumbar pain, and alopecia. Her grandmother and her sister suffered cognitive impairment and bipolar disorder, respectively; whereas her brother died in his 20s of unknown cause. On examination, stuttering with palilalia, impairment in delayed recall ability and processing speed, emotional lability and abulia, as well as tongue and hands tremor were observed.
Results: Laboratory tests, including thrombophilia, immune and metabolic screening, were normal. Brain MRI showed bilateral diffuse white matter abnormalities involving semi-oval centre, periventricular areas and frontoparietal lobes; whereas in a 2-year follow-up MRI new right temporal and left frontal lesions were discovered; SWI: no microbleeds. Angio-MRI: normal. Spine MRI evidenced multilevel degenerative disc disease (C4-C7). Granular osmiophilic materials (GOMs) were not found by electron microscopy examination of skin biopsy. In a genetic panel diagnostic (NOTCH3, HTRA1, and 12 genes related to adult-onset leukodystrophy), a heterozygous mutation, c.148C>G (P.P50A), was identified in the HTRA1 gene.
Conclusions: Heterozygous HTRA1 mutations should be considered in the differential diagnosis of cerebral small vessel disease, even in cases with vascular risk factors, later onset and spondylosis and alopecia typical of CARASIL lacking.

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P1024 / #1785

POSTERS: E05. GENETICS, EPIDEMIOLOGY

POLYGENIC RISK SCORES FOR ATRIAL FIBRILLATION AND HEART FAILURE AND THE RISK OF DEMENTIA AND STROKE -A POPULATION-BASED STUDY

Lina Rydén[1], Hanna Wetterberg[1], Silke Kern[1,2], Kaj Blennow[1,3], Henrik Zetterberg[1,3,4,5,6], Ingmar Skoog[1,2], Anna Zettergren[1]
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Aims: Atrial fibrillation (AF) and heart failure (HF) have been reported to increase dementia risk, but the mechanisms behind are not elucidated. We aim to examine if higher polygenic risk scores (PRSs) for AF and HF increase dementia and stroke risk in the general population.
Methods: Data was obtained from the Gothenburg H70 Birth Cohort Studies 1930 cohort. The participants were systematically selected from the Swedish population register based on birth dates. The first examination was conducted at age 70 in year 2000. Thereafter, examinations have been conducted at age 75, 79, 85, and 88. Genotyping was performed using the Neurochip (Illumina). PRSs were constructed based on genome-wide significant findings from GWASs of HF and AF, including 12 SNPs (HF) and 132 SNPs (AF) respectively. Dementia was identified according to the DSM-III-R criteria based on neuropsychiatric examinations, close-informant interviews, and register data. Cox-regression analyses, adjusted for sex and inclusion year in the study, were performed.
Results: A total of 981 participants were eligible for the study (58% women). Participants with higher HF-PRS had increased dementia risk (HR 4.5; p=0.005), but no increased stroke risk (HR 1.0; p=0.623). Participants with higher AF-PRS had increased stroke risk (HR 1.3; p=0.033), but no increased dementia risk (HR 1.2; p=0.109).
Conclusions: Our study shows that higher PRS for HF increase dementia risk, while higher PRS for AF increase stroke risk. These findings support the previously reported association between HF and dementia. However, there might be other explanations why AF has been associated with dementia than the dysrhythmia itself, such as shared risk factors between AF and dementia or the increased risk of stroke and HF in AF patients.

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P1026 / #1210

POSTERS: E06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

ESTABLISHMENT OF A BLOOD-BRAIN BARRIER MODEL USING HUMAN IPSC-DERIVED CELLS

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Aims: The blood-brain barrier (BBB) is a specialized network of cells that function to maintain a tightly controlled microenvironment around the brain. Modeling the BBB in vitro is needed to evaluate barrier function, test drug permeability, and study the diseases that affect it. Induced pluripotent stem cell (iPSC) technology is a powerful tool to generate the cells that compose the BBB and establish such a model.
Methods: As a leader in iPSC technology and innovation, FUJIFILM Cellular Dynamics, Inc. generated, characterized and utilized the three unique human iPSC-derived cell types for use in BBB model development, i.e. astrocytes, brain microvascular endothelial cells (BMEC), and pericytes.
Results: Differentiation of iPSC into BMEC yields a cell type with distinctive cellular structures (tightly packed, cobblestone morphology, proper organization of tight junctions), appropriate marker expression (transporters: GLUT1, CD98hc and efflux/influx proteins: BCRP, P-gp, MRP1, transferrin receptor), and functional assay performance (effective barrier formation, low permeability). These features separate BMEC from other vascular endothelial cells lining peripheral blood cells. iPSC-derived pericytes shows a characteristic stellate morphology, appropriate marker expression, and phagocytosis function. Establishment of a reliable BBB model required optimization of media and supplements to enable long-term survival of all three cell types in co-culture and to promote high transendothelial electrical resistance (TEER) signal in assays using Transwell inserts. Preliminary data shows the possibility of integrating this cellular BBB system with emerging organ-on-a-chip (OoC) technologies and other 3D culture platforms.
Conclusions: FCDI succeeded in establishing a fully human iPSC-derived BBB model, manufacturing a consistent supply of cells at-scale, and cryopreserving the material for subsequent on-demand use.

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P1027 / #605

POSTERS: E07. ANIMAL MODELS

MORPHOLOGICAL AND FUNCTIONAL ALTERATIONS OF PLATELETS FROM TRANSGENIC APP23 MICE AT EARLY ALZHEIMER DISEASE STATE

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Aims: Deposits of Aβ in brain parenchyma and cerebral vessels are the pathological hallmarks of Alzheimer's disease (AD). Recently, we demonstrated that aged Alzheimer transgenic mice (APP23) have pre-activated platelets in blood and enhanced integrin activation upon agonist stimulation compared to aged control mice. To investigate initial changes of platelets in these mice we analyzed platelets from middle-aged transgenic APP23 mice, which already have amyloid pathology in the brain parenchyma, but still no vascular amyloid deposits.
Methods: FACS analysis and *in vitro/ in vivo* platelet function in middle-aged APP23 mice at the age of 8 to 10 month.
Results: Middle-aged transgenic APP23 mice had unaltered platelet count, platelet size and glycoprotein expression comparable to control mice. However, transmission electron microscopy analysis showed a significantly increased number of dense granules. The number of α-granules was increased only by trend using platelets from middle-aged APP23 mice compared to wild-type controls. Secretion of α- and dense-granules was increased selectively upon stimulation with CRP (collagen related peptide) that stimulates the major platelet collagen receptor glycoprotein (GP) VI. Additionally, we observed enhanced CRP-triggered aggregation of platelets from middle-aged APP23. Flow chamber experiments revealed increased thrombus formation on collagen at high shear rates (1.700 sec-1) *ex vivo* but unaltered formation of thrombi under moderate shear of 1000 s^{-1}. However, the release of vWF from platelet granules as well as binding to its receptor GPIb was unaltered in APP23 transgenic platelets.
Conclusions: APP23 transgenic mice show morphological and functional alterations of platelets before vascular amyloid plaques develop in these mice indicating that platelet changes in aged APP23 mice are not only the result of vascular Aβ deposits. Thus, anti-platelet therapy of AD has to start as early as possible.

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P1028 / #1223

POSTERS: E07. ANIMAL MODELS

IDENTIFYING METABOLIC AND VASCULAR CONTRIBUTIONS TO NEURODEGENERATION USING A NEW PRECLINICAL MODEL FOR ADRDS

Kristen Onos[1], Juan Antonio Chong Chie[2], Olivia Marola[1], Kelly Keezer[1], Phillip Bohn[3], Amanda Bedwell[4], Kierra Eldridge[4], Scott Persohn[4], Michael Sasner[1], Jennifer Whitesell[3], Julie Harris[3], Paul Salama[2], Gareth Howell[1], Paul Territo[4]
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Aims: OBJECTIVES: Since the majority of Alzheimer's and related dementia (ADRD) cases consist of multiple pathologies, new preclinical models and techniques are needed. Here, we highlight the utility of the WSB/EiJ (WSB) genetic context combined with genetic risk factors that drive amyloid pathology for identification of early metabolic, inflammatory, and vascular contributors to neurodegeneration. We assessed this via a novel mouse vascular pathology analysis (MVP) combined with translational PET/CT of perfusion and metabolism to generate a complete model of neurovascular uncoupling.
Methods: METHODS: To assess differences in brain vasculature, 8-month male and female WSB.*APP/PS1* and WT WSB mice were perfused with fluorescent gelatin. Amyloid was visualized by injecting WSB.*APP/PS1* with methoxy-X04 24-hours prior to harvest. Images were reconstructed and vessel morphology was measured using MVP. PET/CT was performed on an additional cohort, and plasma collected for measurements of neurofilament (NFL) and metabolic hormones.
Results: RESULTS: Based on MPV, WSB.*APP/PS1* have significantly greater vascular volume compared to WT WSB, which was driven by an increase in capillary surface area. PET/CT imaging with ^{64}Cu-PTSM and ^{18}F-FDG indicated that female WSB.*APP/PS1* mice showed the greatest number of brain regions significantly different from WT WSB, while male WSB.*APP/PS1* showed regions that were uncoupled: FDG and PTSM signal were opposite within the same region. Higher levels of NFL were detected in female WSB.*APP/PS1*. These differences may be indicative of a sex-difference in the progression or vulnerability to neurodegeneration.
Conclusions: CONCLUSIONS: This work combines translational imaging methods with a novel way to visualize and quantify the mouse brain vasculature in a new preclinical mouse model. Ongoing work is incorporating humanized risk alleles such as humanized APOE$^{4/4}$ and humanized amyloid beta into the WSB genetic context.

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P1029 / #1764

POSTERS: E07. ANIMAL MODELS

FUNCTIONAL RECOVERY CAUSED BY HUMAN ADIPOSE TISSUE MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES ADMINISTERED 24H AFTER STROKE IN SPONTANEOUSLY HYPERTENSIVE RATS

Francieli Rohden[1], João Moreira[1], Jerônimo Neto[1], Luis Bernardi[1], Nicolly Paz[1], Luciele Teixeira[2], Samanta Gundel[3], Karina Paese[3], Fernanda Oliveira[4], Elizabeth Lima[4], Fátima Guma[5], Diogo De Souza[1]
[1]Federal University of Rio Grande do Sul, Biochemistry, Prédio anexo, lab, Brazil, [2]Intituto de Cardiologia de Porto Alegre, Centro De Cardiologia Experimental, Porto Alegre, Brazil, [3]Federal University of Rio Grande do Sul, Faculdade De Farmácia, Porto Alegre, Brazil, [4]Hospital de Clínicas de Porto Alegre, Reproductive and Cellular Pharmacology Laboratory,, Experimental Research Center, Porto Alegre, Brazil, [5]Federal University of Rio Grande do Sul, Biochemistry, Prédio anexo, Brazil

Aims: To analyze whether there is a neuroprotective effect of extracellular vesicles (EV) secreted from human mesenchymal stem cells isolated from adipose tissue (hAT-MSC) in a focal permanent ischemic stroke (IS) model, being an innovative proposal and non-invasive therapeutic intervention with a wide time window.
Methods: Methods: Wistar Kyoto Rats and Spontaneously Hypertensive Rats (SHR), male and female (~120 days) were subjected to focal permanent ischemic stroke (IS), 24 hours after, were treated intranasally with extracellular vesicles (EV), 500 µg/kg, secreted from human mesenchymal stem cells isolated from adipose tissue (hAT-MSC) and we analyzed front paws symmetry (Cylinder Task).
Results: Results: For SHR rats, we can observe that the outcome of ischemia induction is very different and with a chronic effect and without spontaneous recovery in the symmetry of the forepaws in both genders. When treated with EVs, SHR females show improvement in the symmetry of the front paws, whereas the male animals do not fully recover, they average 50% symmetry until the end of the experiment. (Fig 01).

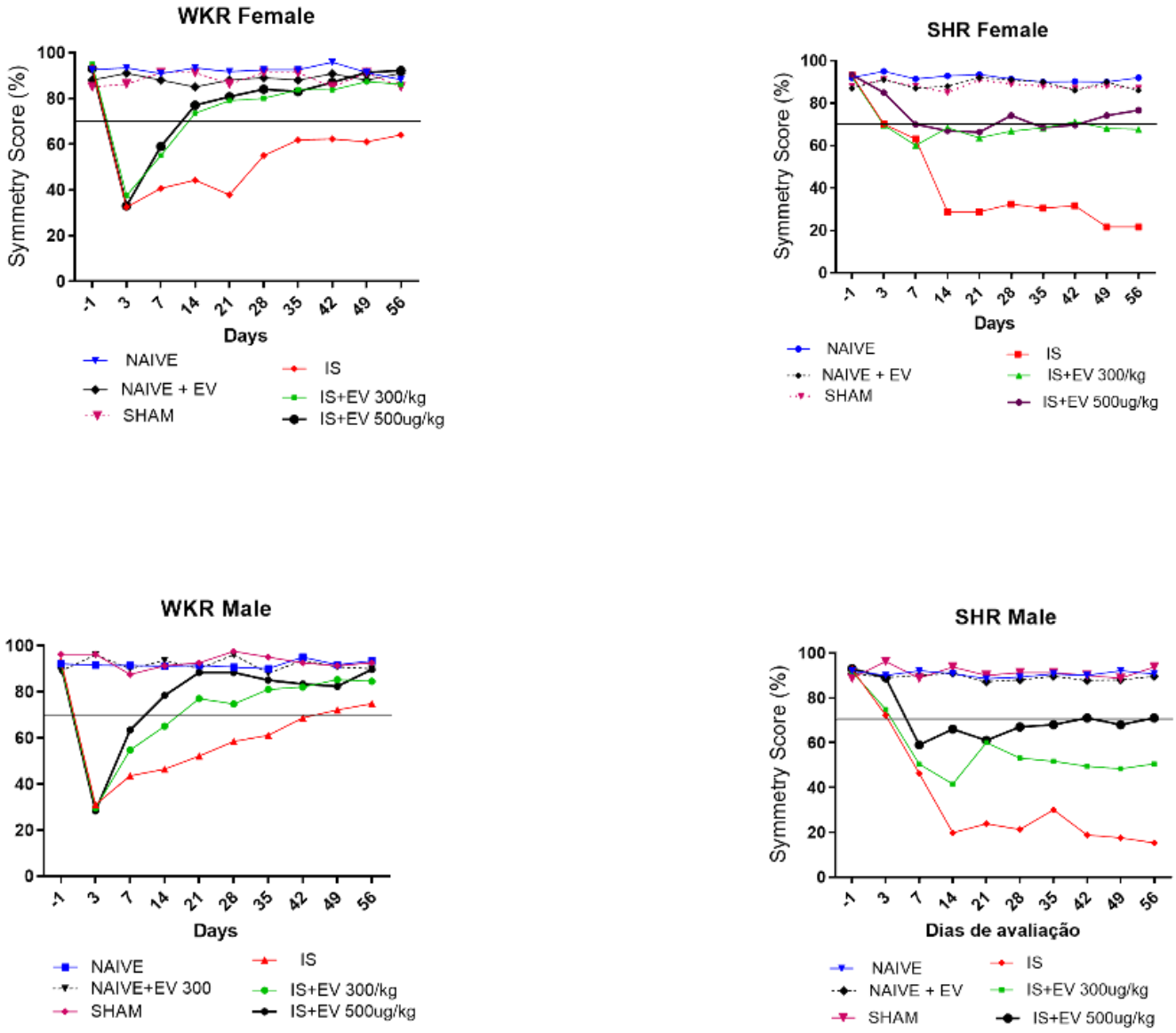

Fig 01: Effect of IS and EV treatment on front paws symmetry.
Conclusions: Conclusions: In line with these findings, our work highlights hAT-MSC-derived EVs as a promising therapeutic strategy for stroke. Although the neuroprotective effect of male SHR was not the same compared to female WKR and SHR, but prevented them from becoming completely asymmetrical.

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P1030 / #855

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

EVIDENCE FOR PRE EXISTING SUBSTRAIN DIVERSITY IN A BIOLOGICALLY CLONED PRION STRAIN

Jason Bartz, Tess Gunnels, Taylor York, Alyssa Block, Ronald Shikiya
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Aims: Prions are comprised of PrP^{Sc}, the prion disease specific conformation of the host encoded prion protein, PrP^{C}. Prion strains are operationally defined by heritable differences in the phenotype of disease under controlled transmission conditions and are encoded by strain-specific structures of PrP^{Sc}. In natural prion disease, mixtures of prion strains are known to exist. In experimental settings, multiple lines of evidence suggest that rodent-adapted biologically cloned prion strains exist as a mixture of a dominant strain and minor substrains. Consistent with this hypothesis, in experimental settings, a dominant prion strain can suppress, but not entirely eliminate, the replication of a minor strain. While it is hypothesized that prions may exist as a quasispecies, a mixture of similar, but not identical, conformations of PrP^{Sc}, direct biochemical evidence for the presence of substrains is lacking.
Methods: To examine if selective reduction of dominant strain replication can reveal preexisting substrains from a single biologically-cloned prion strain, we reduced the abundance of the dominant strain PrP^{Sc} using two distinct biochemical methods.
Results: Here we show that as replication capacity of the dominant strain diminishes, the suppressive effect also diminishes allowing for the emergence of a substrain in experimentally mixed strain populations. Reduction of the suppressive pressure of the dominant strain allowed for emergence of PrP^{Sc} that differs from the parental strain. This material is infectious and has strain properties that are distinct from the parental strain.
Conclusions: Overall, these data indicate that prion strains contain a mixture of a dominant strain and substrains that has implications for prion drug resistance, zoonotic potential and prion evolution.

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P1031 / #767

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

THE CELLULAR PRION PROTEIN AS A POTENTIAL RECEPTOR IN NEURODEGENERATIVE DISEASES

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Aims: Neurodegenerative diseases such as Alzheimer´s disease (AD) or Parkinson´s disease (PD) are related with the accumulation of aggregated proteins. These diseases showed phenotypic diversity and propagation of pathology that is reminiscent of prion diseases. It is proposed that amyloid-β, alpha synuclein, and tau proteins share common structural, biological, and biochemical features, as well as similar mechanisms of aggregation and self-propagation like prions. Propagation of protein misfolding in these diseases may therefore occur via mechanisms similar to those underlying prion pathogenesis. Here, we focused on the cellular prion protein (PrPC) as a potential receptor for misfolded proteins in prion-like diseases, supporting interaction and internalization of each other.
Methods: To investigate a possible direct interaction we used recombinant human PrPC as well as recombinant misfolded proteins (Tau, aSyn) for surface plasmon resonance spectroscopy (SPR). SH-SY5Y (SHWT) and stable PRNP transfected SH-SY5Y PrP (SHPrP) cells were treated with different recombinant misfolded proteins under same conditions.
Results: We observed the effect of PrPC on the internalization of misfolded proteins and the interaction between PrPC and misfolded proteins. SPR results presented misfolded proteins as direct interaction partners of PrPC. SHPrP cells showed a significantly higher amount of internalized misfolded proteins compared to SHWT cells.
Conclusions: Based on our results PrPC could be a receptor for prion-like diseases, which is promoting the internalization and interaction of each other. This could contribute to a better understanding of the pathological mechanism in neurodegenerative diseases, which is important for future diagnostics or therapies.

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P1032 / #518

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

INVESTIGATING NEUROTOXICITY AND CONFORMATION-DEPENDENT SPREADING OF PROTEIN AGGREGATES IN VIVO

Annika Hornberger[1], Joana Petushi[1], Lech Kaczmarczyk[2], Emiel Michiels[3,4], Lisa Maag[1], Frederic Rousseau[3,4], Joost Schymkowitz[3,4], Joachim Degen[5], Walker Jackson[2], Ina Vorberg[1,6]
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Aims: Proteinopathies like Alzheimer's disease involve the deposition of toxic, disease-associated protein aggregates that spread to disease-specific brain regions. In this study we investigated if this neurotoxicity is caused by the protein aggregates per se or by the protein's loss of function. Further, we examined if structural differences of amyloid fibrils influence their spreading behavior in the brain.
Methods: We created a knock-in mouse that expresses the prion-like domain NM of the yeast prion protein Sup35. Two conformationally distinct NM fibril species were injected into the hippocampus of transgenic mice. 11 months post injection, memory function was assessed in various cognitive behavioral tests. After 12 months, mouse brains were analyzed for NM aggregation, spreading, and neurodegeneration.
Results: Fibril conformers seeded NM aggregation in the brain with different kinetics within one month post injection. NM pathology spread to anatomically connected brain regions in a prion-like manner during that time. After 12 months, fibril-injected mice showed mild cognitive decline with no overt phenotype. While the amount of protein deposits in the brain strongly increased over time, spreading occurred without obvious regional selectivity for the different fibril conformers. Fibril injection resulted in degeneration of the ipsilateral CA1 region and whole hippocampus close to the injection site and moderate neuroinflammation.
Conclusions: Our data demonstrate that cytosolic NM aggregates spread along functionally connected routes. The fact that artificially expressed NM lacks any function argues for a toxic gain-of-function of intracellular protein aggregates.

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P1033 / #1733

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

A CASE OF CREUTZFELDT-JAKOB DISEASE ACCELERATED BY COVID-19.

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[1]Military Institute of Medicine, Clinic Of Neurology, Warsaw, Poland, [2]Military Institute of Medicine, Department Of Radiology, Warsaw, Poland

Aims: We report the case of a 68-year-old man with a fulminant CJD evolution associated with SARS-CoV-2 infection, which led to patient death after 6 weeks from first symptoms of the CJD (neurocognitive decline and cortical function deficits).
Methods: A case report with literature discussion.
Results: Our case supports that CJD with SARS-CoV-2 coinfection could be characterized by an accelerated evolution, and how the diagnosis might be more challenging due to concomitant symptoms of COVID-19.
Conclusions: We hypothesize that systemic immune response in COVID-19 could probably accelerate the clinical course of CJD, however, a potential causal link remains unclear.

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P1034 / #2349

POSTERS: F04. IMAGING, BIOMARKERS, DIAGNOSTICS

ULTRASOUND-GUIDED DRY NEEDLING CAN EFFECTIVELY MUSCLE TREMOR ASSOCIATED WITH POSTURAL IMBALANCE, MUSCLE TRIGGER POINTS

Rostyslav Bubnov[1], Lev Kalika[2], Pablo Herrero Gallego[3]
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Aims: Muscle tremor and twitch can appear due to chronic muscle overload and local energy deficit due to posture imbalance. Dry needling under ultrasound guidance (DN-US) can treat myofascial pain, restore muscle function and motion and therefore can be helpful in particular cases of tremor. **Aim** was to evaluate the relevance of DN-US for muscle tremor associated with muscle trigger points (MTrPs) and posture imbalance.
Methods: This study includes 16 patients with signs of tremor and fasciculations in various sites: thigh (7); leg (6); ankle (3); arm (2); hand (4)б associated with long conditions of poor posture positions. All patients were considered for individualized treatment by DN-US protocol by R. Bubnov [https://doi.org/10.1186/1878-5085-3-13].
Results: All patients reported decreasing on tremor in daily life and during professional activities. ***Case presentation:*** Violin player 28 years old had experienced tremor in biceps brachii muscle and arm during professional activity (few minutes of play). Exam included modeling a situation of posture with exertion similar to violin play, tremor appeared 15 sec after; after treatment 5 min of testing did not evoke tremor. Posture restored in shoulder, pelvis, spine; muscle motility restored on US: in supinator, shoulder rotators muscles, etc. Biceps brachii muscle demonstrated spasticity, targeted needle was not key in resolving case, evoked minor LTR short effect.
Conclusions: Inactivating MTrPs and correcting posture has a critical role in alleviating tremor in various sites. Muscle performance depends on muscle overload during exertion. Further research needed for for underlying mechanics, like small fibers neuropathy, muscle ischemia and other related phenomena for appropriate patient stratification on symptoms of tremor.

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P1035 / #2396

POSTERS: F04. IMAGING, BIOMARKERS, DIAGNOSTICS

DISCOVERY OF POTENTIAL BIOMARKERS IN NEURODEGENERATIVE DISEASES IN BODY FLUIDS BY SINGLE MOLECULE ARRAY (SIMOA)

Sezgi Canaslan Eyyuboglu, Matthias Schmitz, Inga Zerr
Universitätsmedizin Göttingen, Neurology, Göttingen, Germany

Aims: The importance of biomarkers for the differential diagnosis of neurodegenerative diseases is undeniable. They are not only helpful for the diagnosis of the disease but also be quite useful to track disease progression and the efficiency of the possible treatments. Then, we have decided to further investigate potential biomarkers in our cohort including patient groups and controls.
Methods: Samples were taken from the biobank of Universitätsmedizin Göttingen. Because a small change in the protein concentration can be specific for a certain diagnosis, we have measured the concentration of target proteins using the ultra-sensitive assay. To detect these changes, we have established the ultrasensitive Single Molecule Array (SIMOA) method which is able to detect protein concentration in femtomolar amount instead of colorimetric ELISAs which are less sensitive. The underlying reason for its ultra-sensitivity is that target proteins are grabbed with capture antibody-coated microscopic magnetic beads and the machine has the ability to detect every single signal coming from the bead-antibody-target complex.
Results: We have analyzed the level of some potential biomarkers including Neurofilament-light, Glial Fibrillary Acidic Protein, Ubiquitin carboxy-terminal hydrolase L1 in body fluids from patients with neurodegenerative diseases in comparison to healthy individuals. We observed an increase in some biomarkers in prion disease.
Conclusions: Our findings showed that regulation of some biomarker proteins can be helpful for the diagnosis and the differentiation of the neurodegenerative diseases.

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P1036 / #413

POSTERS: F04. IMAGING, BIOMARKERS, DIAGNOSTICS

THE DIAGNOSTIC PERFORMANCE OF REAL-TIME QUAKING-INDUCED CONVERSION ASSAY USING A SMALL-SCALE WORKFLOW

Poosanu Thanapornsangsuth[1,2], Adipa Chongsuksantikul[2], Akarin Hiransuthikul[3], Abhinbhen Saraya[1,2], Thiravat Hemachudha[1,2]
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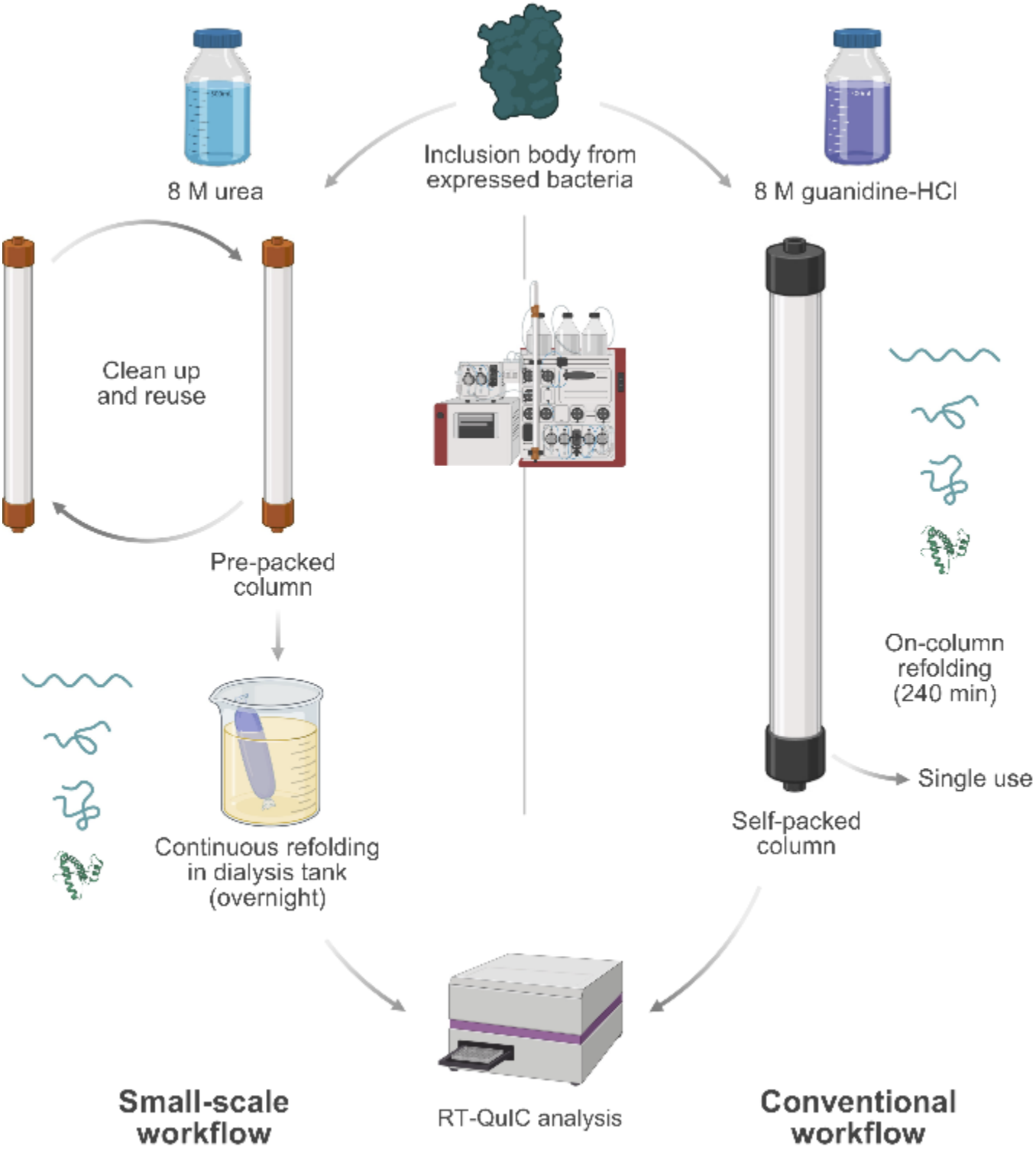
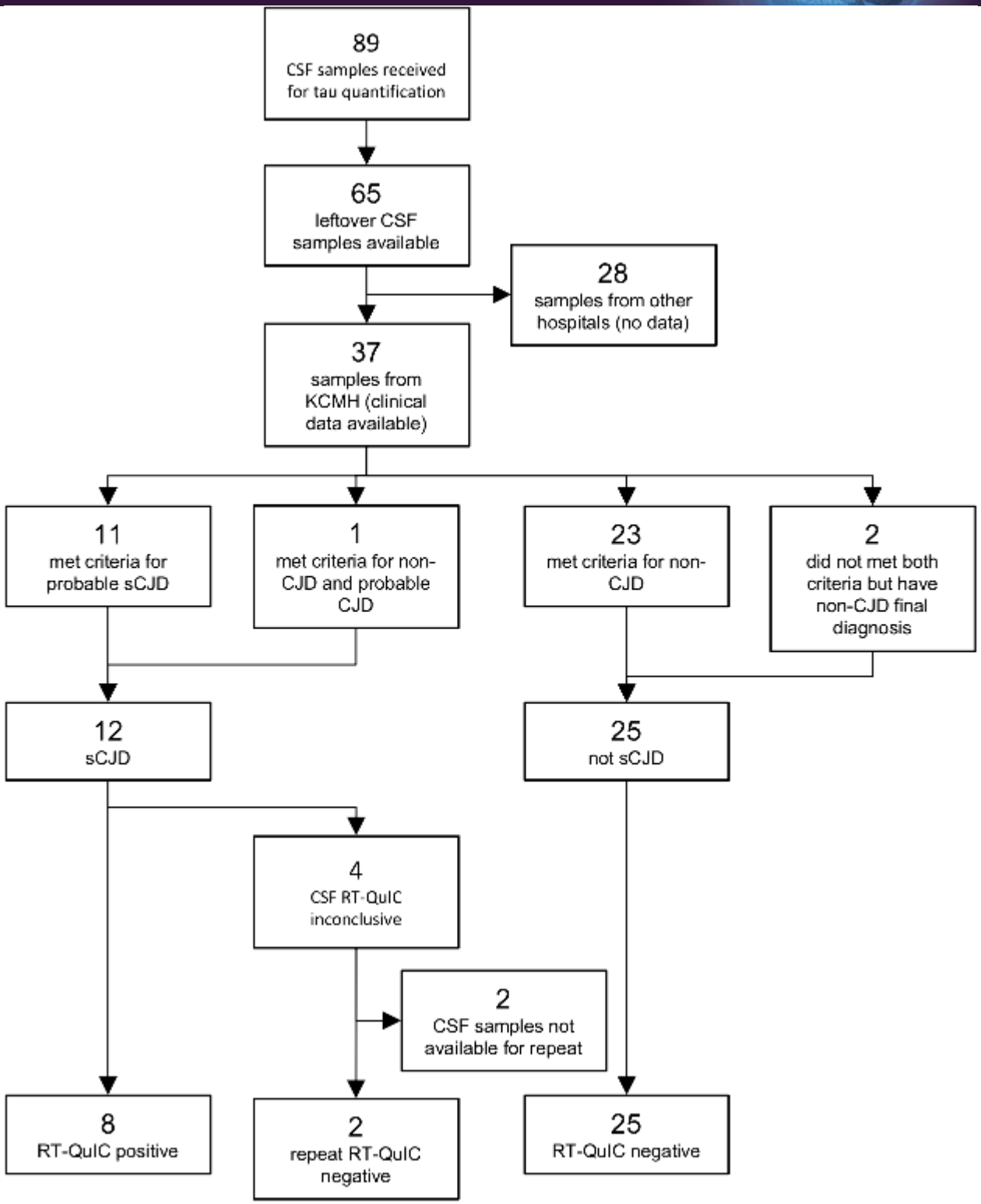
Aims: The lack of a dedicated surveillance program for prion disease, particularly in low- and middle-income countries (LMICs), has hindered the global effort to tackle this public health threat. Due to its cost and technically demanding procedure, there are great challenges in accessing real-time quaking-induced conversion (RT-QuIC) in most LMICs. This study aims to evaluate the performance of RT-QuIC using an adaptive substrate production technique that can be produced on a small scale.
Methods: Participants whom prion disease was suspected were consecutively enrolled between October 2015 and April 2022. Clinical data and cerebrospinal fluid (CSF) were evaluated. Participants were classified as probable sporadic Creutzfeldt-Jakob disease (sCJD) and non-sCJD using the Zerr's criteria (2009). RT-QuIC was performed using a recombinant truncated hamster prion protein substrate which can be done in small-scale production. The specificity and sensitivity for diagnosing probable sCJD were
assessed.



Results: Thirty-five participants were included in the analysis: 10 had probable sCJD and 25 had non-prion disorders. Median (IQR) age was 67 (59-71) years and 14 (40%) were female. Among 10 sCJD cases, RT-QuIC was positive in 8 (80%) and inconclusive in 2 (20%) – both had negative results after a repeated test. All 25 non-prion disorder cases had negative results. The sensitivity and specificity for detecting sCJD were 0.80 (95%CI 0.49-0.94) and specificity 1.00 (0.87-1.00),



respectively.

Conclusions: A small-scale production RT-QuIC can be performed with great performance in LMICs. Further studies on the optimization to meet the standard laboratories' diagnostic performance are warranted to increase the uptake of surveillance programs for prion disease in LMICs.

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P1037 / #2526

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

WIDESPREAD SELENIUM, SODIUM, AND POTASSIUM ALTERATIONS IN THE HUNTINGTON'S DISEASE BRAIN

Melissa Scholefield[1], Jingshu Xu[2], Stefano Patassini[2], Sasha Philbert[1], Stephanie Church[1], Garth Cooper[1,2]
[1]University of Manchester, Division Of Cardiovascular Sciences, Manchester, United Kingdom, [2]University of Auckland, School Of Biological Sciences, Auckland, New Zealand

Aims: Although there is some evidence of metallomic dysregulation in Huntington's disease (HD), studies investigating multiple essential metals across multiple regions of the HD brain are lacking. This study aimed to quantify the concentrations of eight essential metals and selenium in 11 regions of the HD brain and to compare findings with those previously identified in Alzheimer's disease (AD), vascular dementia (VaD), and Parkinson's disease dementia (PDD).
Methods: Inductively coupled plasma mass spectrometry (ICP–MS) was performed on nine HD cases vs nine controls to identify case–control differences in levels of sodium, magnesium, potassium, calcium, manganese, iron, copper, zinc, and selenium across 11 different brain regions, as well as sodium/potassium ratios (Na/K). Non-parametric Mann–Whitney U tests were used to determine case–control differences. Findings in HD were compared to those previously observed in AD, VaD, and PDD.
Results: Selenium was significantly decreased in every single investigated region of the HD brain compared to controls and Na/K ratios were increased in every region except the substantia nigra. More localised alterations in calcium (increased), manganese (decreased), iron (decreased), copper (decreased), and zinc (increased) were also present. Compared to other dementias, HD showed much more widespread perturbations in selenium and Na/K, but fewer brain regions showed copper or manganese changes.
Conclusions: Diminished cerebral selenium levels are widespread in HD and may indicate a reduction in antioxidative ability in the brain. Increased Na/K ratios may be indicative of mitochondrial dysfunction and a resultant decrease in energy production. Although the specific metallomic alterations appear to vary across different dementias, the perturbations present seem to indicate shared mechanisms of oxidative stress and mitochondrial dysfunction.

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P1038 / #2775

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ENERGY METABOLISM DEFICITS IN MICE WITH CONDITIONAL TRKB DELETION FROM STRIATOPALLIDAL NEURONS

Mohd Yaseen Malik, Kerstin Timm, Liliana Minichiello
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Aims: Objective: To explore the role of brain-derived neurotrophic factor (BDNF) signalling in mitochondrial and metabolic homeostasis by conditional deletion of its receptor tropomyosin receptor kinase B (Trkb) from striatopallidal medium spiny neurons.
Methods: Methods: High-resolution respirometry Oxygraph-2k (O2k, Oroboros Instruments, Austria) was used to analyse the various components of the mitochondrial respiratory chain in the striatal tissue homogenates of *Trkb* knock-out mice and wildtype littermates at 3 and 8 months of age. DatLab software 7.4 was used to record real-time oxygen concentration (µM), as well as oxygen flux per tissue mass *(pmol.O2 s−1.mg−1*).
Results: Results: We report a substantial decrease in all major respiratory states of the oxidative phosphorylation and electron transport system in the striatum of Trkb knock-out mice as compared to the wildtype littermates at young ages (3 months), which proceeds to exacerbate with the advanced age (8M) similar to what is seen in HD [1]. 1. Hum Mol Genet:17(20):3144-53, (2008)
Conclusions: Conclusions: Dysregulation of metabolism is known to be an underlying factor in several neurodegenerative diseases, such as Huntington's disease (HD) and others [2]. BDNF is an important regulator of striatal neuron survival and maintenance. Previously we have highlighted the role of BDNF-TrkB signalling in the inhibitory control over locomotor activity in mice. We have shown that impairing this signalling by conditional deletion of its receptor, Trkb, from striatopallidal medium spiny neurons leads to the development of gait abnormalities and age-dependent spontaneous hyperlocomotion [3]. Thus, this study highlights the role of BDNF-TrkB signalling in energy metabolism homeostasis and how its impairment could lead to the onset of motor dysfunction and neurodegenerative diseases such as HD. 2. Cell Rep 30(2332–2348):e2310, (2020) 3. Nature Communications *4*: 2031, (2013)

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P1039 / #599

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

CHARACTERIZATION OF A NOVEL CSF1R T567M MUTATION IN ADULT-ONSET LEUKOENCEPHALOPATHY WITH AXONAL SPHEROIDS AND PIGMENTED GLIA (ALSP)

Haitao Tu[1], Adeline Ng[2], Jayne Tan[2], Weng Khong Lim[3], Eng-King Tan[2], Li Zeng[1]
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Aims: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an autosomal-dominant central nervous system white-matter disease. ALSP is caused by mutations in the colony stimulating factor 1 receptor (*CSF1R*) gene, which is the receptor for *CSF1*, a cytokine controlling the production, differentiation, and function of macrophages. To date, all identified pathological mutations were found to be within the tyrosine kinase domain (TKD) of CSF1R. However, the pathological function and mechanism of the CSF1R in the ALSP disease is still unknow. Here, we report that a novel pathological heterozygous point mutation CSF1R T567M, which is outside of TKD, was identified in an ALSP patient's genome. We aim to characterize the molecular function of the CSF1R T567M mutation *in vitro and* patient iPSC-derived neurons and astrocytes.
Methods: We examined the effects of the CSF1R T567M mutation in protein expression, autophosphorylation, different neuropathological pathways, stress responses, and localization in CSF1R T567M mutation overexpressing neuroblastoma cells and patient-derived neurons and astrocytes.
Results: Functional characterization reveals that auto-phosphorylation of CSF1R was partially impaired specifically at Try546. Mitochondrial function was affected and microglial cell function was suppressed in the T567M neuroblastoma cells. Under ER and oxidative stress, cell survival of CSF1R-T567M was decreased. ER and oxidative responsive pathways were also triggered in the CSF1R-T567M overexpressing cells. We found that under ER stress, post-translational modification was altered by the T567M mutation and CSF1R entered nucleus. Interestingly, similar findings were also observed in patient iPSC-derived neuronal cells.
Conclusions: The functional characterization of CSF1R and the T567M mutation suggests that post-translational modification and nuclear localization of CSF1R may be important in CSF1R-induced pathogenesis of ALSP, which implies the pathological function of CSF1R other than the tyrosine kinase activity.

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P1040 / #1414

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

LRRK2R1628P VARIANT CONTRIBUTES TO PD PATHOGENESIS BY AFFECTING OXIDATIVE STRESS AND ER STRESS.

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Aims: Objectives: Leucine-rich repeat kinase 2 (*LRRK2*) R1628P variant is a well-recognized PD risk factor in Asian populations. So far, the pathological mechanisms of $LRRK2^{R1628P}$ variant in PD remain uncertain. Oxidative stress and endoplasmic reticulum (ER) stress have been implicated in LRRK2 pathogenesis.
Methods: Methods: $LRRK2^{WT}$ and $LRRK2^{R1628P}$ primary fibroblast cells were subjected to either vehicle, H_2O_2 (oxidative stress), or Thapsigargin (TG) (ER stress) for short-term (1 hour) and long-term (24 hours). Subsequently, biochemistry analysis was carried out.
Results: Results: Here we showed a significant increase in LRRK2 protein in the $LRRK2^{WT}$ group after H_2O_2 treatment but not in $LRRK2^{R1628P}$ group. $LRRK2^{R1628P}$ didn't alter the LRRK2 kinase activity and attenuated p-Rab10 increase caused by H_2O_2 treatment compared to $LRRK2^{WT}$. Apoptotic protein cleaved caspase 3 (CC3) levels was found to be diminished after long-term H_2O_2 treatment in $LRRK2^{R1628P}$ group but not true for $LRRK2^{WT}$ cells. An increase in p-AKT was detected in $LRRK2^{R1628P}$ cells after long-term H_2O_2 treatment but not in $LRRK2^{WT}$ cells. A significant increase in LRRK2 was observed in $LRRK2^{WT}$ group with short-term Thapsigargin (TG) treatment, after which LRRK2 levels were found to be decreased considerably (upon long-term TG treatment), but not in $LRRK2^{R1628P}$ group. $LRRK2^{R1628P}$ also attenuated p-Rab10 increase caused by TG treatment compared to $LRRK2^{WT}$ group. The change of p-ERK expression caused by H_2O_2 treatment, along with p-eIF2α and CHOP caused by TG treatment, was similar between $LRRK2^{R1628P}$ and $LRRK2^{WT}$.
Conclusions: Conclusion: Our data indicate that $LRRK2^{R1628P}$ inhibits LRRK2 expression and kinase activity caused by oxidative stress and ER stress and enhance cell response to oxidative stress in mouse primary fibroblast cells while endoplasmic reticulum stress pathway is unaffected.

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P1041 / #674

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

DOWNREGULATION OF BILIVERDIN REDUCTASE-A (BVR-A) IMPAIRS BRAIN ENERGY METABOLISM IN RESPONSE TO INSULIN: A NOVEL MECHANISM LINKING ALZHEIMER'S DISEASE (AD) AND TYPE-2 DIABETES MELLITUS (T2DM).

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Aims: Brain insulin resistance (bIR) is associated with failure of cell energy metabolism, synaptic loss, and ultimately neurodegeneration both in AD and T2DM. We previously reported that BVR-A is a key regulator of insulin signaling while BVR-A downregulation is an early event triggering bIR development in AD. Hence, we hypothesized that reduced BVR-A levels link bIR and mitochondrial defects resulting in AD-like neuropathology in T2DM.
Methods: Hippocampal samples from WT and the goto-kakizaki (GK) model of T2DM rats (6 months, n=8/group) were characterized for brain alterations including: bIR, redox metabolism, mitochondrial functions, mitochondrial unfolded protein response (UPRmt), autophagy, and AD hallmarks. These data were correlated with peripheral metabolic measurements (fasting glucose, insulin, and OGTT) and cognitive tasks (spatial memory). The role of BVR-A was confirmed by using BVR-A KO mice (n=8-10/group). Additional mechanistic insights were gained by evaluating mitochondrial functions (sea-horse) and the above-mentioned intracellular pathways in response to insulin, in neuronal cells lacking BVR-A.
Results: GK rats show impaired spatial memory. Reduced BVR-A levels along with an impairment of insulin signaling (not yet bIR) resulting in the hyper-activation of GSK3β in GK rats hippocampus was observed. Hyperactive GSK3β accumulates in the mitochondria fostering their dysfunction. As result, alterations of cell redox metabolism and the activation of UPRmt occur. Similar alterations in BVR-A KO mice and neuronal cells lacking BVR-A were observed, reinforcing the role of BVR-A in regulating mitochondrial bioenergetics in response to insulin.
Conclusions: These results suggest that early BVR-A loss triggers bIR, the hyper-action of GSK3β and mitochondrial stress in the T2DM brain. bIR-associated impairment of mitochondrial functions is driven by the hyper-active GSK3β. These alterations lead to impaired brain energy metabolism and the development of AD-like neuropathology in T2DM

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P1042 / #882

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

OPTIMIZATION AND VINYL SULFONE DERIVATIVES AS POTENT NRF2 ACTIVATORS FOR PARKINSON'S DISEASE THERAPY

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Aims: We previously developed a novel series of vinyl sulfones as nuclear factor erythroid 2-related factor 2 (Nrf2) activators with therapeutic potential for Parkinson's disease (PD). Among the synthesized compounds, **17e** was the most promising drug candidate with good druglike properties. Compound **17e** showed superior effects on Nrf2 activation in cell-based assays compared to compound **1** (**17e**: half-maximal effective concentration (EC_{50}) = 346 nM; **1**: EC_{50} = 530 nM). Compound **17e** was further confirmed to induce expression of Nrf2-dependent antioxidant enzymes at both mRNA and protein levels. In a MPTP-induced mouse model of PD, **17e** significantly attenuated loss of tyrosine hydroxylase-immunopositive dopaminergic neurons, suppressed microglial activation, and alleviated PD-associated motor dysfunction. Thus, **17e** is a novel Nrf2 activator with excellent drug-like properties and represents a potential therapeutic candidate for PD.
Methods: To a cooled anhydrous tetrahydrofuran solution (−78 °C) of phosphonate derivatives (4, 10, 16 and 22) was added 2 M n-BuLi solution in cyclohexane (1.1 equiv). The reaction mixture was stirred at −78 °C (1 h) and then the desired substituted benzaldehyde (1.1 equiv) was added at −78 °C.
Results: In the present study, we improved the druglike properties and Nrf2 activation potency of compound **1** by introducing morpholine and pyridine groups. Further examination of these compounds revealed that **17e** dose-dependently induced optimal Nrf2 activity, nuclear translocation, and related upregulation of antioxidant enzymes (HO-1, GCLM, and GCLC), as well as excellent druglike properties. In MPTPinduced PD mice, treatment with **17e** was neuroprotective, alleviating loss of DAergic neurons and preventing microglia activation. These effects were accompanied by improvement of movement ability.
Conclusions: In conclusion, **17e** represents a novel therapeutic agent with potential for treating PD.

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P1043 / #1979

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

SURGERY-INDUCED COMPLEMENT C3 FROM ASTROCYTES CONTRIBUTES TO SUSTAINED ACTIVATION OF MICROGLIA

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Aims: Surgery induced systemic inflammation can inflict astroglial activation which contributes to the onset of neuroinflammation and cognitive impairment. However, the pathogenic mechanism of how systemic inflammation can trigger and sustain neuroinflammation in the central nervous system is still unknown. Recent reports have shown that aberrant activation of complement C3 plays an important role in the progress of neurological disorders. In this study, we aim to examine the role of astrocytic derived complement C3 in sustaining neuroinflammation and cognitive impairment during surgery.
Methods: Laparotomy was performed in 3-month-old male C57BL6/N mice. Novel object recognition test was performed from postoperative day 12 to day 14 to access cognitive function. Microglial and astrocytic activation were examined by immunofluorescence microscopy. Synaptic protein expressions were accessed by Western blot. Specific inhibition of C3 in CNS was achieved by intracerebroventricular injection of AAV9-C3shRNA.
Results: Laparotomy induced astroglial activation in the hippocampus with an increase of C3 in the astrocytes, but not in microglia. It was accompanied with the decrease of synaptic proteins and cognitive impairment. Furthermore, inhibition of C3 in the CNS by intracerebroventricular injection of AAV9-C3shRNA attenuated cognitive dysfunction and loss of synaptic proteins after laparotomy.
Conclusions: Taken together, our findings demonstrated that surgery induced C3 expression in astrocytes and it played significant roles in sustained activation of microglia and cognitive dysfunction. Our results suggest that C3 can be a therapeutic target for attenuating transmission of systemic inflammation to neuroinflammation. The work described in this presentation was partially supported by General Research Fund from the Research Grants Council (HKU 17100622).

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P1044 / #2153

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

FOSGONIMETON PROMOTES SURVIVAL AND REDUCES PROTEIN PATHOLOGY IN PRIMARY NEURON MODELS OF ALZHEIMER'S AND PARKINSON'S DISEASE.

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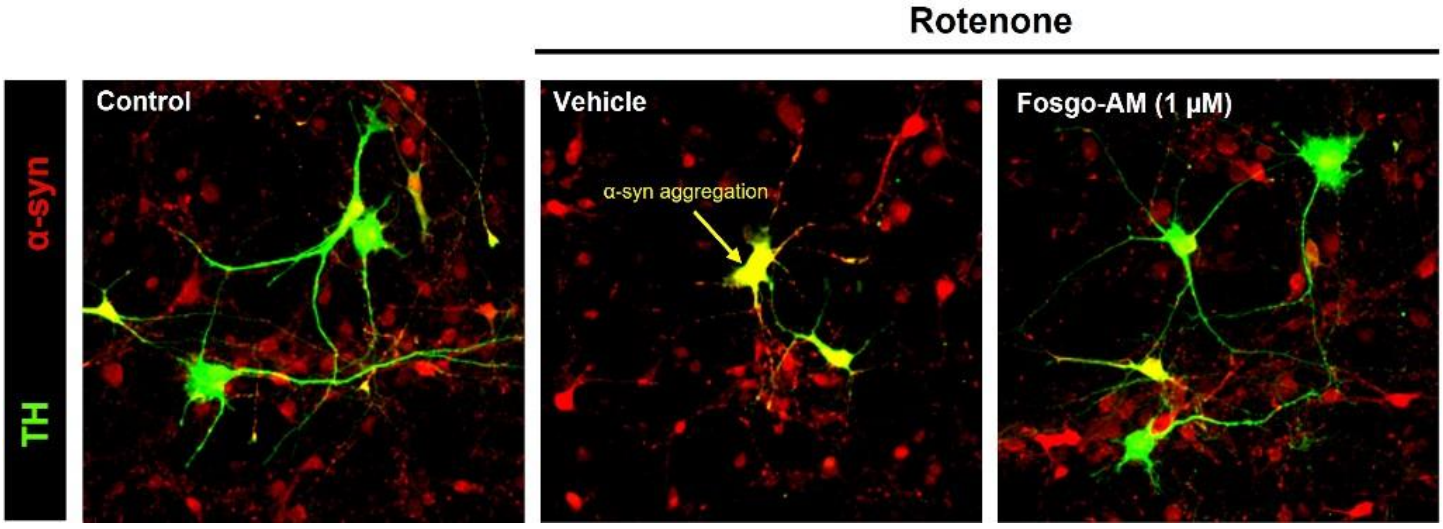
Aims: We have previously shown that fosgonimeton, a small molecule positive modulator of the hepatocyte growth factor (HGF)/MET system, exhibits neuroprotective, anti-inflammatory, and pro-cognitive effects in vitro and in vivo. Here, we investigate additional neuroprotective effects of fosgonimeton on pathological hallmarks of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD), including glutamate excitotoxicity, beta-amyloid toxicity, neurofibrillary tangle formation, alpha-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and neuronal loss.
Methods: Rat cortical neurons were challenged with beta-amyloid (Aβ1-42) or glutamate with or without the active metabolite of fosgonimeton (fosgo-AM), and immunostained for microtubule-associated protein-2 (MAP-2) and phospho-tau (AT100) to determine neuronal survival, neurite network integrity (total neurite length), and phospho-tau levels. Rat dopaminergic neurons were treated with fosgo-AM and subjected to 1-methyl-4-phenylpryidinium (MPP^+), 6-hydroxydopamine (6-OHDA), or rotenone. Co-immunostaining for tyrosine-hydroxylase and alpha-synuclein was performed to determine dopaminergic neuron survival, neurite network integrity, and alpha-synuclein aggregation. Effects of fosgo-AM on cell viability vs. H_2O_2-induced oxidative stress and lipopolysaccharide (LPS)-induced neuroinflammation were also assessed via Cell-Titer Glo.
Results: Fosgo-AM treatment significantly improved survival of cortical neurons, protected neurite networks, and reduced phospho-tau levels after injury with Aβ1-42 or glutamate. Similarly, fosgo-AM treatment significantly improved the survival of dopaminergic neurons, protected neurite networks, and reduced alpha-synuclein aggregation after injury with MPP^+, 6-OHDA, or rotenone. Furthermore, treatment with fosgo-AM rescued neuronal viability against H_2O_2-induced oxidative stress and LPS-induced
cytotoxicity.



Conclusions: We demonstrate the potential of fosgonimeton to mitigate neuronal damage and protein pathology induced by neurological insults central to AD and PD. Such neuroprotective effects of fosgonimeton, in addition to its neurotrophic activity, highlight its potential to address multiple modes of neurodegeneration, and modify clinical deterioration. Fosgonimeton is currently in clinical trials for AD and PD.

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P1045 / #1302

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

USING XGBOOST, CATBOOST AND LIGHTGBM TO FORECAST WEARING-OFF OF PARKINSON'S DISEASE PATIENTS

May Ouir, John Victorino
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Aims: Parkinson's Disease (PD) patients experience both motor and non-motor symptoms such as tremor, rigidity, sleep, speech, and mental health problems. Doctors and patients use Levodopa treatment to alleviate motor symptoms. They regularly evaluate the effectiveness of the treatment by monitoring motor symptoms. Doctors adjust the treatment to minimize the periods of symptom re-emergence. These "wearing-off" periods affect the patient's quality of life as these periods happen more frequently and the aim of this study is to forecast them using Gradient Boosting methods.
Methods: Previous work proposed using a fitness tracker's non-motor datasets and self-reported symptoms to detect and forecast wearing-off periods. Wearing-off detection model produced a balanced accuracy of at least 70% using gradient boosting and logistic regression. Forecasting the next hour's wearing-off was also explored using deep learning methods. With the recent popularity of XGBoost, CatBoost, and LightGBM, this study compares the performance of these gradient boosting methods in forecasting wearing-off for the same datasets.
Results: Our results showed that personalized models produced an average balanced accuracy of 66% across 10 participants. One patient's model reached 85% accuracy using CatBoost. This patient was assisted by a nurse while doing the symptom self-reporting. Regarding feature analysis, the last drug intake time was used mainly to forecast the next 30 minutes of wearing-off with CatBoost. On the other hand, XGBoost used sleep duration and step count to obtain similar performance. Finally, participants were clustered to train the models with more data. This approach showed promising results in some clusters.
Conclusions: Our results indicate that CatBoost is more accurate than XGBoost and LightGBM and that it is a promising method to predict wearing-offs alongside with group calibration.

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P1047 / #492

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

SELF-ASSEMBLED CYCLIC D, L-ALPHA-PEPTIDE INHIBITS TOXIC HTT AGGREGATIONS AND AMELIORATES BEHAVIORAL DEFICITS IN AN HUNTINGTON'S DISEASE MOUSE MODEL

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Aims: Aggregation of mutated huntingtin (mHtt) has been linked to neuronal atrophy, impaired motor coordination and cognitive dysfunctions in Huntington's disease (HD). The aim of this study was to target the aggregation of mHtt using HD models of Caenorhabditis elegans (C. elegans) and R6/2 mice. Self-assembled cyclic D, L-α-peptide nanotube CP-2 has been tested as a therapeutic agent to reduce impaired motor coordination and cognitive dysfunctions in a mouse model of HD.
Methods: Thioflavin T (ThT) and electron microscopy, as well as immunochemical methods, were used to study the effect of cyclic D, L-α-peptide CP-2 on HD-associated mHtt aggregation and toxicity. In vivo biodistribution and efficacy, experiments were performed in transgenic C. elegans and R6/2 mice, and a relevant battery of behavioral tests were performed.
Results: In ThT-based assays, CP-2 retarded the aggregation of mHtt and reduced its toxicity by decreasing the levels of mHtt oligomers. In the motility test, CP-2 improved movement in transgenic C. elegans overexpressing mHtt and reduced the amount of mHtt oligomers. Furthermore, three weeks of chronic treatment with CP-2 ameliorated the motor coordination in the ledge test, grip strength test, and in footprint analysis in R6/2 transgenic HD mice. The rotarod test did not however show significant improvement in CP-2 treated HD mice. Additionally, HD mice treated with CP-2 showed reduced anxiety in open field test as compared to vehicle-treated HD mice.
Conclusions: Targeting the pre-amyloid stage of mHtt aggregation could be a promising therapeutic strategy for HD.

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P1048 / #2006

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

INHIBITION OF TRMT2A, A PRIME TARGET TO CURE POLYGLUTAMINE DISEASES

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Aims: Genes causing polyglutamine (polyQ) diseases share expanded CAG stretches within the coding region, translated into expanded polyQ tracts in disease-linked proteins. These polyQ tracts are eponymous and causative for disease. As there is no therapy available to interfere with the neuronal decline in polyQ patients, we aimed to identify modifiers of polyQ-induced toxicity that could serve as therapeutic targets for intervation.
Methods: We performed an unbiased screen in *Drosphila* and identified TRMT2A as a suppressor for polyQ toxicity. We confirmed that a TRMT2A deficiency ameliorated polyQ-induced toxicity as measured by cell survival. Reduced polyQ aggregation was confirmed by filter retadation assay in yeast, human cells and mice.
Results: We show that loss of the tRNA-methyl transferase 2 homolog A (TRMT2A) suppresses polyQ-induced toxicity and aggregation in serveral organisms. Although we show that an inhibition of TRMTAs enzymatic function is sufficient to protect from polyQ-induced toxicity and aggregation. Interestingly, loss of TRMT2A did not result in any obvious phenotypic abnormalities in analyzed organisms, including mice. In mice, we show that a TRMT2A deficient background rescued polyQ-induced neuronal decline and ameliorated behavior alterations in polyQ-diseased animals. The reported function of TRMT2A is tRNA methylation of uridine (C5, m^5U_{54}) at position 54. Our analysis of the underlaying molecular mechanism relveals that loss of m^5U_{54}-tRNAs enhances errors in translation, especially glutamate/glutamine mis-incorporation. As a result polyQ stretches are interrupted by randomized intergration of glutamates. We show that interrupted polyQ streches have a dramatically reduced propensity for aggregation and confer strongly reduced toxicity.
Conclusions: We conclude that specific inhibition of TRMT2A 1) is prime target for the design of therepeutic approaches to treat all polyQ-disease. 2) is possible using small molecules. 2) should not cause any side effects.

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P1049 / #866

POSTERS: G03. DRUG DEVELOPMENT, CLINICAL TRIALS

CLINICAL AND PRECLINICAL EVALUATIONS OF NPT520-34, AN ORALLY ADMINISTERED SMALL MOLECULE UNDER DEVELOPMENT AS A DISEASE-MODIFYING THERAPEUTIC FOR NEURODEGENERATIVE DISORDERS

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Aims: Neuropore Therapies is developing therapeutics guided by the position that successful disease-modifying therapeutics will rectify the constellation of common underlying pathogenic mechanisms that drive neurodegenerative disorders, including protein aggregation, deficient housekeeping mechanisms, neuroinflammation, and mitochondrial dysfunction. NPT520-34 is an orally administered small molecule that effectively addresses many of the underlying drivers of neurodegeneration in animal models of Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS). NPT520-34 reduces the accumulation of aggregated proteins, normalizes markers of inflammation and mitochondrial dysfunction, and increases housekeeping-related markers. NPT520-34 treatment normalized disease-relevant profiles were accompanied by improved motor endpoints in PD and ALS models and improved health indices in the ALS model (delayed weight loss and improved survival). Based upon these exceptionally promising actions in animal models demonstrating that NPT520-34 addresses multiple key underlying drivers of neurodegeneration, NPT520-34 was advanced into clinical development.
Methods: The safety, tolerability and pharmacokinetics of NPT520-34 was assessed in healthy volunteers in a randomized, double-blinded single and multiple ascending dose trial (NCT03954600).
Results: NPT520-34 was well tolerated with no serious adverse events or subject discontinuations. The maximum tolerated dose was not determined in single (up to 1000 mg) or multiple dose evaluations (up to 250 mg BID for 14 days). The administration of repeat doses of 125 and 250 mg BID NPT520-34 for 14 days in healthy volunteers achieved pharmacokinetic parameters that met or exceeded the projected therapeutic dose as based on study results in animal models of PD and ALS.
Conclusions: The combination of robust effects in animal models of neurodegenerative disease and the promising safety and pharmacokinetic results from initial clinical evaluations in healthy volunteers support the continued development of NPT520-34 in PD and ALS.

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P1050 / #1104

POSTERS: G03. DRUG DEVELOPMENT, CLINICAL TRIALS

COULD PHOTOBIOMODULATION THERAPY BE SAFE AND EFFECTIVE IN THE TREATMENT OF SPORTSPEOPLE WITH ACUTE CONCUSSION SYNDROME? DESIGN OF A SINGLE-BLIND TRIAL

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Aims: The primary objective of this clinical trial is to evaluate the safety of a photobiomodulation (PBM) device, named RGn550, investigating the incidence of Adverse Events in acute concussion syndrome. Secondary objectives relate to treatment performance. For this, automated oculomotor and oculopostural functions, balance and executive functions will be measured, as well as blood markers involved in the pathogenesis of acute concussion.
Methods: The RGn550 is a non-invasive medical device, manufactured by REGEnLIFE, which takes the form of a helmet combining PBM technology from red to near-infrared wavelengths and static magnetic stimulation. This study is a prospective, comparative, randomized, single-blind, monocentric clinical investigation. It is planned to include 50 patients who will be separated into two parallel groups. Each group will be treated with RGn550 but with a different setting in order to compare them. Each patient will receive 2 sessions of 20 minutes of treatment one week apart. Safety and performance of the device will be evaluated after the first and second treatment session and then 45 days after the second treatment session.
Results: The sponsor of this study, REGEnLIFE, has already obtained clinical trial authorization from the CPP (French Ethics Committee). The Fist Patient First Visit is expected for October 2022 and Last Patient Last Visit for February 2023.
Conclusions: This pilot clinical trial, that will be conducted by REGEnLIFE, will determine whether this PBM therapy could offer a safe and well-tolerated method to treat acute concussion syndrome in sportspeople. In this perspective, this treatment could also become a tool for the prevention of chronic traumatic encephalopathy.

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P1051 / #1740

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

ASSOCIATIONS BETWEEN BRAIN TSPO AND [18F]FDG-PET SIGNALS IN NEURODEGENERATIVE DISORDERS

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Aims: Recent evidence indicates that activated microglial cells contribute to the brain [^{18}F]FDG-PET signal changes in neurodegenerative disorders. In this context, radiopharmaceuticals targeting the 18 kDa translocator protein (TSPO) have been used as an index of microglial activation. The combination of [^{18}F]FDG and TSPO-PET allows for assessing, in-vivo and non-invasively, whether they associate in brain regions vulnerable to neurodegeneration. So far, multiple studies utilized both [^{18}F]FDG and TSPO-PET but, to the best of our knowledge, no systematic evaluation to assess whether they are associated has been conducted. We aimed to systematically summarize the current data on brain TSPO-PET and [^{18}F]FDG-PET signals in individuals with neurodegenerative disorders.
Methods: Pubmed and Web of Science were searched for original articles assessing brain alterations in neurodegenerative diseases using TSPO-PET and [^{18}F]FDG-PET. Included studies performed both brain TSPO-PET and [^{18}F]FDG-PET in healthy age-matched controls and individuals with neurodegenerative disorders. This review complied with PRISMA(2020) guidelines and was registered at PROSPERO(CRD42022354520).
Results: A total of 272 articles were found after the database search, with eight studies meeting the inclusion criteria. We included articles with individuals presenting: Alzheimer's Disease(AD); Parkinson's Disease(PD) and other neurodegenerative disorders, including corticobasal syndrome and progressive supranuclear palsy, behavioral variant frontotemporal dementia, and progressive nonfluent aphasia. In AD (6 studies), five studies presented negative associations and one presented a positive association between tracers' signals in brain regions vulnerable to AD. In PD (3 studies) and other neurodegenerative disorders (2 studies) evaluated, a negative correlation between [^{18}F]FDG and TSPO-PET signals was found in vulnerable regions.
Conclusions: In summary, all studies presented associations between [^{18}F]FDG and TSPO signals, most of them being negative. Our findings suggest that microglial activation, indexed by TSPO-PET, impacts brain glucose metabolism, indexed by [^{18}F]FDG-PET.

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P1052 / #299

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

COGNITIVE IMPAIRMENT IS ASSOCIATED WITH POOR GAIT QUALITY IN PEOPLE WITH PARKINSON'S DISEASE

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Aims: To determine whether objective measures of gait differ between people with Parkinson's Disease (PD) who have mild cognitive impairment (MCI) from those who have normal cognitive function.
Methods: One-hundred and six people with PD were separated into two groups (42 MCI versus 64 nonMCI) based on the Montreal Cognitive Assessment (MOCA) score of 26. Participants wore 8 synchronized inertial sensors (Opals) while performing a 2-min walking test across a 10 m walkway with 180-degree turns (single-task and dual-task with counting backwards by 3s). In this exploratory analysis, gait measures (Mobility Lab by APDM) were compared between groups using a logistic regression, with adjusting for disease severity (MDS-UPDRS Part III) and freezing of gait (FoG) status, which are known to affect gait.
Results: Dual-task walking condition revealed more differences between the MCI groups compared to single-task walking. Toe-off angle (p=0.01), gait speed (p=0.02), stride length (p=0.04), foot-strike angle variability (p=0.04), turn velocity (p=0.04), and double support (p=0.04) were significantly different between MCI groups in the dual-task condition. In contrast, only toe-off angle (p=0.02) and turn duration (p=0.02) (not gait speed) were significantly different between groups in the single-task walking condition.
Conclusions: Our results showed significantly more impairment of gait in people with PD who have MCI, compared to those without MCI, even after adjusting for disease severity and FoG covariates. This relationship between cognition and gait suggests that brain networks controlling cognition and gait overlap and that MCI increases fall risk for people with PD.

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P1054 / #2322

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

ACCEPTANCE OF NEW PROGNOSTIC CLINICAL DECISION SUPPORT TOOLS AMONG PRIMARY CARE PHYSICIANSTREATING ALZHEIMER'S DISEASE IN CANADA

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Aims: Recent advances in big data analytics and artificial intelligence (AI) have led to the emergence of a new generation of clinical decision support systems (CDSSs), designed to leverage the full potential of data to inform decision making in patient monitoring, triaging, and diagnosing, particularly in general medicine and remote care. Current research in dementia, with Alzheimer's disease (AD) being its most common form, is focused on innovations that enable early identification of individuals at risk of developing dementia, given the clinical and economic benefits associated with early diagnosis. However, lack of resources to support accurate and timely diagnosis of dementia is a major bottleneck for disease management in primary care.Research indicates that low dementia detection rates in primary care are mainly related to the absence of standardized and reliable screening tools, inadequate training on dementia of general practitioners (GPs), and the GP's lack of confidence in providing a correct diagnosis.In this market research project, we aim to explore the acceptance of using prognostic decision support tools by primary care physicians treating AD.
Methods: We conducted an online survey with 100 PCPs covering different geographical regions in Canada.
Results: PCPs are much more likely to use a new clinical decision support tool if it had elements such as a validated algorithm that uses clinical, laboratory, and brain imaging inputs to generate a diagnosis probability, recommendation for further diagnostic tests, simplified reports summarizing aggregated test results, links andeducational materials about Alzheimer's disease from credible, verified sources to distribute to patients and patient access and a patient-facing interface that explains test results to diagnose AD patients early.
Conclusions: There is a reasonable level of acceptance by PCP for prognostic CDS tools.

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P1055 / #1749

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

FUNCTIONAL EFFECTS OF PLASMA-DERIVED EXTRACELLULAR VESICLES OF PATIENTS WITH PARKINSON'S DISEASE IN-VITRO CAN REVEAL NOVEL PATHWAYS OF NEURODEGENERATION

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Aims: Extracellular vesicles (EVs), are secreted membrane particles involved in cell-to-cell communication. CNS-derived and plasmatic EVs may mediate the spread of neuroinflammation and pathological proteins in Parkinson's disease (PD) and other neurodegenerative diseases. We aim at analyzing plasmatic EVs' functional pathways as pathway/ biomarkers and for novel therapeutic approaches.
Methods: EVs were isolated from plasma of PD subjects, and sex and age-matched healthy control (HC) by size exclusion chromatography using Izon qEV. NTA (Nanoparticle tracking analysis) was used to determine the concentration and size of plasma derived-EVs. The functional effect of plasma derived-EVs on SHSY-5Y cells was determined by apoptosis assay and axonal length measurement using immuno-fluorescence and ImageJ software applications. The impact of plasma derived-EVs from PD vs. HC on glial cell lines and primary mixed culture from mice brains is also analyzed.
Results: The average axon length of neuronal cells was significantly reduced when treated with plasma derived-EVs (C_1: 6.5 * 10^6EV/well; C_2: 1*10^9EV/well) from PD patients for 48h as compared to HC. The percentage of apoptotic cells, when treated with plasma-derived EVs from PD patients for 48h, gradually increased compared to when treated with plasma derived-EVs from healthy controls.
Conclusions: These preliminary results suggest that plasma-derived EVs from PD patients may have a direct toxic effect on neurons and influence the initiation and progression of the disease.

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P1056 / #128

POSTERS: G05. GENETICS, EPIDEMIOLOGY

EFFECT OF UNDERESTIMATED EPIDEMIOLOGY OF HUNTINGTON'S DISEASE ON MEDICAL COST IN SOUTH KOREA

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Aims: Epidemiology of Huntington's disease has been known rare in South Korea. Prevalence had been believed only 10% of those of Western countries. Personnels in health administration are unaware of HD, although Rare Disorder Wellcare system is developed. Aim is to retrospective analysis of the medico-economic burdens.
Methods: The Korean National Health Insurance database between 2010 and 2019 were used with genetically confirmed HD. We analyzed the pattern of individuals' medical use and yearly medical expenditures, and percentage of referral status according to their illness.
Results: Unlike the previous wrong concept of HD epidemiology in South Korea, prevalence based on database is five-times higher than those of previously described. Although most HD patients are detected average on 40s, Korean patients with HD are diagnosed at the 6th decade (50-59 years; 23.3%). About 56.4% of HD patients were followed-up at referral or general hospitals, and 32.2% of patients were managed at long-term care hospitals in 2019. The mean annual medical cost for an individual was approximately 6,569,341±895,097.5 KRW (≈5,653.27 USD). Medical expenditure was the highest in their 60s and 70s. In all age groups, the annual medical expenditures showed the highest for the initial nine years although following diagnosis.
Conclusions: Systemic epidemiologic approach revealed the actual prevalence of HD in South Korea. This previous unfortunate persistent high medical expenditure situation will be corrected with previous old report and will increase international trials including Asian countries.

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P1057 / #1653

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

POLYQ-EXPANSION CAUSES MITOCHONDRIA FRAGMENTATION INDEPENDENT OF HUNTINGTIN (HTT) AND IS DISTINCT FROM TRAUMATIC BRAIN INJURY-MEDIATED FRAGMENTATION WHICH IS THE RESULT OF CELL DEATH.

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Aims: Mitochondrial dysfunction has been reported in several Huntington's disease (HD) models. However, it is unclear how mitochondrial dysfunction occurs during HD neuropathogenesis. Here we test the hypothesis that excess pathogenic HTT impairs mitochondrial homeostasis.
Methods: Using *Drosophila* genetics, *in vivo* mitochondrial homeostasis markers, and pharmacological inhibitors, we examined mitochondrial health in HD and other polyQ-expansion disease models and in a mechanically-induced traumatic brain injury (TBI) model.
Results: Excess pathogenic HTT caused fragmented mitochondria compared to normal HTT, but HTT did not co-localize with mitochondria under normal or pathogenic conditions, indicating that fragmentation is not due to defects in HTT function. Excess pathogenic polyQ alone (127Q) or Machado Joseph Disease (MJD)/(SCA3) also caused fragmented mitochondria. While polyQ-mediated fragmentation was not dependent on the cellular location of polyQ accumulations, expression of a chaperone protein rescued fragmentation, suggesting that polyQ aggregations likely cause fragmentation. Pathogenic polyQ-mediated fragmentation is likely due to mitochondrial fission and/or fusion since excess mitofusin (MFN) or depletion of dynamin-related protein 1 (DRP1) rescued fragmentation. Intriguingly, inhibition of nitric oxide (NO) rescued polyQ-mediated fragmentation, confirming that fragmentation is likely due to nitrosylation of DRP1 which increases GTPase activity. Further, polyQ-mediated fragmented mitochondria are newer, and are not affected by H_2O_2/GSH-dependent oxidation, but are depolarized with decreased levels of ca+, perhaps due to increased NO. PolyQ-fragmentation was not the result of cell death since excess PI3K rescued polyQ-induced cell death, but not fragmentation. In contrast, TBI-mediated fragmentation and damage are caused by neuronal cell death.
Conclusions: Together, our observations suggest that polyQ expansion alone is sufficient to cause DRP1-dependent mitochondria fragmentation and that fragmentation is upstream of cell death. This work uncovers distinct physiological mechanisms for how mitochondrial dysfunction occurs in polyQ-mediated degeneration and TBI.

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P1058 / #1252

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

RETINOIC ACID EXERTS NEUROPROTECTIVE EFFECTS BY CONTROLLING BCL-2 FAMILY PROTEINS IN A STROKE ANIMAL MODEL

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Aims: Cerebral ischemia is a neurological disorder that leads to cognitive decline. Retinoic acid is a metabolite of vitamin A that has anti-apoptotic and anti-inflammatory effects. Bcl-2 and Bcl-xL are proteins that inhibit apoptosis, and Bax and Bad induce apoptosis. This study investigated whether retinoic acid exerts a neuroprotective effect against ischemic stroke damage by regulating Bcl-2 family proteins.
Methods: We performed middle cerebral artery occlusion (MCAO) to induce ischemic stroke in adult male rats. Retinoic acid (5 mg/kg) or vehicle was injected intraperitoneally for 4 days prior to MCAO. Neurological behavior deficit tests were performed 24 h after MCAO. Brain edema and infarct volume were measured, and TUNEL histochemistry was carried out. We also investigated the changes in apoptosis-related proteins including Bcl-2 family proteins and caspases.
Results: MCAO injury induced severe neurological behavior deficits and histopathological damages. However, retinoic acid pretreatment attenuated MCAO-induced neurological behavior deficits, brain edema, and infarction. It also alleviated histopathological lesion and decreased the number of TUNEL-positive cells. MCAO injury induced a decrease in Bcl-2 expression and an increase in Bax expression, and retinoic acid pretreatment alleviated these changes. The interaction of Bax with Bcl-2 or Bcl-xL decrease in MCAO animals, and the binding of Bad with Bcl-2 or Bcl-xL increased. However, retinoic acid treatment reduced these changes. Moreover, our result showed increases in caspase-9, caspase-3, PARP protein levels in MCAO-operated animals. Retinoic acid pretreatment prevented these increases. Activation of caspases and PARP proteins are considered to be representative apoptosis indicators.
Conclusions: This study showed that retinoic acid regulates bcl-2 family proteins and caspase proteins in focal cerebral ischemia. Thus, our findings demonstrate that retinoic acid exhibits a neuroprotective effect against ischemic damage by controlling Bcl-2 family protein interactions.

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P1059 / #689

POSTERS: G07. ANIMAL MODELS

PARKINSONS'S DISEASE EXPERIMENTAL MODEL AND EFFECTS OF EXTRACT FROM HELIX ASPERSA

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Aims: Objectives: Parkinson's disease (PD) is a progressive, neurodegenerative and debilitating disease. Currently, there are no strategies that can stop the brain cell injury in PD. Since snail extract (SE) possess antioxidant, anti-inflammatory and antiapoptotic properties, we studied its effects in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of PD.
Methods: The snail mucus was collected from *Helix aspersa* snails, grown in Bulgarian eco-farms using patented technology without the suffering of snails. Male mice (C57BL/6, male, 8 weeks old) were used for mouse Parkinson's disease model via MPTP treatment. MPTP+SE (0.1 ml/10g b.w) group received fresh snail extract through a special food tube for 12 consecutive days. All animals were submitted to motor coordination and memory tests on the 16th and 17th day. At the end of experiment two brain structures related to memory (prefrontal cortex and hippocampus) were separated for the biochemical and histological analyses.
Results: After 12 days with SE treatment (7 days before and 5 days simultaneously with MPTP) an improvement in motor and memory performance in Parkinsonian animals was observed. SE protected dopaminergic neurons as proved via histological studies as well as with biochemical evaluation. Twelve days after first MPTP treatment the reduction in brain DA content was by 73 % as compared to control. Multiple SE administration increased DA brain level (by 176 %) and decreased those of NA (by 42 %,) as compared to Parkinsonian group. We also observed significant anti-inflammatory effect of SE.
Conclusions: Our results provide insight on the beneficial effects of *Helix aspersa* extract in experimental PD model. **Acknowledgements:** Supported by Grant D01-217/30.11.2018 under National Research Programme "Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)" approved by DCM # 658 / 14.09.2018.

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P1060 / #1337

POSTERS: G07. ANIMAL MODELS

EEFECTS OF SNAIL HELIX ASPERSA EXTRACT IN EXPERIMENTAL MODEL OF ALZHEIMER'S TYPE DEMENTIA IN VIVO

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Aims: Aim of the study was to evaluate effect of snail extract (SE) on macrophages and microglia in a model of Scopolamine (Sco)-induced Alzheimer's type dementia (ATD).
Methods: ATD was induced by intraperitoneal injection of Sco in male adult rats for 11 consecutive days. SE was administered orally for 16 days starting 5 days prior to first Sco injection and following by 11 consecutive days of application. At 11th day blood and hippocampus samples were collected. Blood samples were used to determine macrophages and their intracellular level of TNF-α and IL-10 by flow cytometry. Hippocampus samples were frozen at -80°C and then disintegrated to prepare extract. The expression of purinergic receptor P2Y (P2RY12), glial fibrillary acidic protein (GFAP) and CD68 was evaluated by flow cytometry. Production of nitric oxide (NO) in hippocampus extract was determined by colorimetric Griess assay.
Results: Snail application in Sco group increased percentage of blood macrophages and of those producing IL-10 and restored reduced percentage of TNF-α positive macrophages in comparison to untreated Sco group. However, this effect was due to Snail extract activity on macrophages rather than to Sco-induced alteration in macrophage number or function. In hippocampus Snail treatment inhibited Sco-induced P2RY12 protein expression and CD68+ cells elevation. Sco slightly increased GFAP expression but in the treated with Snail extract group it was restored. NO production in hippocampus was increased by Snail application.
Conclusions: SE application regulates microglial function by elevating reparative phenotype of blood macrophages and by reducing CD68+ cells, increasing P2RY12 and restoring GFAP expression in hippocampus. SEmay improve synaptic plasticity via increased NO production, that in turn leads to altered pre- and/or postsynaptic function. ***Acknowledgments:*** Supported by Grant D01-217/30.11.2018 under NRP "BioActiveMed".

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P1061 / #1354

POSTERS: G07. ANIMAL MODELS

PILOT STUDY ON MEMORY RECOVERY EFFECT OF NEW INNOVATIVE BIOACTIVE COMBINATION ON EXPERIMENTAL DEMENTIA IN RATS

Lyubka Tancheva[1], Reni Kalfin[1], Hristian Staykov[2], Yordan Hodzhev[3], Stela Shekerdjiyska[4], Nikolay Georgiev[4], Rahamim Shekerdjiyski[4]
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Aims: Complex neurodegenerative mechanisms of Alzheimer's disease require new multi-target strategies of prevention and treatment. An original product, containing seven natural bioactive components in an experimental combination (EC) was created recently by our team. Aim was to evaluate memory restoring effect of EC in experimental model of Alzheimer's type dementia *in vivo*.
Methods: Animal model of dementia in male Wistar rats was produced by 11 days Scopolamine (Scop) treatment (2 mg/kg, intraperitoneally). EC was applied daily orally in an effective dose for 40 days before and 11 days simultaneously with Scop (i.e. 51 days). Several behavioral tests were used to evaluate changes in short-term and long-term memory (Step through passive avoidance test, Novel Object Recognition test, T-maze test and Barnes maze test), followed by some histological and biochemical studies. Advanced exploratory analysis of the principle components (rotation Equamax) and additional hierarchical cluster analysis were used for calculation of the coefficient of memory restoration in each group.
Results: The behavioral studies revealed a significant memory recovery effect in EC-treated rats (the coefficient of memory restoration is 91 %). Statistical analyses which integrated behavioral and histological data showed clear distinguished groups organized in separate clusters: healthy controls, Scop-treated dement rats and EC-treated group. Last cluster is very near to those of control healthy animals. At least three different mechanisms are involved in observed memory protective effect of EC: antioxidant capacity, anti-inflammatory effect and neuromodulatory activity confirmed in two brain structures, related to memory - prefrontal cortex and hippocampus. Future clinical studies will reveal if this effect should be confirmed in volunteers.
Conclusions: Treated with EC dement group is practically undistinguished by the healthy controls. EC is safe and effective after long term administration.

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P1062 / #2697

POSTERS: H01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

CORRELATIONS OF GUT ALTERATION WITH THE PROGRESSION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE) IN C57BL/6 MICE

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Aims: Although vast majority of MS patients experience gastrointestinal (GI) problems, there are limited number of studies investigating the link between gut alterations and immune cells in the gut influencing the outcome of the disease. Hereby, we aimed to investigate changes in the gut lymphocytes frequencies, gut microbiota, Paneth cells count during EAE.
Methods: Experimental autoimmune encephalomyelitis **(**EAE) was actively induced in female C57BL/6 mice with MOG_{35-55} peptide. Stool samples and intestines were collected at different stages of the disease; baseline, onset, and peak. Flow cytometry was performed to assess changes in the levels of $CD4^+$, $CD8^+$ T cells, and NK cells, as well as their activation status at the three time points. This was done along with real-time PCR to determine the fold change of the selected bacterial species that were previously reported to be altered in MS patients; *Lactobacillus reuteri*, *Prevotella copri*, *Bacteroides fragilis*, *Clostridium perfringens*, and *Akkermansia muciniphila*the. Additionally, counts of Paneth cells whose role is essential in maintaining the balance of the normal flora were investigated by histochemistry.
Results: Our results showed no change in the frequencies of both gut $CD4^+$ and $CD8^+$ T cells at all time points. Yet, there was a change in the frequency of gut NK cells and their activity along with a reduction in beneficial gut microbiota (*L.reuteri* and *P.copri*) at the peak of the disease. This was associated with significant Paneth cells hyperplasia.
Conclusions: These data indicate a compromised balance of the normal gut microbiota and altered immune cell response throughout the disease progression. Our findings suggest possible interactions between gut microbiota and NK cells that may contribute to EAE pathogenicity, which may suggest possible targets for therapeutic intervention.

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P1063 / #2139

POSTERS: H01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

CENTRAL NERVOUS SYSTEM DISEASE IN PRIMARY SJÖGREN'S SYNDROME

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Aims: The purpose of our work was to study the clinico-radiological characteristics during the central neurological attack of primary Sjögren's syndrome (SS).
Methods: A retrospective study including patients with SS revealed by neurological disorders collected in the Neurology department of the Tunis military hospital between 2011 and 2021. All patients underwent cerebral and spinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis.
Results: Twenty-one patients were included. The average age was 44 years old. A focal lesion was present in 62% of the cases made by a spinal cord syndrome (19%), a cerebrovascular accident (5%) and by epilepsy (5%). Diffuse damage was made up of cognitive disorders (4%). MRI showed demyelinating lesions in T2 and Flair hypersignal at the level of the supra and subtentorial floors (76%), and vascular lesions (5%). CSF analysis was normal in all patients.
Conclusions: Central neurological involvement during SS is rarely described. We must think about it in the face of any unexplained neurological manifestation, especially in an inflammatory context or vasculitis lesions.

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P1064 / #2699

POSTERS: H02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

INVESTIGATING THE ROLE OF NATURAL KILLER (NK) CELLS IN OZANIMOD-MEDIATED REMISSION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE) IN C57BL/6 MICE

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Aims: To Study the effect of ozanimod treatment on the EAE disease induced in C57BL/6 mice. To assess the effect of ozanimod on the level of NK cell subsets and level of activation. To investigate the effect of depletion of NK cells in influencing the outcome of treatment with ozanimod.
Methods: Active induction of EAE was done in C57BL/6 mice and comparing levels of lymphocytes in blood and CNS by flowcytometry in diseased and/or treated with ozanimod. Histological analysis of the lumbar spinal cord was performed to assess mononuclear cell infiltration and demyelination in study groups. Depletion of peripheral NK cells was done using anti-NK1.1 mAb.
Results: Ozanimod was effective in reducing the clinical severity of EAE with 60% of ozanimod-treated mice scoring 0 and 40% scoring 1 on the disease severity scale. Additionally, ozanimod treatment significantly reduced inflammation by preventing lymphocytes migration and reducing the percentage of circulating $CD4^{+}$T cells (16.78%) compared to ozanimod non-treated EAE mice (36.86%) (P=0.01) which contributed to reduced demyelination in the spinal cord. Our findings also revealed an increase in the frequency of both circulating and CNS NK cells in ozanimod-treated mice compared to control and their expression of NKG2D receptor on the $CD27^{low/-}$ NK subset. The use of anti-NK1.1 reduced the effectiveness of ozanimod in improving the clinical picture of EAE.
Conclusions: Depleting peripheral NK cells using anti-NK1.1 reduced the effectiveness of ozanimod in improving the clinical picture of EAE, suggesting that ozanimod and anti-NK1.1 oppose each other's action. Collectively, our data suggest that ozanimod-mediated remission is associated with an increased percentage of total NK cells and $CD27^{low/-}$ NK cells expressing NKG2D in the CNS.

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P1065 / #153

POSTERS: H02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

C-PHYCOCYANIN AS REMYELINATION THERAPY FOR MULTIPLE SCLEROSIS: A PRECLINICAL PERSPECTIVE

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Aims: Multiple sclerosis (MS) is an autoimmune demyelination disorder. C-phycocyanin (CP) is a major phycobiliprotein that possesses antioxidant and anti-inflammatory activity and can lead to remyelination and regeneration of white matter. This study was undertaken to evaluate the neuroprotective efficacy of CP in the cuprizone model of multiple sclerosis in mice.
Methods: Disease was induced by cuprizone (400 mg/kg orally) administration for 6 weeks. CP was administered from week 3 to 6 (CP1: 100 mg/kg, CP2: 250 mg/kg, CP3: 500 mg/kg, orally). At the end of 6 weeks, behavioral parameters (Morris water maze (MWM), Rota rod, Tail flick, and Y-maze) were performed and serum and brain samples were collected for further biochemical, immunohistochemical, and histopathological analysis.
Results: The CP treatment improved motor coordination in Rota rod, improved working memory and spatial learning as evaluated through MWM ($p<0.05$) and Y-maze, and improved acute nociceptive response (CP1, CP2: $p<0.01$) which indicated remyelination and improved nerve response. It increased the levels of superoxide dismutase ($p<0.001$), catalase, β-Nerve Growth Factor ($p<0.05$), and neprilysin ($p<0.05$) and reduced the levels of nitric oxide ($p<0.05$), interleukin-6 ($p<0.05$), TNF-α ($p<0.01$), and nuclear factor-kappa B when compared to disease control. The histopathology showed that treatment ameliorated cell damage by reducing eosinophilia, inflammation, and cell apoptosis. Immunohistochemistry showed increased immunoreactivity to GFAP in comparison to the disease control group.
Conclusions: It can be inferred from the study that CP possesses anti-inflammatory, antioxidant activity and promotes neuronal health and thus can be further researched for the treatment of MS.

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P1066 / #152

POSTERS: H02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

EVALUATION OF NUTRACEUTICAL VALUE OF ASPHALTUM PROMOTING THE NEURONAL HEALTH AGAINST CUPRIZONE MODEL OF MULTIPLE SCLEROSIS IN BALB/C MICE

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Aims: Multiple sclerosis (MS) is an autoimmune demyelination disorder. *Asphaltum* (Shilajit) possesses neuroprotective, anti-inflammatory, and anti-oxidant properties. This study was undertaken to evaluate the neuroprotective efficacy of *Asphaltum* (AP) in the cuprizone model of multiple sclerosis in mice.
Methods: Disease was induced by cuprizone (400 mg/kg orally) administration for 6 weeks. AP was evaluated at the dose of 50 mg/kg orally from week 3 to 6. At the end of 6 weeks, behavioral parameters (Morris water maze (MWM), Rota rod, Tail flick, and Y-maze) were performed and serum and brain samples were collected for further biochemical, immunohistochemical, and histopathological analysis.
Results: The AP treatment improved motor coordination in Rota rod, improved working memory and spatial learning as evaluated through MWM and Y-maze, and improved acute nociceptive response ($p<0.05$) which indicated remyelination and improved nerve response. It increased the levels of superoxide dismutase ($p<0.05$), catalase ($p<0.05$), β-Nerve Growth Factor ($p<0.05$), and reduced the levels of nitric oxide, TNF-α ($p<0.05$), neprilysin ($p<0.05$), p53/Tp53 ($p<0.05$), and nuclear factor-kappa B ($p<0.05$) when compared to disease control. The histopathology showed that treatment protected the perineural space inside the oligodendrocytes and ameliorated cell damage. Immunohistochemistry showed increased immunoreactivity to GFAP in comparison to the disease control group.
Conclusions: It can be inferred from the study that AP possesses anti-inflammatory, antioxidant, anti-apoptotic, and nitrosative stress inhibitory activity and promotes neuronal health and thus can be further researched for the treatment of MS.

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P1067 / #2575

POSTERS: H03. DRUG DEVELOPMENT, CLINICAL TRIALS

SAFE AND EFFICIENT SIGMA1 LIGAND: A POTENTIAL DRUG CANDIDATE FOR MULTIPLE SCLEROSIS

Benedicte Oxombre-Vanteghem[1], Fahima Madouri[1], Anne-Sophie Journé[1], Severine Ravez[1], Eloise Woitrain[2], Pascal Odou[3], Nathalie Duhal[3], Sandro Ninni[2], David Montaigne[2], Nadira Delhem[4], Patrick Vermersch[1], Patricia Melnyk[1]
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Aims: Current management strategies in multiple sclerosis (MS) suppress or modulate immune function with high level of success in limiting new relapses. However, the degenerative process still affects the central nervous system (CNS). The sigma1 ligand-regulated protein (S1R) is implicated in many biological processes, acting on neural plasticity, myelination and neuroinflammation. S1R has therefore emerged as a promising new target.
Methods: Standard and robust methods have been adopted to analyze the adsorption, distribution, metabolism, excretion (ADME) properties, safety pharmacology and toxicology of a simple benzamide-derived compound with nanomolar affinity for S1R and high selectivity. Agonist characterization was performed prior to *in vivo* investigations.
Results: *In vitro* properties essential for later stages of drug development and the absence of cytotoxicity, immunotoxicity and cardiotoxicity were validated. Brain diffusion greater than 60% and right balance between free blood and brain fractions were observed. Involvement of S1R and pre-clinical efficacy was established using a curative protocol in a valuable MS experimental model. Very interestingly, a significant decrease in clinical intensity was observed after oral administration, as soon as the treatment was implemented. Disease progression was stopped at clinical grade 2 and the action of compound was maintained despite the interruption of the treatment.
Conclusions: The implementation of a typical preclinical program demonstrates that simple benzamide-derived compound has all the characteristics of an excellent CNS drug candidate specifically targeting S1R. The results obtained in an MS experimental model validate its positive role in the modulation of demyelinating diseases. This new drug candidate presents a moderate risk regarding its use in clinical trials. S1R agonists may also be useful for adjunct treatment of MS and/or further development in progressive MS due to their manifold properties.

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P1068 / #2741

POSTERS: H04. IMAGING, BIOMARKERS, DIAGNOSTICS

BLOOD SAMPLE MATRIX VALIDATION, IMPACT OF SAMPLE FREEZING AND METHOD COMPARISON ANALYSIS USING THE LUMIPULSE G NFL PROTOTYPE ASSAY

Aurélie Ladang[1], Guy Mersch[2], Martine Dauwe[2], Koen De Geyter[2], Paul Vandeponseele[2], Stéphanie Kovacs[1], Els Huyck[2], Nathalie Le Bastard[2], Ina Vandenbroucke[2], Etienne Cavalier[1]
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Aims: Neurofilament light (NfL) is expressed in myelinated axons and secreted in blood. Blood NfL levels are elevated in multiple neurological disorders. Only a limited number of fully automated assays are currently available for determination of blood NfL levels. Our study investigated the agreement of matched serum and plasma samples on a prototype Lumipulse G NfL test, the impact of fresh and frozen plasma samples on NfL concentrations, and a method comparison between Lumipulse and the Quanterix Simoa NF-light Advantage kit.
Methods: The LUMIPULSE *G* System is a chemiluminescent enzyme immunoassay platform enabling automated processing of samples using ready-to-use immunoreaction cartridges. (i) 20 paired serum, K3EDTA, and heparin plasma samples were collected; (ii) 40 fresh plasma samples were split in two: one aliquot was tested the same day and the other was tested after freezing at -20°C, (iii) 41 non-matched serum and K3EDTA plasma samples each across the measurement range were selected for the method comparison.
Results: Passing-Bablok regression and Spearman rank correlation analysis showed:

	Slope	95%CI	Intercept
(i) Serum vs. heparin plasma	1.089	0.893-1.338	0.127
(i) Serum vs. K3 EDTA plasma	0.974	0.718-1.142	1.163
(ii) Fresh vs. frozen	0.995	0.960-1.025	0.163
(iii) Method comparison: serum	1.000	0.818-1.160	0.750
(iii) Method comparison: K3EDTA plasma	1.007	0.903-1.133	0.787

Conclusions: The Lumipulse G NfL prototype assay shows strong correlation between serum and plasma samples, no impact between fresh and frozen samples, and equivalence between both platforms examined (Lumipulse vs. Simoa).

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P1069 / #1543

POSTERS: H04. IMAGING, BIOMARKERS, DIAGNOSTICS

ANALYTICAL PERFORMANCE OF THE LUMIPULSE G NFL CSF RUO ASSAY

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Aims: Neurofilaments provide structural support to neurons. Neurofilament light (NfL) is strongly expressed in myelinated axons, secreted in the cerebrospinal fluid (CSF). CSF NfL levels are elevated in multiple neurodegenerative disorders, including Alzheimer disease (AD) dementia, frontotemporal dementia (FTD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and traumatic brain injury (TBI). The objective of the study was to demonstrate the analytical performance of the newly developed Lumipulse *G* NfL CSF RUO assay.
Methods: The LUMIPULSE *G* SYSTEM is a chemiluminescent enzyme immunoassay platform enabling automated processing of samples using ready-to-use immunoreaction cartridges. Time to result takes 30 minutes. The analytical performance of the Lumipulse *G* NfL CSF RUO assay, using antibodies directed to the coil 2B region of the NfL protein, was determined. Parameters analysed were: a method comparison with CE certified NF-light® ELISA for CSF samples from UmanDiagnostics (Sweden), precision, sensitivity, proportional linearity, and impact of interfering substances.
Results: Correlation coefficient with NF-light® ELISA = 0,993. The total imprecision was ≤ 3,3 % CV. The observed LoQ was 4,7 pg/mL. Proportional linearity was shown across the range of 7 – 10.000 pg/mL and 10.000 – 45.000 pg/mL. No impact of endogenous substances was observed: bilirubin, haemoglobin, albumin, Human IgG/IgM/IgA, whole blood, rheumatoid factor (RF), HAMA and Chyle.
Conclusions: The analytical performance studies demonstrate – amongst other characteristics – low variability and high sensitivity enabling measurement of NfL in CSF. The Lumipulse *G* NfL CSF RUO assay is now ready to be explored further for clinical utility in various contexts of use.

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P1070 / #2259

POSTERS: H04. IMAGING, BIOMARKERS, DIAGNOSTICS

ANALYSIS OF THE NEUROLOGICAL STATUS OF PATIENTS WITH MULTIPLE SCLEROSIS AND DETERMINATION OF THE SEVERITY OF NEUROLOGICAL DEFICIT

Elnora Shamukhamedova, Dilbar Rasulova
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Aims: Analyze the neurological status of patients with multiple sclerosis and learn to determine the severity of neurological deficit with scores.
Methods: 27patients(P) with MS who were treated in the Department of Neurology of the Tashkent Medical Academy from 2015-2020 were analyzed according to the case histories, including 10men,17women,from 20-52years old.
Results: According to the complaints of patients with motor disorders,weakness of the legs and arms was often observed in 74%P, limitation of movements in 59%.In the NS:from CN:lesions of the II CN in 14.8%;III-IV-VI CN in 5;VII CN in 96%;IX-X CN in 25%;XII CN in77%P.In the motor sphere,tetraparesis was observed in 44%P.Tendon hyperreflexia in 25%P.Of the pathological reflexes,Babinsky was described in 92.5%,Yakobson-Laska in 40.7%.Cerebellar disorders - cerebellar ataxia was observed in 62.9%P, scanned speech in14%P, intentional tremor in70.3%P.Pelvic disorders were noted in 55.5%P,of which 29.6% had disorders of the central type,in 7(25%) of the peripheral type.Cognitive disorders in the form of memory loss in 77%,and CNS asthenia in 18.5%patients.All patients were assessed the severity of neurological deficit using a 10-point(p) Kurtzke scale.6P on the scale scored 2-3p(in14.8%P -2p,in 7.4%-3p) which is assessed as II degree,10P scored 3-4p(in 22%-4p, in 14.8%-5p, which corresponds to the III degree. 4P scored 6-7p each (in 3.7%-6p, in 11.1-7p),which corresponds to the IV degree,7P scored 8-9p each (in 22.2%-8p, in 11.1%-9p)which corresponded to the V degree of severity of the neurological deficit.
Conclusions: Multiple sclerosis in the debut of the disease as a "chameleon" can mask many diseases in which motor disorders are observed, and a scale assessment of the neurological status of patients with multiple sclerosis helps to determine the severity of neurological deficit and objectify the dynamics of the process

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POSTERS: H07. ANIMAL MODELS

AGE RELATED NEUROPATHOLOGY IN A NOVEL MOUSE MODEL OF ADULT-ONSET LEUKOENCEPHALOPATHY (ALSP)

Sepideh Kiani Shabestari[1], Hamsanandini Radhakrishnan[2], Winston Chang Rothermich[3], Amandine Jullienne[1], Kayla Nhi Tran[3], Jesse Pascual[4], Alessandra C Martini[1], Elizabeth Head[1], David A Hume[5], Clare Pridans[6], Andre Obenaus[1], Craig Stark[1], Hayk Davtyan[3], Matt Blurton-Jones[1]
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Aims: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare human disease that is caused by mutations in CSF1R, a gene that is critical for the differentiation, proliferation, and survival of microglia. ALSP patients typically develop dementia, motor impairments, and seizures during their 30s or 40s. Upon autopsy, patients' brains exhibit decreased numbers of microglia, white matter atrophy, astrocytosis, axonal spheroids, enlarged ventricles, and calcification. Two recent reports have further described rare cases of homozygous CSF1R mutations that lead to perinatal lethality, a complete absence of microglia, and an acceleration of ALSP pathologies. Unfortunately, there is currently no effective treatment for this devastating disease.
Methods: To better understand the role of microglia in the development and progression of ALSP we utilized the 'FIRE' mouse model that harbors a homozygous deletion in a microglial-specific enhancer within the CSF1R gene. Ongoing examinations of 2- and 10-month-old FIRE mice are exploring the sex-related impact of microglia absence on synaptic density and utilizing MRI imaging to examine white matter integrity and calcification.
Results: Surprisingly, at 2 months of age, despite absence of microglia, FIRE mice exhibit normal brain gross anatomy, minimal white matter alterations, and little to no pathology. However, by 10-months of age FIRE mice exhibit many of the pathologies and symptoms observed in ALSP patients, including axonal spheroids, calcification, demyelination, seizures, and behavioral deficits. Importantly, postnatal transplantation of wildtype murine microglia prevents nearly all of these pathologies, demonstrating the importance of decreased microglial numbers on the development of ALSP.
Conclusions: Taken together, these data suggest that aged FIRE mice may provide a novel and informative, albeit rapidly progressing, model of human ALSP.

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P1072 / #1938

POSTERS: H07. ANIMAL MODELS

NEUROPROTECTIVE EFFECT OF A GANGLIOSIDE-CONTAINING DRUG ON ALLERGIC AUTOIMMUNE ENCEPHALOMYELITIS.

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Aims: Experimental autoimmune encephalomyelitis (EAE) in rats is an experimental model of human multiple sclerosis. The aim of the work was to study the effect of ganglioside-containing drugs on the development of free radical lipid oxidation, protein oxidative modification in the brain and spinal cord in rats with experimentally induced allergic encephalitis. As a therapeutic agent, we used the drug Cronassial, the structure of which includes mono-di-tri-sialgangliosides.
Methods: The experiments were conducted using 30 inbred white rats weighing 180-200 g. EAE was induced by immunization homogenate of bovine spinal cord+ Freund's Adjuvant, Complete according to the immunization protocol. Lipid peroxidation activity was assessed by the content of hydroperoxides and Malone dialdehyde. The content of diene and triene conjugates, Schiff bases were registered by Deryugina methodology . The level of oxidative modifications of the proteins in the homogenate of brain was evaluated by the content of carbonyl derivatives of amino acids in proteins.
Results: Cronassial administration resulted in partial normalization of oxidative processes of proteins. Myelin destruction is considered as a universal mechanism of reaction to a damage. In case of progression of demyelination and in case of damage of 40-60% of all myelin sheath different neurological syndromes are developed, which are generally called demyelinating diseases . We suppose, that one of the most probable reasons of myelin damage may be increased formation of the products of oxidative stress – peroxides, hydroperoxides, oxidized proteins. This leads to mitochondrial disfunction, lack of energy necessary for the normal conduction of cellular processes.
Conclusions: Therefore, the obtained data indicates of neuroprotector and antioxidant effects of Cronassial upon its administration to the animals with autoimmune encephalomyelitis.

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P1073 / #1047

POSTERS: I01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

ALPHA-SYNUCLEIN IN SPHINGOLIPIDOSES

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Aims: A number of rare sphingolipidoses, including Gaucher disease, Krabbe disease and metachromatic leukodystrophy, are the result of bi-allelic pathogenic variants in genes that are also associated with risk of Lewy body disease (LBD), a common age-associated neurodegenerative disorder. As LBD is pathologically characterised by the accumulation of the protein alpha-synuclein, we sought to investigate how alpha-synuclein is affected in these conditions.
Methods: We evaluated *post-mortem* human brain tissue from infantile Krabbe disease and metachromatic leukodystrophy cases for the topography of alpha-synuclein expression compared to age-matched controls. Frozen tissue was used to examine molecular properties of the alpha-synuclein protein. Additionally, we exposed cultured cortical human brain slices derived from surgical patients to substrates that accumulate in Krabbe disease (psychosine) and metachromatic leukodystrophy (sulphated cerebroside).
Results: Alpha-synuclein deposits were observed in Krabbe disease and metachromatic leukodystrophy cases, and these differed from the topography of alpha-synuclein in age-matched control cases. Molecular analyses revealed brain tissue from infants with Krabbe disease manifested alpha-synuclein with seed-competence, an attribute only previously identified in older individuals with LBD. Discovery proteomics of human cortical slices exposed to psychosine demonstrate a number of changes to membrane binding and protein phosphorylation that are reminiscent of those observed in LBD.
Conclusions: These findings suggest mechanistic overlaps between two paediatric sphingolipidoses that may be relevant for the repurposing of novel therapeutics from LBD to lysosomal storage disorders. Furthermore, these studies suggest that understanding mechanisms of Krabbe disease and metachromatic leukodystrophy may be relevant to understanding the aetiology of alpha-synuclein aggregation in LBD.

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P1074 / #1125

POSTERS: I02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

DEVELOPMENT OF A CELLULAR PLATFORM TO STUDY LYSOSOMAL FUNCTIONS IN NEURODEGENERATION

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Aims: Several neurodegenerative disorders converge on the lysosome, with genetic links to endo-lysosomal dysfunction in both familial and sporadic forms of disease (for example LRRK2 mutations in Parkinson's disease (PD), GBA mutations in PD, Gaucher's disease, and dementia with Lewy bodies, GRN in frontotemporal dementia, and PLD3, BIN1, RIN3, APOE in Alzheimer's disease). *In vitro* and *in vivo* disease models, and post-mortem tissue also show strong evidence of lysosomal dysfunction. As well as playing a role in intracellular signalling and homeostasis, lysosomes are a key site of protein degradation, both of intracellular material via autophagy, and of extracellular endocytosed material. Altogether this makes lysosomes an attractive therapeutic target for neurodegenerative diseases.
Methods: Disorders featuring the build-up of misfolded protein aggregates may benefit from targeting lysosomal and autophagy pathways. To this end we have established *in vitro* assays of lysosomal functions and autophagy for use in drug discovery. The assays are established in multi-well format enabling simultaneous multiple compounds testing.
Results: We have developed a number of cellular assays measuring a) lysosomal GCaMP calcium, b) lysosomal activity using DQ-BSA and GCase readouts, c) autophagy flux and d) TFE3/TFEB nuclear localization. A set of tool molecules, such as mTOR inhibitors, VPS34 inhibitors, GCase modulators, lysosomal blockers and autophagy activators were tested in such assays, validating our platform for broader compound profiling.
Conclusions: This platform allows us to test therapeutic hypotheses and various small molecules for their potential to target and modify lysosomal function in brain-relevant cell types.

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P1075 / #1888

POSTERS: I02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

PARTIAL REDUCTION OR DELETION OF TMEM106B DOES NOT RESCUE PHENOTYPES IN HUMAN AND MOUSE MODELS OF GRN HAPLOINSUFFICIENCY

Amy Easton[1], Sara Dominguez[1], Arundhati Sengupta Ghosh[1], Gaia Ruggeri[1], Maheswara Reddy Emani[1], Bill Meilandt[1], Ben Laufer[1], Qingling Li[1], Wendy Sandoval[1], Hai Ngu[1], Oded Foreman[1], Mike Reichelt[1], Ben Chih[1], Helene Gylling[2], Lukasz Kielpinski[2]
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Aims: Heterozygous mutations in the granulin (GRN) gene, lead to haploinsufficiency of the progranulin (PGRN) protein, a leading cause of frontotemporal lobar degeneration with TDP-43 aggregates (FTLD-TDP). Polymorphisms in the TMEM106B gene have been shown to impact disease onset and progression in GRN mutation carriers. Here we test the impact of deletion or partial reduction of TMEM106B in mouse and human GRN KO models of FTLD.
Methods: GRN +/+, +/- and -/- KO mice were crossed with TMEM106B +/+, +/- and -/- KO mice and characterized at 4 or 13 mo. of age. Lysosomal , inflammation, and neurodegeneration markers were measured in brain by histology, transcriptomics, and lipidomics. Tolerability and tissue analyses were conducted on GRN +/+, +/-, and -/- mice of different ages treated with TMEM106B-targeting ASOs. Human wild-type microglia, single TMEM106B and GRN KO, and dKO human microglia were characterized using imaging methods and "omics".
Results: Homozygous TMEM106B deletion led to motor dysfunction and early mortality in GRN -/- mice. Heterozygous deletion of TMEM106B was tolerated but did not ameliorate GRN -/- pathology. Surprisingly, partial reduction with TMEM106B ASO treatment was not tolerated in GRN -/- mice, causing seizure or mortality by 7 days post-dose. Deletion of TMEM106B did not normalize phenotypes in human GRN KO microglia with the exception of a subset of proteins involved with NFkappaB signaling and immune function.
Conclusions: Neither complete nor partial loss of TMEM106B was able to ameliorate GRN KO phenotypes in mice or human microglia. Lowering wild-type TMEM106B transcript is not likely to be a viable therapeutic strategy for treating FTLD due to progranulin insufficiency. Analyses of human microglia revealed novel biological effects of TMEM106B warranting further study in the future.

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P1076 / #2721

POSTERS: I07. ANIMAL MODELS AND BRAIN ORGANOIDS

MITOCHONDRIAL, AUTOPHAGY, AND LYSOSOMAL DEFECTS IN A NIEMANN-PICK TYPE C DROSOPHILA MELANOGASTER ANIMAL MODEL

Melissa Vos, Merle Trautmann, Christine Klein
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Aims: Niemann-Pick Type C (NPC) is a lysosomal storage disorder caused by mutations in *NPC1* or *NPC2.* The proteins NPC1 and NPC2 function together in the transport of cholesterol; hence, cholesterol accumulation is the disorder's hallmark. In mammalian models, defects in mitochondria, autophagy, and lysosomal function have been observed; nonetheless, the underlying disease mechanisms remains elusive. A fly model for NPC that shows the accumulation of cholesterol exists; however, other cellular defects were previously not described. Hence, our aim was to evaluate mitochondrial, autophagosomal, and lysosomal function in this fly model and assess if this model is suitable for studying the underlying mechanisms in-depth.
Methods: Survival and locomotion of control flies, *npc1/npc2*-mutant flies, and homozygous *npc2*-mutant flies were analyzed. In addition, immunolabeling experiments were performed on these larvae to assess mitochondrial morphology (anti-ATP5A), autophagosome (anti-dLC3; gabarap), and lysosomal function (LAMP1).
Results: Survival rates were not affected upon loss of npc; however, locomotion deteriorated in an age- and gene dosage-dependent fashion. Furthermore, loss of npc induced mitochondrial, autophagosomal, and lysosomal abnormalities.
Conclusions: We validated the observations in cellular models for NPC in a drosophila model for npc in a gene dosage-dependent manner. Thus, these flies allow further dissection of the underlying mechanisms in the pathogenesis of NPC

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P1077 / #226

POSTERS: I07. ANIMAL MODELS AND BRAIN ORGANOIDS

ROLE OF NARINGIN ON THE CA1 FIELD OF THE HIPPOCAMPUS IN VANADIUM-INDUCED NEUROTOXICITY

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Aims: This study is aimed at exploring the therapeutic effects of naringin on the hippocampus (CA1) following vanadium induced neurotoxicity in an adult wistar rats
Methods: The Animals were randomly dividded into four groups. Group A (Control) were given double distilled water; Group B (Naringin only) was administered Naringin only at 30 mg/kg BW; Group C (Vanadium+ Naringin) was administered Vanadium at 10 mg/kg BW for seven (7) days followed by treatment with Naringin at 30 mg/kg BW for another seven (7) days; Group D (Vanadium only) was administerd vanadium only at 10 mg/.kg BW intraperitoneally for seven (7) days. Novel object recognition test (NOR) and Y-maze test were the neurobehavioural study carried out to assess the cognitive function. Markers of oxidative stress were also analysed using glutathione peroxidase (GPx) and catalase (CAT). NeuN was used to identify mature neurons in the tissue sections while NLRP3 inflammasome was also used as a marker for inflammed or damaged cells in the CA1 field of the hippocampus sections immunohistochemically.
Results: There was a decrease in the oxidative stress markers (GPx and CAT) of the brain in the Vandium group only but an increase was observed in following naringin treatment as observed in the naringin and vanadium (NAR +VAN) group. Numbers of viable cell count of the CA1 field of the vanadium only (VAN) group was less when compared to the control (CTRL) and naringin (NAR) group. Increase in NLRP3 positive cell count observed in the vanadium only (VAN) group while little or no NLRP3 were seen in the control (CTRL) group. There was a decrease cognitive function with vanadium which later changes positively with the effect of naringin.
Conclusions: Naringin have neuroprotective effect

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P1078 / #2159

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

DEPRESSIVE SYMPTOMS AND PLASMA NFL AMONG COGNITIVELY HEALTHY AND MILD COGNITIVELY IMPAIRED MEXICAN AMERICANS AND NON-HISPANIC WHITES

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Aims: We aimed to investigate the association between depressive symptoms and plasma Neurofilament light chain (NfL) among cognitively healthy and mild cognitively impaired Mexican Americans and Non-Hispanic Whites.
Methods: 1,112 participants (724 Mexican Americans (MAs); 380 non-Hispanic Whites (NHWs) from The Health & Aging Brain Study—Health Disparities (HABS-HD) study were included (mean age 67.5, SD= 8.6). Mild cognitive impairment (MCI) was ascertained using an algorithm (decision tree) verified by consensus review. Plasma NfL samples were assayed using Simoa technology. Depressive symptomology was assessed using the Geriatric Depression Scale 30-item, dichotomized as high (≥10) versus low (<10). The association between Log-transformed NfL concentration (pg/mL) and strata of depressive symptoms with or without MCI was evaluated using linear regression adjusted for age, sex, and education.
Results: In total, 191 (17.2%) participants had high depressive symptoms and 167 had MCI (15.0%). High depressive symptoms were significantly associated with higher NfL concentrations in NHWs (p= 0.007) but not in MAs (p= 0.158). Among NHWs, high depressive symptoms/no MCI and high depressive symptoms/MCI were significantly associated with higher NfL (adj. mean: 19.47, 95% CI: 15.99; 22.95 and adj. mean: 18.76, 95% CI: 16.15; 21.37, respectively), but not MCI only (adj. mean: 17.28, 95% CI: 14.28; 20.29), compared to the reference (low depressive symptoms/no MCI). Among MAs, MCI only and MCI/high depressive symptoms were associated with significantly higher NfL concentrations (adj. mean: 22.97, 95% CI: 19.81; 26.12 and adj. mean: 23.66, 95% CI. 10.17; 27.16, respectively), but not high depressive symptoms only (adj. mean: 21.27, 95% CI: 19.23 to 23.32).
Conclusions: There may be ethnic differences in the interplay between depressive symptoms and MCI on neurodegeneration; longitudinal follow-up is necessary to understand whether such differences persist over the AD continuum.

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P1079 / #1109

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

A CASE-CONTROL SEROPREVALENCE STUDY ON THE ASSOCIATION BETWEEN TOXOCARIASIS INFECTION AND PARKINSON'S AND ALZHEIMER'S DISEASES

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Aims: Toxocariasis is a zoonotic disease that human infection that occurs by eating the embryonated eggs of *Toxocara* spp. Various studies have investigated the association of toxocariasis with central nervous system (CNS) disorders and in some cases, a significant association has been found. The present study examined the association between toxocariasis infection and Parkinson's disease (PD) and Alzheimer's disease (AD).
Methods: A total of 186 patients with AD and PD (93 patients in each group) and as the control group, 93 healthy people that were statistically matched with the case group were included in the study. Blood samples were collected from all participants and the anti-*Toxocara* spp. IgG antibodies were detected using the ELISA kit
Results: All participants' overall seroprevalence of toxocariasis was 5.1% (95% CI, 4.5-5.6%; 14/279). The anti-*Toxocara* IgG antibodies were found in 8/93 PD cases (8.6%; 95% CI, 7-10.1%), 3/93 AD cases (3.2%; 95% CI, 2.6-3.7%), and in 3/93 healthy controls (3.2%; 95% CI, 2.6-3.7%). There was no significant association regarding the *Toxocara* infection seropositivity and PD (OR, 2.82; 95% CI, 0.72-11.00) and AD (OR, 1.00; 95% CI, 0.20-5.09).
Conclusions: Based on the results, it could be concluded that there was no significant relationship between AD, PD, and *Toxocara* infection.

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P1080 / #533

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

LOSS OF MEMORY AWARENESS IN ALZHEIMER'S DISEASE IS ASSOCIATED WITH STRUCTURAL DISCONNECTION OF NETWORK SUBSERVING SELF-REFERENTIAL PROCESSING

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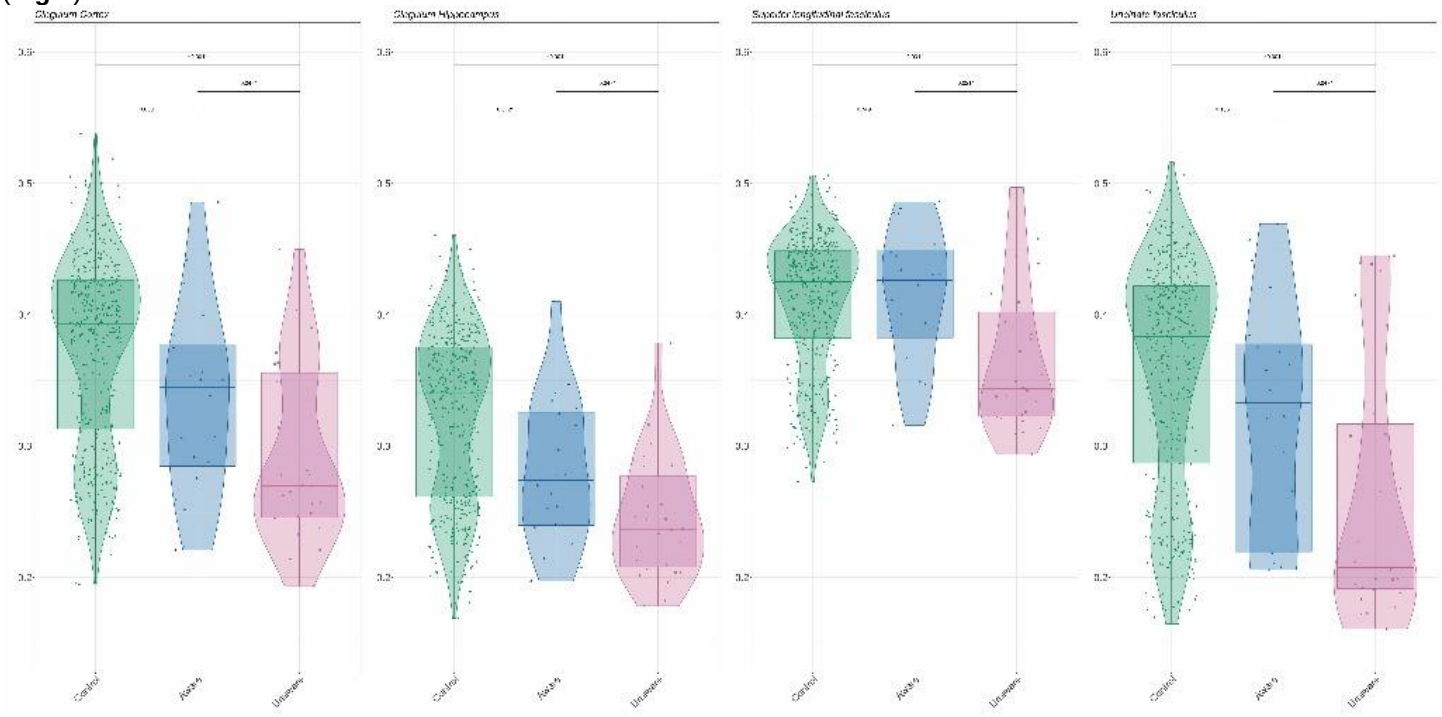
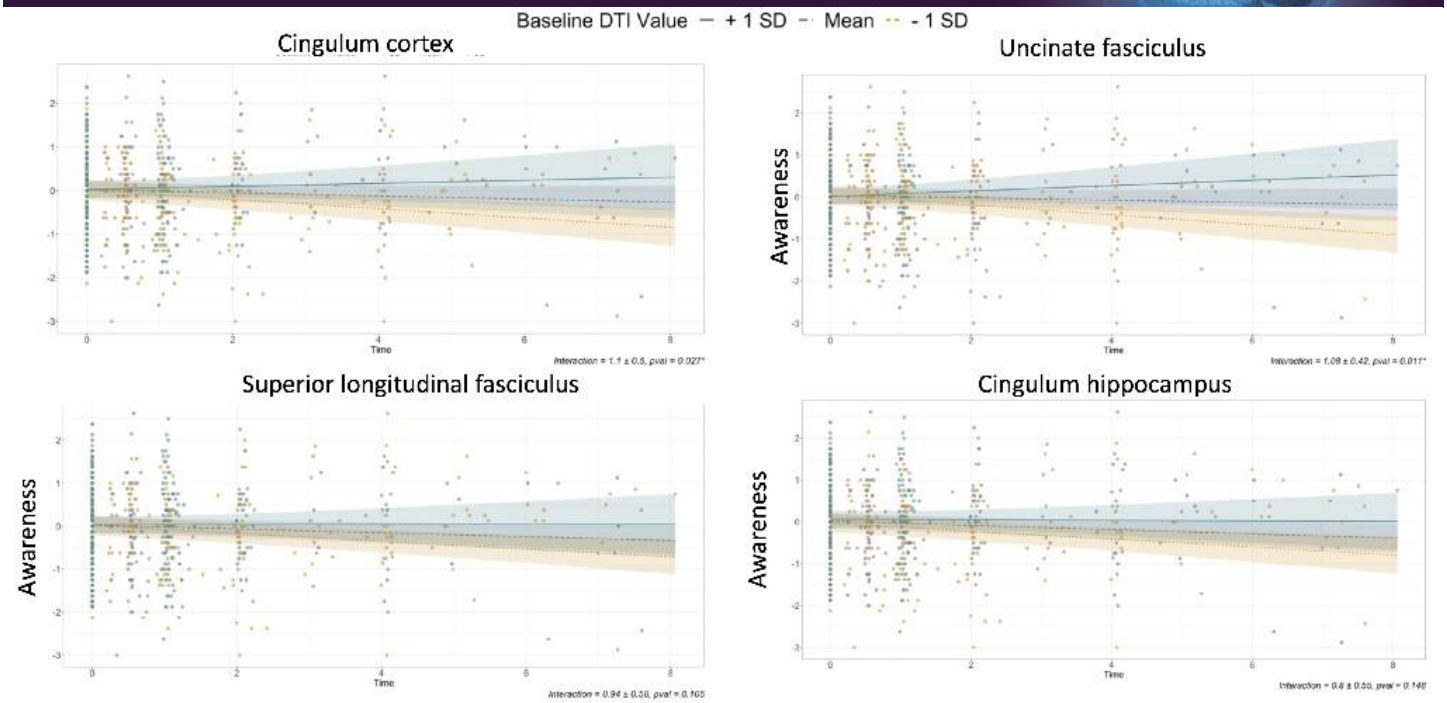
Aims: Disordered awareness of cognitive deficits, i.e. anosognosia, is a common symptom of Alzheimer's disease (AD) that is particularly frustrating to families and may impact early detection. However, the mechanistic underpinnings of this debilitating symptom are unknown. Here, we used diffusion tensor imaging (DTI) to investigate the structural integrity of the default mode network (DMN), known to subserve self-referential processing in prodromal and clinical AD patients who were aware and unaware of their memory decline.
Methods: 676 participants (378 controls, 242 MCI, and 56 AD-patients) from the ADNI cohort were included. Region-of-interest DTI analyses were performed on DMN pathways, i.e., cingulum cortex (CC), cingulum hippocampus (CH), superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF). Awareness was defined as the discrepancy between the participant and informant everyday cognition questionnaires and AD-patients were classified as being aware or unaware. Two-sample t-tests were used to investigate differences in fractional anisotropy (FA) between groups. Linear mixed-effects models (LMM) were used to assess the effect of baseline DTI on awareness over time.
Results: Significantly increased FA values were observed for controls as compared to the unaware AD-patients (all p<0.001) for all tracts and compared to aware AD-patients in the CC(p=0.05) and CH(p=0.015). Significant lower FA values were observed in the SLF (p=0.02) and UF (p=0.045) in the unaware as compared to the aware AD-patients (**Fig.1**).



In the MCI patients, lower baseline FA predicted decreased awareness over time (CG p=0.027;UF p=0.01; **Fig.2**).



Conclusions: These findings converge onto a hypothetical model suggesting that anosognosia occurs as a symptom of structural changes in self-referential brain networks. These results may have important clinical and practical implications for patients and their families, particularly for the development and use of dementia management interventions

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P1081 / #2646

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

NEUROPROTECTIVE POTENTIAL OF NON- FEMINIZING ESTROGEN IN AN EXPERIMENTAL MODEL OF POSTMENOPAUSAL PARKINSON'S DISEASE

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Aims: The main aim of our study was to evaluate the role of a non-feminizing estrogen 17alpha-estradiol in 6-hydroxy dopamine-induced Parkinsonism in ovariectomized rats and its comparative analysis with 17beta-estradiol.
Methods: Female Wistar rats (6-8 weeks old) were divided into nine groups. 6-hydroxy dopamine was administered after 1 week of ovariectomy in all the rats to induce Parkinson's Disease (PD) except in control and sham group rats. 17alpha-estradiol and 17βeta-estradiol were injected 10 µg/kg/s.c. for 14 days after administration of 6-hydroxy dopamine. After 14 days various behavioral, biochemical, and molecular markers, expression of ER-alpha and ER-beta, Bcl-2, and caspase-3 were quantified in the striatal region followed by striatal histopathology.
Results: 17alpha-estradiol and 17 beta-estradiol equally modulated behavioral changes, rise in oxidative stress markers, inflammatory markers, neurotrophic factors, and striatal neuron morphology. The 17beta-estradiol treatment restored the uterine weight and serum estradiol levels towards normal along with the expression of ER-α and ER-β in the striatum. However, 17alpha-estradiol did not show any effect on uterine horns and serum estradiol levels and ER expression indicates the receptor-independent effect of 17alpha-estradiol.
Conclusions: Both 17alpha-estradiol and 17beta-estradiol are equally effective in Parkinsonism, however, 17α-estradiol may prove to be a safer alternative of 17beta-estradiol in Parkinsonism due to the lack of feminizing effects.

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P1082 / #2685

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

MINDFULNESS PREVENTS DEPRESSION IN ELDERLY PEOPLE WITH ALZHEIMER'S DISEASE: A RANDOMIZED CLINICAL TRIAL, LONGITUDINAL STUDY CANARY ISLANDS

Domingo Jesús Quintana Hernández
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Aims: This longitudinal study "Canary Islands" has addressed whether the daily Mindfulness Based Alzheimer´ Stimulation practice prevents the course o mood disorders in Alzheimer's disease.
Methods: Design: Longitudinal, non-inferiority and equivalence randomized clinical trial, repeated-measures design, with a control group and three experimental treatments based on mindfulness, cognitive stimulation and relaxation. The pharmacological treatment of all participants was donepezil (10 mg). **Participants**: Patients with probable AD diagnosed by the public neurology services of the Canary Health Service, Spain (n=520). Only those who were treated with donepezil 10 mg and MMSE ≥18 were included (n = 120). **Non-pharmacological treatments**: Each experimental group performed three weekly sessions of mindfulness-based stimulation, cognitive stimulation or relaxation for two years. **Measures**: Mini Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Hamilton Depression Rating Scale (HDRS) and Neuropsychiatric Inventory (NPI-Q). **Statistical analysis**: Repeated-measures ANOVA ($p < 0.05$). Effect size was calculated with partial eta-squared (η^2_p).
Results: The results showed significant differences with large effect sizes ($\eta^2_p > 0.14$) between mindfulness and the rest of the experimental groups as well as the control in the GDS, HDRS and NPI-Q scales. The mindfulness group showed significant scores compared with the control and muscle relaxation groups ($p < 0.05$) in the MMSE, while mindfulness and cognitive stimulation therapy were equivalent ($p \geq 0.05$).
Conclusions: Compared to the other experimental groups, the practice of mindfulness maintained cognitive function over a period of two years, while only mindfulness prevented the onset of depression in early-stage Alzheimer's disease. Based on its effectiveness in maintaining cognitive functions and preventing the course o mood disorders, we recommend mindfulness as the first-choice non-pharmacological treatment for mild to moderate Alzheimer's disease.

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P1084 / #434

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

IMPLEMENTING TRANSCRANIAL PULSE STIMULATION AGAINST DEMENTIA AT PSYCHIATRIC DEPARTMENT SCHAFFHAUSEN

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Aims: Our very first patient treated with TPS (80y, mixed dementia) improved after the first block of 6 sessions in MMSE from 21 to 25 points (maximum 30). Even after pausing for 10 weeks, the result remained stable and after another block of 6 sessions TPS, the MMSE improved to 27 points, including improvement of short term memory. These results encouraged us to boost this therapy in our psychiatry clinic and the results are here demonstrated as well as tolerability and safety and maintenance aspects of TPS.
Methods: to be presented with poster
Results: to be presented with poster
Conclusions: to be presented with poster

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P1085 / #1913

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

A NOVEL ELECTROACUPUNCTURE STIMULATION FOR CHEMOTHERAPY-INDUCED COGNITIVE IMPAIRMENT (CHEMOBRAIN) IN BREAST CANCER PATIENTS: A RANDOMIZED CONTROLLED TRIAL

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Aims: Chemotherapy causes various side effects, including cognitive impairment, known as 'chemobrain'. In this study, we determined whether a novel acupuncture mode called electroacupuncture trigeminal nerve stimulation plus body acupuncture (EA/TNS + BA) could produce better outcomes than minimum acupuncture stimulation (MAS) as controls in treating chemobrain and other symptoms in breast cancer patients.
Methods: In this assessor- and participant-blinded, randomized controlled trial, 93 breast cancer patients under or post chemotherapy were randomly assigned to EA/TNS + BA (n = 46) and MAS (n = 47) for 2 sessions per week over 8 weeks. The Montreal Cognitive Assessment (MoCA) served as the primary outcome. Digit span test was the secondary outcomes for attentional function and working memory. The quality of life and multiple functional assessments were also evaluated.
Results: EA/TNS + BA treated group had much better performance than MAS-treated group on reverse digit span test at Week 2 and Week 8, with medium effect sizes of 0.53 and 0.48, respectively, although no significant differences were observed in MoCA score and prevalence of chemobrain between the two groups. EA/TNS + BA also markedly reduced incidences of diarrhoea, poor appetite, headache, anxiety, and irritation, and improved social/family and emotional wellbeing compared to MAS.
Conclusions: These results suggest that EA/TNS + BA may have particular benefits in reducing chemotherapy-induced working memory impairment and the incidence of certain digestive, neurological, and distress-related symptoms. It could serve as an effective intervention for breast cancer patients under and post chemotherapy (trial registration: https://www.clinicaltrials.gov: NCT02457039).

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P1086 / #2615

POSTERS: J03. DRUG DEVELOPMENT, CLINICAL TRIALS

INSTRUMENTAL AND AERODYNAMIC ASSESSMENT OF HYPOKINETIC DYSARTHRIA IN WOMEN

Clara Ponchard[1], Didier Demolin[1], Lise Crevier-Buchman[1], Alain Ghio[2], François Viallet[3]
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Aims: The main goals of our research are to: (1) Provide a robust and innovative methodological framework for segmenting dysarthric speech data ; (2) Define an aerodynamic model of female speech ; (3) Compare aerodynamic performance between healthy and pathological subjects and finaly (4) Identify vocal markers that characterize parkinsonian speech
Methods: Our corpus is composed of 40 French female speakers aged between 40 and 90 years (20 parkinsonian patients and 20 control subjects). The descriptors analyzed in this study are intraoral pressure, estimated subglottic pressure, F0 and duration of production.
Results: Our results indicate that age must be taken into account in experimental studies because age varies the pressure which will increase in older subjects. Before 60 years, the pressure of healthy subjects and parkinsonian subjects without treatment is the same. After 60 years, the pressure of healthy subjects is significantly higher than the pressure of parkinsonian subjects with or without treatment. L-Dopa treatment has an impact on pressure only in subjects under 60 years. Parkinsonian subjects under 60 years of age have poorer pneumophonic control with a pressure that decreases during the sentence. The decrease of pressure during the sentence increases with age. Pressure is a robust parameter to characterize parkinsonian speech with a 91% success rate in automatic detection.
Conclusions: The analysis of the aerodynamic data showed the relevance of these measures for the detection and description of hypokinetic dysarthria in women.

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P1087 / #2035

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

THE JOINT WORK OF SIGNATURE CONSORTIUM: INTERNATIONAL SCENARIOS FOR THE ASSESSMENT OF SOCIAL COGNITION IN THE DIAGNOSIS OF NEUROCOGNITIVE DISORDERS

Alessandra Dodich[1], Marina Boccardi[2], Claudia Meli[1], Giulia Funghi[1], Andrea Panzavolta[3], Cristina Festari[4], Stefano Cappa[3], Thanos Chatzikostopoulos[5], Fabricio Oliveira[6], Marco Filardi[7], Nicola Girtler[8], Thibaud Lebouvier[9], Giancarlo Logroscino[7], Sarah Macpherson[10], Jordi Matias-Guiu[11], Andreas Monsch[12], Petr Novak[13], Leonardo Sacco[14], Ann-Katrin Schild[15], Harro Seelaar[16], Steven Shirk[17], Marc Sollberger[12], Magda Tsolaki[5], Esther Van Den Berg[16], Maxime Bertoux[9], Fiona Kumfor[18], Jan Van Den Stock[19], Chiara Cerami[3]
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Aims: At present, there is no consensus on a uniform operationalization of social cognition measures for the diagnosis of neurocognitive disorders (NCDs) in memory clinics. To overcome this limitation, the international consortium "clinical use of SocIal coGNnition measures for the AssessmenT of neURocognitivE disorders" (SIGNATURE) has been established in May 2022.
Methods: An international call was opened in May 2022. Two methodologists (MBo, CF) and three researchers expert in social cognition (MBe, FK & JVdS) were also involved in the project. The first phase of the project, which was aimed at identifying clinicians'/stakeholders' needs and making recommendations based on research priorities and implementation in clinical settings, was launched in July 2022 by collecting information using an ad hoc online survey.
Results: As of September 2022, a total of 96 participants (40% Female, 67 institutions, 18 countries) joined the consortium (https://sites.google.com/unitn.it/signature-initiative/home). 230 survey responses were collected (54% psychologists, 46% physicians). Only 45% of centers reported to routinely assess all six core DSM-5 cognitive domains. Among the others, 97% of respondents reported that social cognition was not routinely assessed due to the lack of guidelines and instruments. However, the majority of respondents agree on the utility of social cognition measures in early (85%) and differential (91%) diagnosis of NCDs, as well as in the identification of new cognitive phenotypes (89%).
Conclusions: This is the first international initiative using a combined top-down/bottom-up approach to define the best implementation strategy for social cognition tasks in harmonised neuropsychological assessments of memory clinics. The results of the first phase of the SIGNATURE initiative will clarify the international scenario and provide the basis for guidelines on the most effective plan for the ultimate benefit of patients and healthcare services.

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POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

SUBCORTICAL SALIENCE NETWORK NODE CONNECTIVITY PATTERNS ACROSS NEURODEGENERATIVE DISEASES

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[1]University of Toronto, Tanz Centre For Research On Neurodegenerative Disease, Toronto, Canada, [2]Krembil Brain Institute, University Health Network, Memory Clinic, Toronto, Canada, [3]The Edmond J. Safra Program in Parkinson's Disease, Morton And Gloria Shulman Movement Disorders Clinic, Toronto, Canada

Aims: Social cognition is affected in Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD)-related syndromes and Parkinson's disease (PD). This study examined changes in functional connectivity relating to social cognition across these groups by investigating nodes of the Salience network (SN).
Methods: 83 participants (19 AD, 29 FTLD, 18 PD and 17 healthy controls (HC)) from the UHN Memory and Movement Disorder Clinics underwent resting state fMRI and informants reported on participant's empathy and socioemotional sensitivity using the Interpersonal Reactivity Index (IRI) and the Revised Self-Monitoring Scale (RSMS), respectively. Resting state fMRI was analyzed using an ROI-to-ROI analysis, with ROIs centred on 2 cortical and 6 subcortical SN nodes.
Results: IRI sub-scores were significantly lower in FTLD compared to all other groups ($p<0.05$) and RSMS sub-scores were significantly lower in FTLD compared to HC ($p<0.05$), and although lower, no significant differences were found between AD and PD scores and HC scores for IRI or RSMS. After controlling for age, the FTLD group showed decreased connectivity between anterior cingulate cortex (ACC) and left lateral periaqueductal gray (PAG), ACC and left ventrolateral PAG (vlPAG), right amygdala and right vlPAG, and ACC and right ventral anterior insula (AI), compared to HC ($p<0.05$). The AD group showed a trend for decreased connectivity between subregions of PAG compared to HC while the PD group showed a trend for decreased connectivity between the right amygdala and vlPAG, similar to the FTLD group.
Conclusions: These results show that functional connectivity between cortical and subcortical nodes of the SN is decreased in the FTLD group, the group with the greatest alterations in social cognition. Our results also highlight the role of the PAG in social cognition across groups.

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P1090 / #1397

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

HIGH CONSUMPTION OF ALCOHOL IS ASSOCIATED WITH PREFRONTAL ATROPHY, WHILE VERY HIGH CONSUMPTION IS ASSOCIATED WITH WIDE-SPREAD CORTICAL ATROHY IN 70-YEAR-OLD MEN

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Aims: Long-term consumption of high levels of alcohol have previously been linked to cortical thinning mainly in the prefrontal cortex in cognitively normal individuals. However, it remains uncertain at what level of consumption that alcohol become deleterious to grey and white matter structures in the brain.
Methods: We divided a cross-sectional sample of 324 70-year-old men, derived from the population-based H70 study, into seven subgroups, based on weekly amount of consumed alcohol (0-50, 51-100, 101-150, 151-200, 201-250, 251-300 and above 300 gram per week). Cortical thickness and subcortical volumes were obtained on from structural magnetic resonance images using Freesurfer 5.3. Cognitive status of the participants was assessed using the clinical dementia scale (CDR). Alcohol consumption was assessed in a face-to-face interview in which participants estimated the amount of consumed alcohol per week during the past month.
Results: High consumption (251-300 gram/week) was associated with decreased cortical thickness in the right caudal prefrontal cortex. Very high consumption (>300 gram/week) was associated with reduced thickness in the bilateral caudal prefrontal cortex. In addition, we observed reduced thickness in several cortical regions that becomes atrophic in Alzheimer´s disease, such as the bilateral parietal cortex, medial temporal lobe, precuneus and the bilateral posterior cingulate. High or very high consumption was not linked to subcortical volume loss. 79 participants hade mild cognitive problems (CDR=0.5), however these participants did not display more thinning in high consuming groups compared with participants with CDR=0.
Conclusions: High consumption of alcohol (above 250 gram/week) is associated with a specific right-side prefrontal pattern of cortical thinning, while very high consumption (above 300 gram/week) is linked to wide-spread cortical thinning encompassing several areas that is known to become atrophic in Alzheimer´s disease in 70-year-old men.

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POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

HARMONIZING AD/PD RESEARCH DATA ACROSS DIVERSE NEUROIMAGING STUDIES THROUGH A COMMON ONTOLOGY

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Aims: Pooling data across multiple data collection sites in AD/PD-related neuroimaging research increases statistical power in studies relating risk factors to the neurodegenerative process and clinical outcomes. Current efforts such as ENIGMA and GAAIN are successful in collating clinical and biomarker measurements, such as neuroimaging scans from different sites. A major barrier in pooling diverse data sources is the heterogeneity in data collection paradigms and lack of harmonization. As part of ENIGMA and GAAIN, we propose a hierarchical framework to harmonize common elements and meta-data across diverse datasets, allowing researchers to query data elements across independently collected AD or PD studies.
Methods: The OASIS, PREVENT-AD and ADNI cohorts in GAAIN include differing labels for features corresponding to sex, diagnosis, and handedness, preventing cross-database searches. We build an ontology to harmonize and capture the similarity across terms in these datasets. Neuroimaging derived data were sorted into region, hemisphere, metric, unit, file, and software/version. Demographics properties were harmonized across sex, handedness, socio-economic status, and age. In the ENIGMA Parkinson's group, we harmonized 70 unique identifiers across 9 cohorts.
Results: Figure 1 highlights the harmonization process for the OASIS and ADNI data-sets hosted by GAAIN. The ENIGMA-PD information is stored in a Semantic Media Wiki accessible to collaborators, who can also query specific

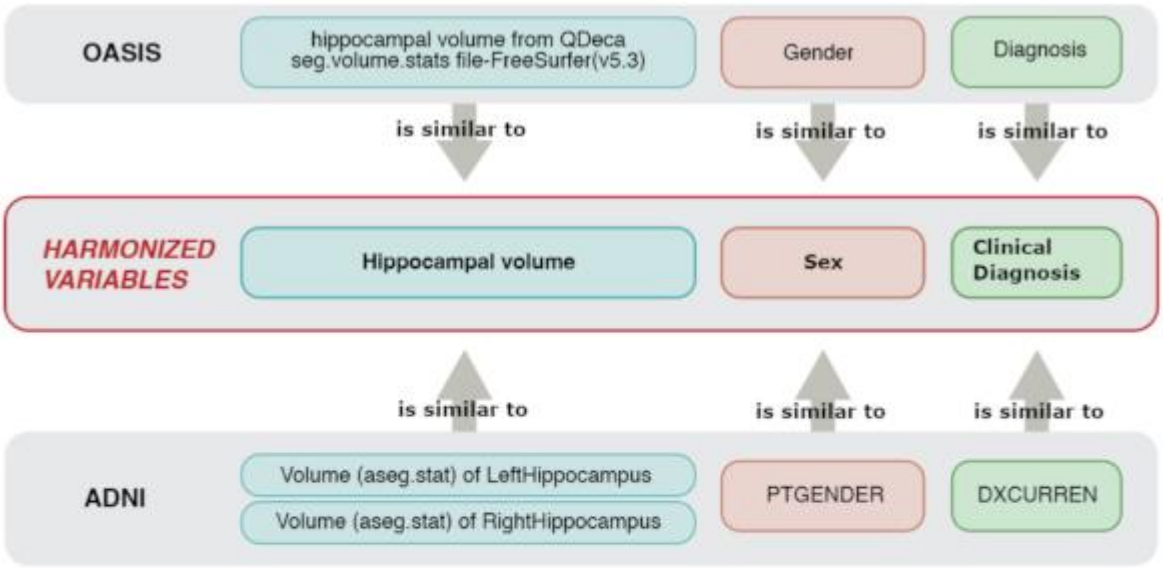

Figure 1: The ADNI cohort encodes data as "DXCURREN"[sic] and "PTGENDER," respectively, while the OASIS cohort encodes their data as "Diagnosis" and "Gender." These properties were retained in their original encoding and also harmonized by linking them to the top-properties "Clinical Diagnosis" and "Sex," with "is similar to" links to indicate potential data collection variability (ie, genetic determined sex vs self-reported gender identity).

cohort data.

Conclusions: Harmonization of AD/PD data across diverse cohorts allows for efficient and automated multi-site analyses. Work will continue to harmonize remaining GAAIN cohorts and provide a public ontology, integrated with current platforms, for future AD/PD studies to use.

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P1092 / #1578

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

LONGITUDINAL CHANGE IN NEUROPSYCHIATRIC SYMPTOM SEVERITY IS A SIGNIFICANT PREDICTOR OF TAU PATHOLOGY IN OLDER ADULTS

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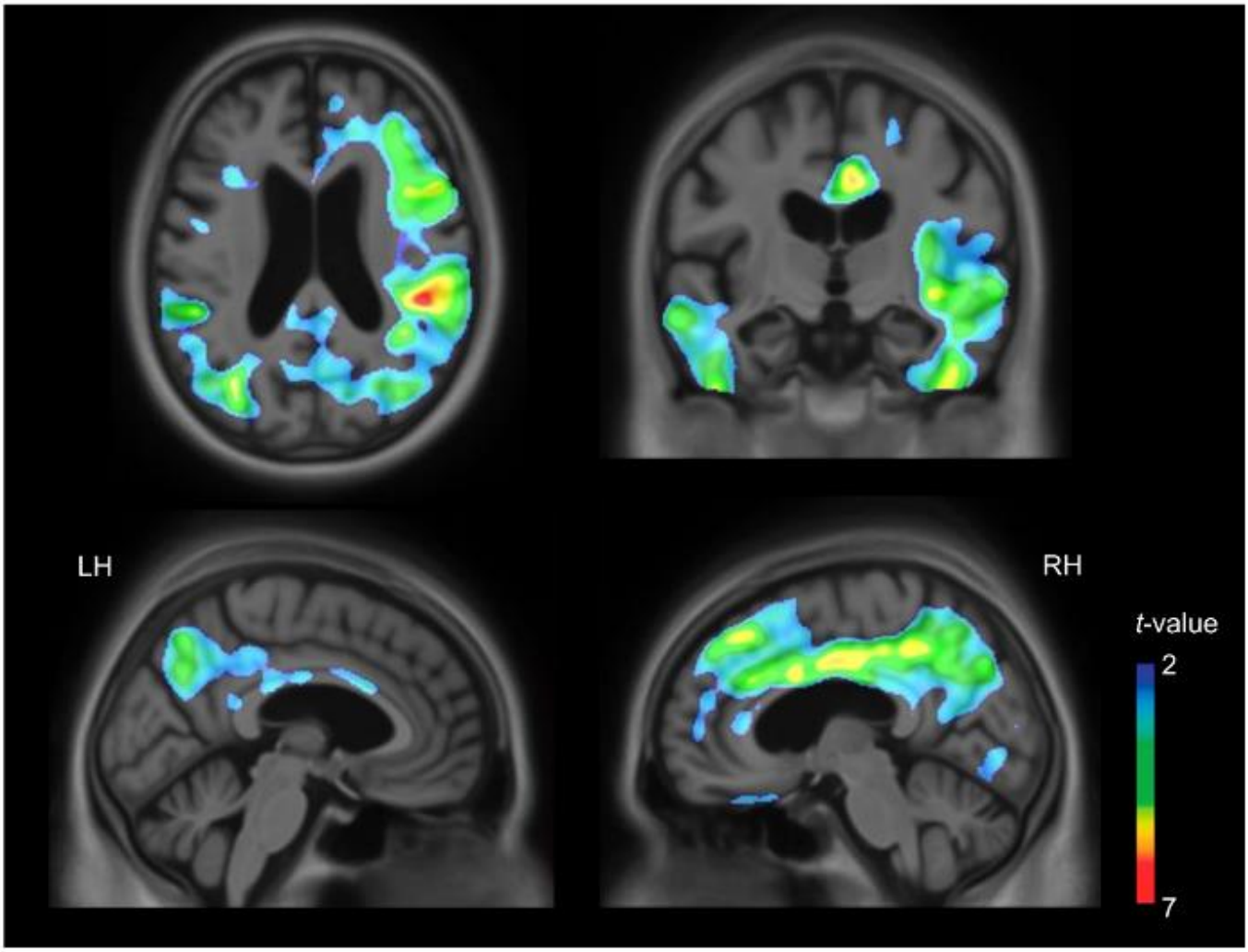
Aims: To evaluate whether longitudinal change in mild behavioral impairment (MBI) symptom severity is a significant predictor of tau burden derived from both PET and plasma in older adults.
Methods: In individuals across the AD spectrum from the TRIAD cohort, neuropsychiatric symptom burden was assessed longitudinally using the MBI-Checklist (MBI-C). Tau-PET was acquired with [^{18}F]MK6240 from 90-110 minutes and voxelwise SUVR maps were generated using cerebellar grey matter as the reference region. Plasma p-tau181 and p-tau231 were quantified at the University of Gothenburg, and log-transformed due to right skew. Multiple linear regression models tested for associations between annual rate of change in MBI-C score and both tau-PET and plasma p-tau, adjusting for age, sex, education, amyloid-β positivity, and group.
Results: Longitudinal MBI data (mean follow-up time = 1.4±0.4 years) were available for 151 individuals with tau-PET, and 128 individuals with plasma p-tau measurements (Table 1). Longitudinal change in MBI symptom severity was significantly associated voxelwise with tau-PET tracer retention bilaterally in the precuneus, posterior cingulate, and temporal cortex (Figure 1). Linear regressions also showed that annual change in MBI-C score was a significant predictor of baseline levels of plasma p-tau181 and p-tau231 (Table 2). Moreover, we observed that the interaction of plasma p-tau level and annual change in MBI-C score was significant in predicting cognition (MMSE total score) in our sample (Table 2).

Table 1: Sample characteristics

	CU	MCI	AD	*p*-value
N	94	35	22	
Sex = M (%)	36 (38.3)	16 (45.7)	10 (45.5)	0.675
Age	71.23 (6.23)	71.96 (6.14)	70.10 (7.76)	0.569
Education (years)	15.53 (3.56)	14.26 (3.53)	14.86 (4.25)	0.201
APOEε4 carrier (%)	67 (71.3)	22 (62.9)	12 (54.5)	0.274
Amyloid-β positive (%)	21 (22.3)	22 (62.9)	20 (90.9)	<0.001
MMSE score	29.09 (1.23)	27.89 (1.66)	22.18 (4.74)	<0.001
MBI-C follow-up time (years)	1.43 (0.39)	1.55 (0.58)	1.32 (0.43)	0.146
Annual change in MBI-C total score	0.25 (2.28)	1.25 (5.35)	6.05 (7.58)	<0.001

Figure 1: Voxelwise associations between longitudinal change in MBI symptom severity and [^{18}F]MK6240 PET



Longitudinal change in MBI-C score was significantly associated with tau-PET tracer retention bilaterally in the precuneus, posterior cingulate, and temporal cortex. Voxel-based regression analyses were corrected for multiple comparisons using random field theory with a cluster threshold of $p < 0.001$.

Table 2: Summary of regression analysis of plasma p-tau181 and p-tau231 on longitudinal change in MBI-C score

	Adjusted R^2	β coefficient	SE	p-value
P-tau181 ~ ΔMBI-C	0.370	0.022	0.009	0.021*
P-tau231 ~ ΔMBI-C	0.300	0.037	0.012	0.003**
MMSE ~ P-tau181*ΔMBI-C	0.276	0.072	0.024	0.004**
MMSE ~ P-tau231*ΔMBI-C	0.217	0.048	0.022	0.029*

Conclusions: This study provides novel findings on the longitudinal assessment of MBI and its association with tau pathology in the context of AD. These results suggest that the repeated assessment of neuropsychiatric symptoms may be an accessible, inexpensive tool for the detection of underlying tau pathology and support the prognostic utility of the MBI syndrome in identifying AD.

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P1093 / #2440

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

DECIPHERING BEHAVIOURAL AND PSYCHIATRIC SYMPTOMS IN LOGOPENIC VARIANT OF PRIMARY PROGRESSIVE APHASIA

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Aims: The logopenic variant of primary progressive aphasia (lvPPA) is a distinctive variant of primary progressive aphasia, in which recent evidence shows that Alzheimer disease (AD) might be the most common underlying pathology. Our goal is to evaluate the frequency of behavioural and psychiactric symptoms (BPS) in lvPPA.
Methods: This is a descriptive study that prospectively recorded data of 20 consecutive patients who met lvPPA criteria proposed by Gorno-Tempini: word retrieval and sentence repetition deficits, phonologic paraphasias, sparing of single-word comprehension and motor speech, absence of frank agrammatism and predominant left posterior perisylvian or parietal atrophy on MRI and/or hypoperfusion or hypometabolism on SPECT or PET at the Hospital Universitario de Salamanca, Spain (mean age at onset 73.1 ± 4.9 years, mean duration of dementia 3.8 ± 2.3 years, 55% women), 20% living in nursing homes. The Neuropsychiatric Inventory (NPI) was used to assess BPS.
Results: At least one BPS occurred in 100% of lvPPA participants; the median NPI score was 34 (range:10-86), with a median number of 5 symptoms per patient. The most frequent symptoms were anxiety (80%), depression (70%), apathy (70%) and sleep disturbances (60%), followed by agitation (50%), disinhibition (50%), appetite/eating abnormalities (45%), irritability (40%), aberrant motor behaviour (40%), hallucinations (35%), delusions (25%) and euphoria (10%). 45% received antidepressants, 40% antipsychotics, 15% anxiolytics and 10% hypnotics. In terms of appetite/eating disturbances, hyperphagia prevailed (35%) over appetite loss (10%).
Conclusions: BPS are frequent in lvPPA. New investigations are required to better evaluate the relationship between histopathologic evidence of specific neurodegenerative pathologies in lvPPA (e.g. AD, frontotemporal lobar degeneration [FTLD]-tau, FTLD-TDP, other) and different BPS profiles.

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P1094 / #2037

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

TELENEUROPSYCHOLOGY PLATFORM FOR THE REMOTE ASSESSMENT OF MILD NEUROCOGNITIVE PATIENTS: A USABILITY AND USER EXPERIENCE PILOT STUDY OF TENEPSIA SYSTEM

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Aims: Prevention, diagnosis and management of neurocognitive disorders has been radically changed by digital technologies. In the last few years, the focus on technologizing and digitizing the care of chronic patients has increased. We present a pilot study on usability and user experience of a high quality, tablet-based remote neuropsychological platform developed with the methodological expertise of a joint working group of three Italian scientific societies (SIN, SINP and SINdem) and the support of Biogen and REPLY.
Methods: Two groups of 10 healthy volunteers were enrolled for testing the Examiner and User interfaces of the platform. Examiner participants logged-in the platform website on their personal computer/laptop, while user participants downloaded the platform APP on their own tablet/iPad. A 60-min teleneuropsychology session including assessment of depression and functional status as well as assessment of main cognitive domains was carried out. System usability and user experience were assessed via self-reported validated questionnaires (i.e., System Usability Scale – SUS and User Experience Questionnaire – UEQ). The Information Technology Familiarity Questionnaire (ITFQ) evaluated familiarity with technology.
Results: Questionnaire scores showed an overall satisfying usability and user experience with perceived ease of use, enjoyability and high motivation during the session. ITFQ score did influence usability or user experience.
Conclusions: Our preliminary results suggest that the digital platform we developed is a user-friendly tool for both examiners and users. Future steps include validation and procedure standardization in patients. Our findings encourage the possible use of this technology in clinical settings, with potential benefit for patients, families, and healthcare facilities.

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P1095 / #2042

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

SIMULATED PREDICTIONS OF MILD COGNITIVE IMPAIRMENT WITH REMOTE NEUROPSYCHOLOGY ASSESSMENT PLATFORM

Andrea Panzavolta[1], Federico Sternini[2,3], Chiara Cerami[1,4], Paolo Caffarra[5], Dalila De Vita[6], Alessandra Dodich[7], Federica L'Abbate[8], Luigi Lavorgna[9], Valentina Laganà[10], Camillo Marra[8,11], Costanza Papagno[7], Francesca Ferrari Pellegrini[12], Andrea Stracciari[13], Luigi Trojano[6], Tiziana Iaquinta[14], Roberta Pandolfi[15], Monica Calore[16], Alice Ravizza[3], Stefano Cappa[1,4]
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Aims: In the last few years, the focus on technologizing and digitizing the care of neurocognitive patients has become paramount. Many platforms for the teleassessment of cognitive functioning have been developed. Only a few, however, have been registered as medical devices in Europe and declared suitable for clinical settings since tests assessing comparability with the standard of care (i.e. in person neuropsychology evaluation) can be expensive and time-consuming. The use of synthetic data can overcome this limit accelerating innovation and providing comprehensive evidence of long-term safety and effectiveness. Hereby, we present results of a simulation approach able to proof comparability of remote and digitized test performances with the state-of-the-art for the neuropsychological patterns of mild cognitive impairment (MCI) subjects.
Methods: A literature search identified normal and pathological reference scores. Using data from the state-of-the-art, a simulation of teleneuropsychology cognitive profiles of single and/or multidomain amnestic and non-amnestic MCI was performed and validated by clinical experts.
Results: Using synthetic data to describe the target population, the teleneuropsychology platform was able to provide to the clinical expert an adequate description of the different cognitive profiles identified in literature giving proof of clinical performance under Medical Device Regulation (MDR) requirements.
Conclusions: The use of teleneuropsychology platforms should be strongly recommended after testing performance with simulation models. Normal and pathological profiles can be successfully simulated by novel simulation approach. Digital platforms for the diagnosis and monitoring of cognitive disorders may strive towards a more sustainable and equitable future, especially for the most fragile segments of the population.

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P1096 / #2202

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

CORRELATION OF MR IMAGE BASED HIPPOCAMPAL TEXTURE PATTERNS AND NEUROPSYCHIATRIC SYMPTOMS FOR DIFFERENTIATION OF ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA

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Aims: Noncognitive behavioral and psychiatric symptoms are common in dementia and affects nearly 90% of the patients across the disease course. Despite its pervasiveness, the manifestation of these psychiatric symptoms in dementia subtypes and its association with neuroimaging characteristics has not been extensively explored. In this study, the correlation between Magnetic Resonance (MR) image-based hippocampal textural patterns and psychiatric symptoms in Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD) is analyzed.
Methods: Structural MR images of AD and FTD subjects obtained from a public database are preprocessed and the hippocampal brain regions are segmented. From the segmented volumetric structures, histogram based and gray level co-occurrence matrix based textural patterns are extracted. Significant texture features for differentiating AD and FTD are assessed using the Wilcoxon rank sum test. Point biserial correlation coefficient is employed to evaluate the association between significant hippocampal textural pattern and severity of neuropsychiatric symptoms determined by Neuropsychiatric Inventory (NPI).
Results: MR based hippocampal textural features are able to characterize the dementia subtypes. Histogram based skewness and gray level co-occurrence matrix-based correlation features show statistical significance ($p < 0.01$) in differentiating AD and FTD. Hippocampal textural features of AD subjects exhibit a significant correlation with agitation, depression, disinhibition and aberrant motor behavior. In FTD subjects, an inverse correlation is observed between skewness feature and apathy. Thus, a significant association is obtained between the behavioural symptoms and hippocampal texture features extracted from FTD and AD images.
Conclusions: Hippocampal texture descriptors are observed to be reliable markers for the differentiation of FTD and AD. Further, the significant correlation between image characteristics and NPI severity suggest that the psychopathology of dementia subtypes could be captured by the textural alterations in the hippocampus.

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P1097 / #602

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

PREDICTION OF POST-OPERATIVE DELIRIUM BY USING QUANTITATIVE ELECTROENCEPHALOGRAM: A PILOT STUDY

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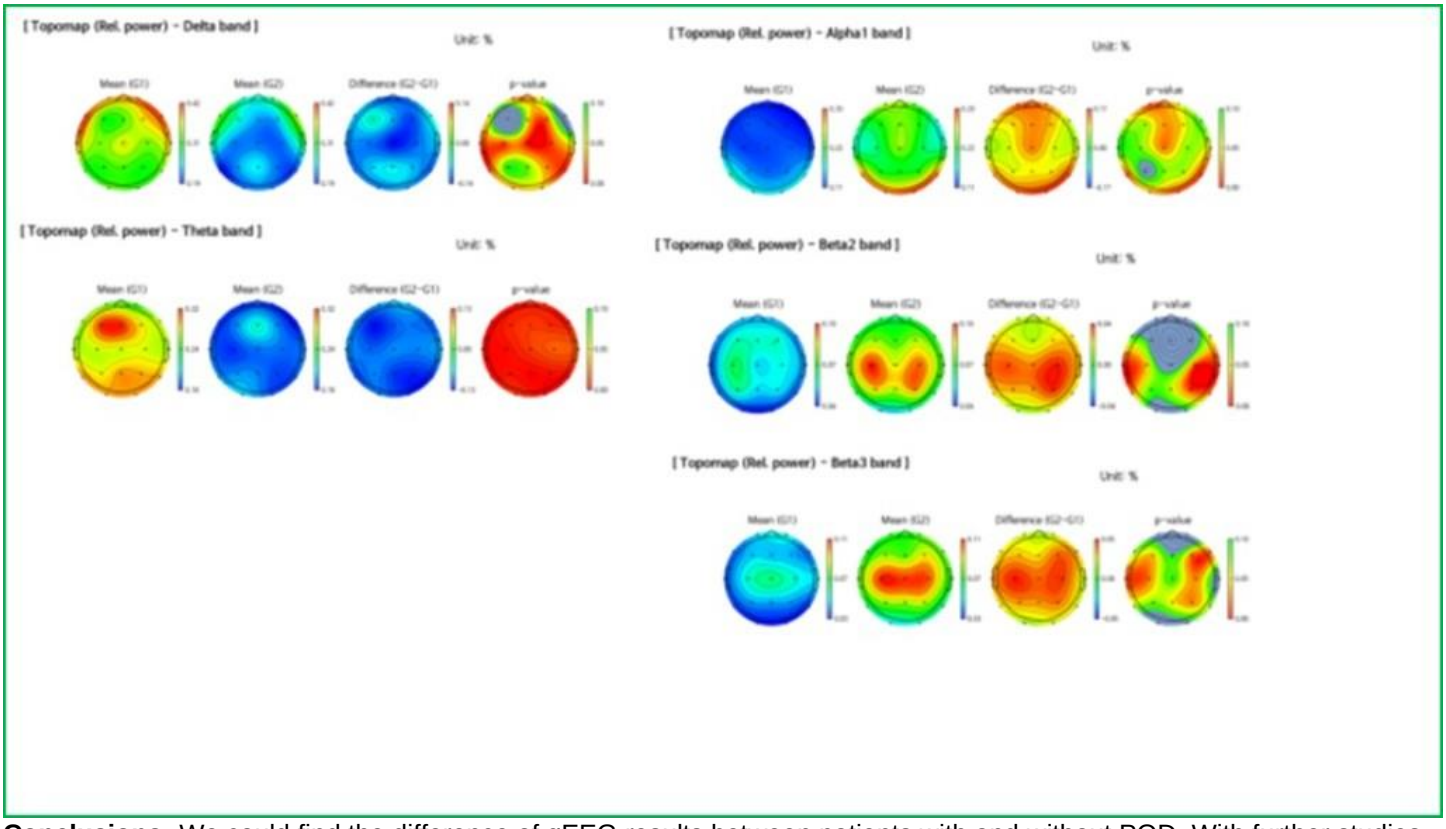
Aims: Objectives: Post-operative delirium (POD) is the most common complication of surgery for older adults, affecting up to 50% of seniors. If not identified early and treated, POD can lead to long-term health issues, including cognitive decline and functional decline. We investigated the possibility of prediction of POD by using the quantitative electroencephalogram (qEEG).
Methods: Ten patients with POD and 16 without POD were included, who performed EEG before surgery. For qEEG measurement, power spectrum was measured and compared between two groups.
Results: Patients with POD showed relatively increased delta and theta activities and decreased alpha1, beta2, and beta3 activities in all brain areas, compared with those without POD (all, $p<0.05$). Slow to fast activity ratios, such as theta/beta, delta/alpha, and theta/alpha ratios, were increased in patients with POD. Decreased connections in slow wave activity and increased connections in fast wave activity were observed in patients with POD, compared with patients without POD.



Conclusions: We could find the difference of qEEG results between patients with and without POD. With further studies of larger sample size, prediction of POD before surgery by using qEEG would help older adults to have safe and healthy post-operative care.

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P1098 / #176

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

VISUAL ASSESSMENT OF [18F]MK-6240 PET SCANS IN EARLY ALZHEIMER'S DISEASE

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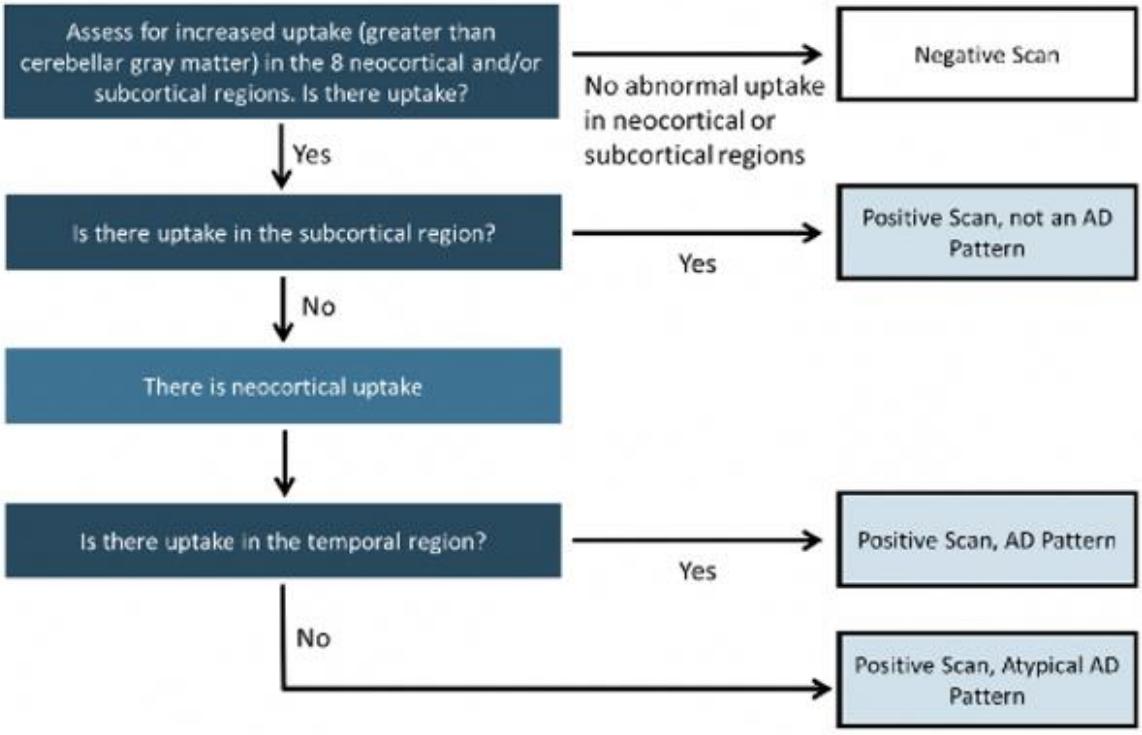
Aims: Assessment of tau deposition plays an important role in the selection of subjects for clinical trials. [^{18}F]MK-6240 tau PET scans were included in a substudy of the Phase 2 study of tilavonemab in early Alzheimer's disease (AD) (NCT0288095) at baseline, week 44, and week 96. Here we report the application of a visual read algorithm which provides both a categorical outcome and regional characterization of abnormal tau deposition.
Methods: [^{18}F]MK-6240 scans were assessed by evaluating for abnormal tau deposition and the extent of tracer retention (readers mark 'none', '<25%', '25%-75%', or '>75%' of a region) in 16 brain regions from the temporal and extra-temporal lobes, relative to cerebellar gray matter. Subjects were binned into four categories according to the decision tree in **Figure 1**. Each scan was read by up to 3 readers to reach a consensus. Scans were processed and prepared for SUVR analyses in Braak regions I-VI and whole brain, normalized to inferior cerebellar gray
matter.

Figure 1. Read decision tree and image features for each read category



Overall Score	Image Features
Negative Scan	Regional cortical tracer uptake in neither the neocortical regions nor the subcortical regions
Positive Scan, AD Pattern	Abnormally increased regional cortical tracer uptake in at least 1 neocortical region, which must include the temporal lobe, and no uptake in any subcortical region
Positive Scan, Atypical AD Pattern	No uptake in the temporal lobe; abnormally increased regional cortical tracer uptake in any other neocortical region (often the occipital region); and no uptake in any subcortical region
Positive Scan, *not* an AD Pattern	Abnormally increased uptake in 1 or more subcortical regions (regardless of uptake in neocortical regions)

Results: The demographic, clinical, and imaging data from 378 scans across 217 subjects are given in **Table 1**, mean images for each group are shown in **Figure 2**. Readers 1 & 2 agreed on 92% of scans. The visual read extent score (VRES) correlated strongly with SUVR in whole brain and Braak regions III-VI (ρ>0.80, **Figure 3a**). Change in VRES correlated most strongly with percent change in Braak III and IV SUVR (ρ=0.49, **Figure 3b**). A representation of the visual extent (**Figure 4**) shows good agreement with *in vivo* Braak stages assigned to each subject.

Table 1. Demographic, clinical and imaging data for each visual read category

	Negative (N=21)	Positive, Not AD (N=2)	Positive, Atypical AD (N=1)	Positive, AD (N=354)
Mean age, years (SD)	77.8 (4.2)	79.5 (3.5)	73	72.5 (7.4)
Sex, % male	61.9	100	0	46.6
APOE ε4 carrier %	61.9	100.0	0.0	72.0
Mean Centiloid (SD)	83.3 (32.8)	105.0 (35.4)	121	99.8 (30.0)
Mean MMSE (SD)	24.6 (3.5)	26.5 (0.7)	27	22.0 (4.8)
Mean CDRsb (SD)	3.69 (1.91)	1.5 (2.12)	2	4.60 (2.48)
Mean AD Temporal MetaROI SUVR (SD)	1.28 (0.31)	1.10 (0.00)	1.21	2.56 (0.72)
Mean Whole Brain SUVR (SD)	1.01 (0.17)	0.96 (0.01)	1.39	1.92 (0.66)
Tau Load (% Braak 0-II/III-IV/V-VI/nonBraak)	95/0/5/0	100/0/0/0	0/0/0/100	9/31/55/5

Figure 2. Mean SUVR images for each category in the Tilavonemab study

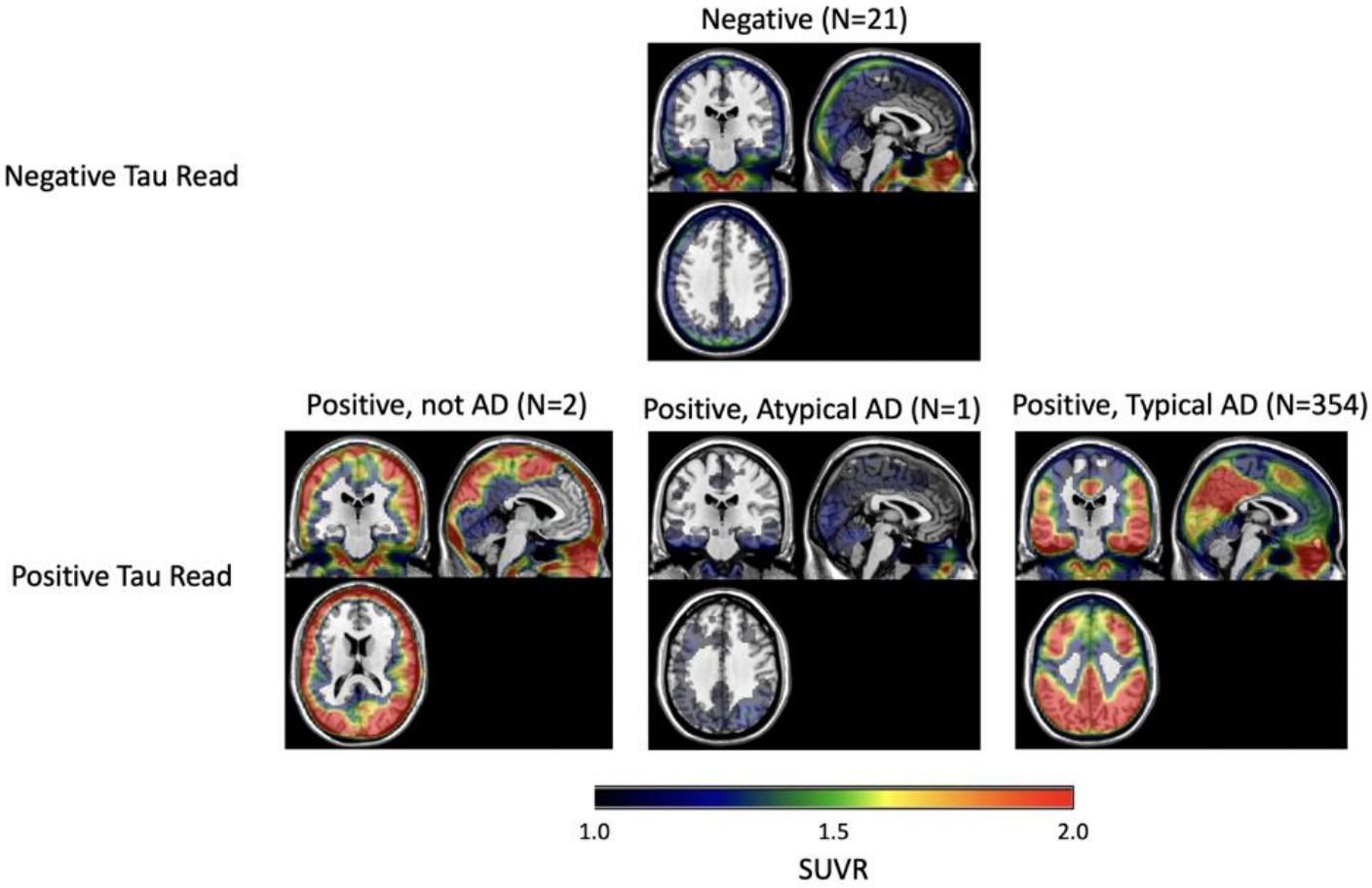
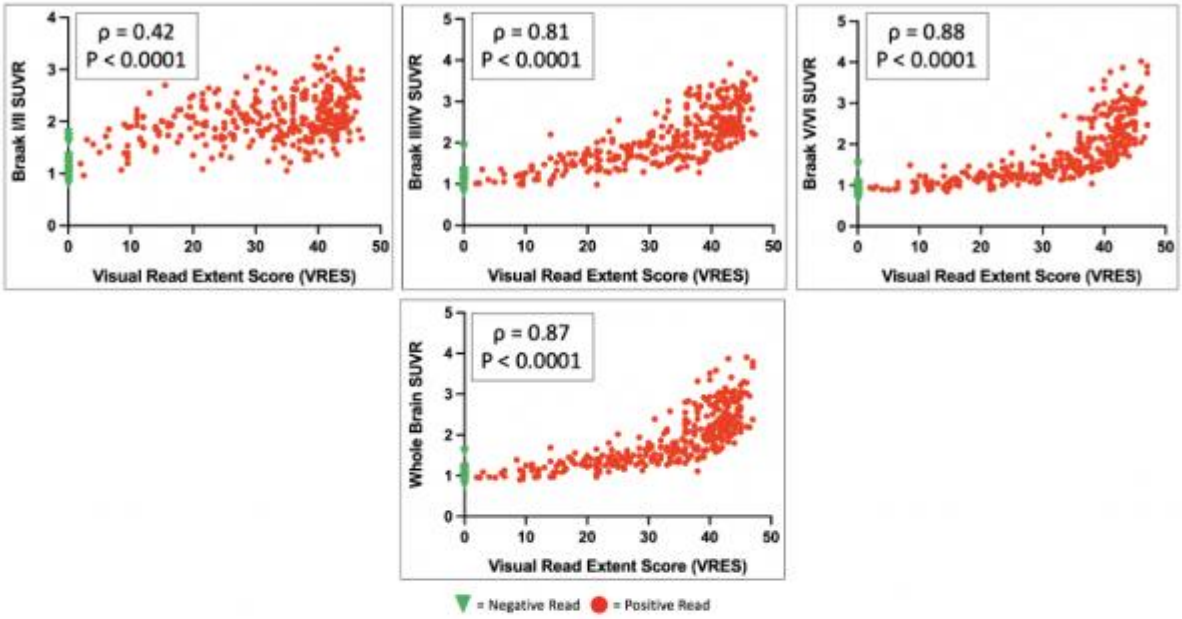


Figure 3. Spearman correlation between SUVR and Visual Extent

a. Correlation between SUVR and VRES



b. Correlation between % Annual Change in SUVR and Annual Change in VRES

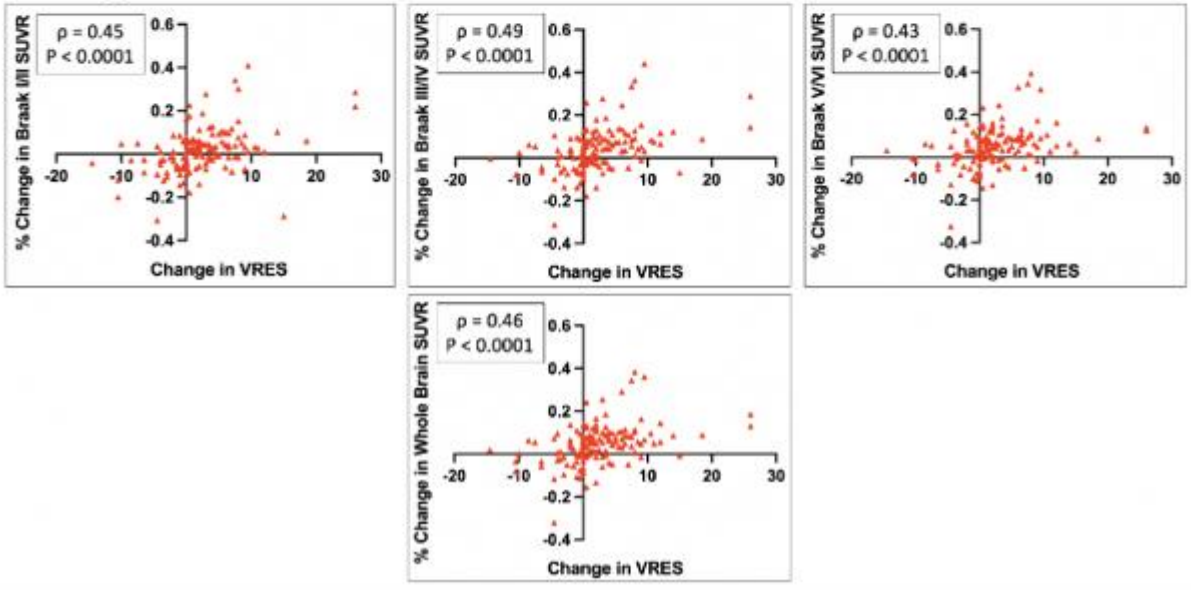
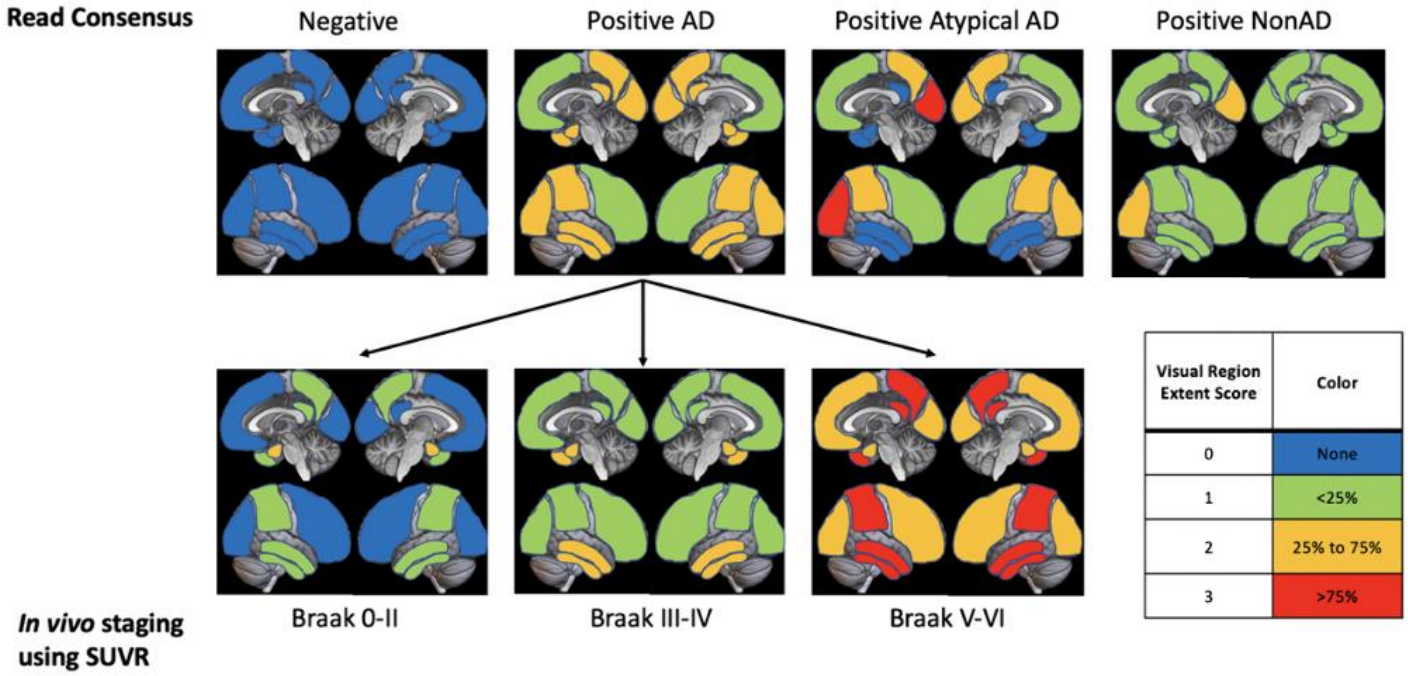


Figure 4. Visual Read Extent by Read Category and SUVR Braak Stage



Conclusions: Our visual assessment of [^{18}F]MK-6240 PET scans showed good agreement between readers. The use of a novel extent score may allow us to select AD patients by Braak stage using solely a visual read.

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P1099 / #841

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

GENDER DIFFERENCES, ALCOHOL USE AND COGNITIVE IMPAIRMENT

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Aims: The aim of this study was to investigate whether there are gender differences in the association between alcohol use and cognitive performance at the MCI stage, secondly to examine whether alcohol pose a greater risk for development of Alzheimer in females than males at the MCI stage and lastly to learn whether there are gender differences in the association between alcohol use and brain atrophy in MRI at the MCI stage.
Methods: This study has a cross-sectional observational design.The cohort included 251 subjects, females (n=130) and males (n=121), with an MCI diagnosis. Subjects were selected from the memory clinic at Karolinska University Hospital, Stockholm County. We compared MMSE-score, cerebrospinal fluid biomarkers (beta amyloid, tau protein and phosphorylates tau protein) for Alzheimer's disease and MRI rating scales for mediotemporal atrophy, global cortical atrophy and white matter hyperintensities of non-users, light to moderate users and heavy-users in females and males.
Results: There were no significant gender differences regarding MMSE score and CSF-biomarkers for Alzheimer's disease. There were statistically significant gender differences regarding MRI scans. Females showed high grade of medial temporal atrophy, global cortical atrophy and white matter hyperintensities at significantly lower quantities of alcohol than males. This significant difference was more pronounced in the left temporal lobe.
Conclusions: No significant gender differences were found regarding MMSE or CSF-biomarkers, but there was a statistically significant gender difference in MRI rating scales scores in this study. The results suggests that females generally are more affected by alcohol than males in accumulating signs of impairment on MRI scans. Females show the same damage as males at a significantly lower consumption level than males. However, the results should be interpreted with caution due to the small sample size.

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P1100 / #1393

POSTERS: J05. GENETICS, EPIDEMIOLOGY

EPIGENETIC NETWORK ASSOCIATION WITH COGNITIVE AND PSYCHIATRIC SYMPTOM PRESENTATION IN PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a highly heterogeneous disorder, encompassing a complex spectrum of clinical presentation including motor, sleep, cognitive and neuropsychiatric symptoms. We aim to investigate genome wide DNA-methylation networks in post-mortem PD brain samples and test for region specific association with common secondary sleep, psychiatric and cognitive symptoms.
Methods: DNA methylation data was generated on the Illumina 450K microarray for a cohort of 97 PD cases encompassing 259 individual post-mortem brain samples from the Frontal Cortex (FC), Caudate Nucleus (CN) and Substantia Nigra (SN). Networks of inter-correlated DNA methylation loci were detected using weighted gene correlation network analysis (WGCNA) and associations were tested using regression analysis, controlling for biological and technical confounders and with associated modules interpreted using gene ontology analysis.
Results: Of traits tested, sleep disorder, anxiety, hallucinations and depression symptoms were most robustly associated, specifically within the SN, with depression being associated to the highest number of modules and showing the highest level of significance ($p = 0.007$). This association was observed when controlling for predicted proportion of NeuN+ neuronal cells and no significant difference in these proportions was observed between PD cases with or without depression. Gene ontology analysis of the most highly associated module showed enrichment for terms related to neuronal functioning (growth cone, synapse part, neuronal cell body, calcium ion binding).
Conclusions: These findings potentially highlight the involvement of neuronal changes within the SN with regards to depressive symptom presentation and identify the epigenetic networks associated. Further ongoing work is currently testing for genetic risk enrichment within associated networks, as well as using publically available snRNA-seq data to validate cell-specific changes.

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P1101 / #2112

POSTERS: J05. GENETICS, EPIDEMIOLOGY

DOES PHYSICAL ACTIVITY MODIFY THE RISK OF NEW ONSET OF NEUROPSYCHIATRIC SYMPTOMS IN OLDER ADULTS FREE OF DEMENTIA?

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Aims: To examine associations between mid- and late-life physical activity (PA) with new onset of various neuropsychiatric symptoms (NPS) in older adults.
Methods: Longitudinal study with a median follow-up of approximately 5.3 years derived from the population-based Mayo Clinic Study of Aging. We included up to 2474 persons (sample size varies by outcome) aged ≥ 70 years (mean 79 years) who were free of dementia and the given NPS measures at baseline. PA in midlife (between 50-65 years) and late-life (within one year of baseline) was assessed using a self-reported questionnaire. We created composite scores for overall PA and three PA intensities, separately for mid- and late-life. Onset of 12 different NPS was assessed using the Neuropsychiatric Inventory Questionnaire. Cox proportional hazard models were calculated, adjusting for age (time scale), sex, education, APOEε4 status, and medical comorbidities.
Results: Late-life overall PA was associated with a decreased risk of new onset of depression (HR 0.960; 95% CI 0.933, 0.987; p=0.005), nighttime behavior (HR 0.963; 95% CI 0.930, 0.998; p=0.036), and appetite change (HR 0.956; 95% CI 0.927, 0.987; p=0.005). Light intensity late-life PA was associated with a decreased risk of incident nighttime behavior, and appetite change; moderate intensity late-life PA with a decreased risk of incident anxiety, depression, hallucinations, and appetite change; and vigorous intensity late-life PA with a decreased risk of incident irritability. Light intensity midlife PA was associated with a decreased risk of incident nighttime behavior; and moderate intensity midlife PA with a decreased risk of incident appetite change.
Conclusions: Late-life PA, particularly at light and moderate intensities, may decrease the risk of new onset of NPS in old age, albeit effect sizes are small in this community-based sample.

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P1102 / #971

POSTERS: J06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

EFFECTS OF ASTROCYTES SENESCENCE IN NEURONAL FUNCTIONS AND NEURODEGENERATIVE DISORDERS

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Aims: In this study, we investigated whether long-term culture induces senescence and functional alterations in rat astrocytes and their effects on neuronal function.
Methods: We used long-term culture method that mimic the physiological aging over time in rat astrocytes. The aging phenotypes were investigated senescence-associated β-galactosidase (SA-β-gal) activity as a cellular senescence marker and the changes in aging-related factors including nuclear size and senescence associated secretory phenotypes (SASPs). The presence of astrocytic dysfunctions in cell migration, phagocytosis, and mitochondrial function in aged astrocytes were also investigated as well as the effects of aged astrocytes on neuronal functions.
Results: The results indicated that long-term cultured astrocytes showed cellular senescence phenotypes including an increase in SA-β-gal-positive cells associated with an increase in nuclear size and SASPs such as IL-6 and IL-1β. We also observed dysregulation of cellular functions based on wound-healing, neuronal protection, and phagocytosis assays. Finally, mitochondrial dysfunction was noted through the determination of mitochondrial membrane potential using tetramethylrhodamine methyl ester and the measurement of mitochondrial oxygen consumption rate.
Conclusions: Our data suggest that long-term cultured astrocytes show aged cell-like phenotypes through mitochondrial dysfunction, immune activation which may have implications in brain aging and neurodegenerative conditions.

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P1103 / #1555

POSTERS: J06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

LABEL-FREE FUNCTIONAL CHARACTERIZATION OF HUMAN BRAIN ORGANOIDS AT SINGLE-CELL RESOLUTION

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Aims: Three-dimensional neural organoids are self-organizing *in vitro* models that recapitulate fundamental aspects of human brain development. Thus, neural organoids are becoming widely used to study neuronal development and investigate mechanisms of progressive neurologic disorders such as Alzheimer's disease and Parkinson's disease. The ability to measure the electrical activity of human brain organoids in real time, live and label-free can provide much needed insight into the complexity of neuronal networks. High-density microelectrode arrays (HD-MEAs) provide unprecedented means for non-invasive high-content electrical imaging and was used to acquire real time measurements from neural organoids.
Methods: In this study, the HD-MEA platform featuring 26,400 electrodes per well (MaxWell Biosystems AG, Switzerland) was used to capture fast propagating action potentials in organoids at different scales, ranging from network through single-neuron to subcellular features.
Results: Metrics such a firing rate, spike amplitude, burst shape and synchronicity specific figures were extrapolated in a high throughput manner. Finally, at the subcellular level, we characterized the axonal signal and computed the conduction velocity across multiple neurons within a network.
Conclusions: The parameters used in this study can be applied to investigating disease progression and the effects of different pharmacological tools.

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P1104 / #1548

POSTERS: J07. ANIMAL MODELS

HIPPOCAMPAL EFFECTS OF STREPTOZOTOCIN-INDUCED NEURODEGENERATION IN FEMALE RATS

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Aims: Sporadic Alzheimer's disease (sAD) is the most common form of dementia worldwide associated with several neurodegenerative events in the hippocampus. Animal models are critical for elucidating dementia-related processes. An established sAD model is induced by the intracerebroventricular (icv) injection of Streptozotocin (STZ) in rats. Despite the fact that women show an increased risk of sAD, female animals are often excluded from basic research. Our objective was to study the female brain changes in rats with experimental sAD, using animals with ovaries (Sham) and ovariectomized (OVX, a menopause model).
Methods: Rats were submitted into 4 experimental groups: Sham, Sham+STZ, OVX, and OVX+STZ. OVX and OVX+STZ groups were ovariectomized and, 14 days later, Sham+STZ and OVX+STZ groups were injected with 3 mg/kg icv-STZ. During the last two weeks until the end of the study (day 30 post icv-STZ), we performed several tests aiming to assess species-typical behavior, object recognition memory, spatial learning and memory, and depressive-like behavior. Besides, neuronal cells and glial cells analysis were performed in hippocampus.
Results: Our results show that STZ affected behavioral performance and cell morphology differently in our model depending on the ovarian steroid of female rats.
Conclusions: Overall, sex differences on brain function are a relevant issue and should be considered in future sAD research.

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P1105 / #2516

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

CHRONIC REST:ACTIVITY PATTERNS AND POLYSOMNOGRAPHIC SLEEP PATTERNS OF DYADS OF PEOPLE WITH DEMENTIA AND CAREGIVERS

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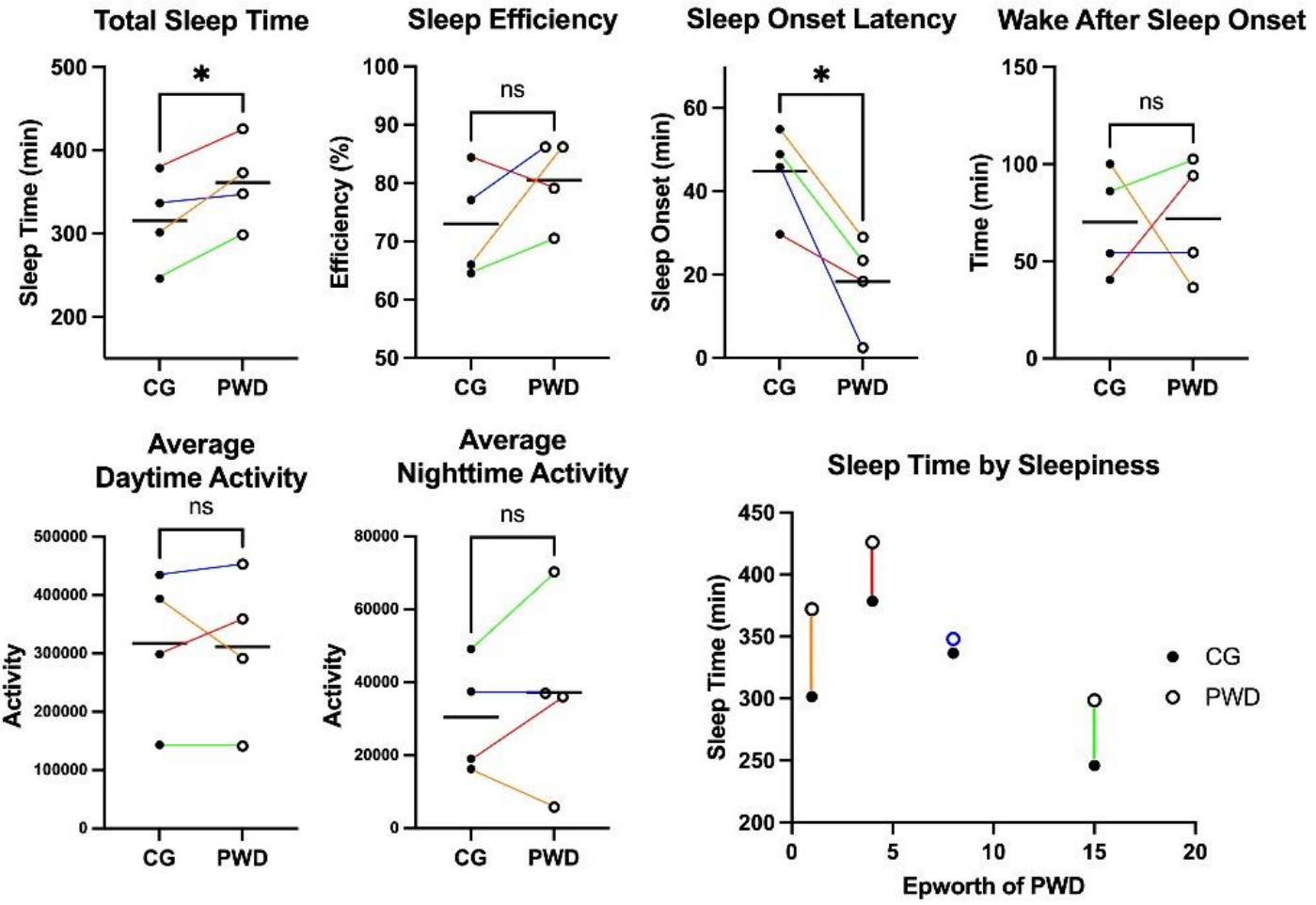
Aims: Sleep disturbances including insomnia, poor sleep quality, and sleep fragmentation appear to play a role in the development and progression of Alzheimer's disease (AD) in older adults, but may also affect the health of caregivers. The purpose of this pilot study was to objectively quantify the chronic rest:activity and polysomnography of the sleep of patients with dementia (PWD) and their caregivers (CGs).
Methods: Patients: Four dyads with PWD and their primary CGs. Actigraphy: Wrist actigraphy recorded for 14 days divided into fixed rest (2200-0600) and fixed activity (0600-2200) periods. Polysomnography: recorded and scored for 1 night for each dyad member separately. Variables: sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO), sleep efficiency (SEff). Survey: Epworth Sleep Scale.
Results: Actigraphy indicated no differences within dyads for average daytime or nighttime activity, indicating the activity levels of CGs reflect the activity of their PWD partners. Despite similar activity levels, CGs displayed sleep deficits compared to their partners, with lowered TST and increased SOL on polysomnography when sleeping separately. Polysomnographic measurements correlated with subjective sleepiness; dyads who had worse sleep had worse subjective daytime
sleepiness.



Conclusions: The main findings of this pilot dyadic study reveal that the daily rest:activity patterns of CGs reflects that of their partners. Importantly, despite similar day- and nighttime activity, CGs had worse overall sleep than their demented partners, with significantly lowered TST and increased SOL when sleeping separately, implying persistent sleep dysregulation in CGs. Our dyadic model currently is being applied to studies with larger sample sizes in order to determine the impacts of sleep on caregiving.

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P1106 / #2535

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

THE EFFECT OF PSYCHOSOCIAL INTERVENTION ON FAMILY CAREGIVERS OF PATIENTS WITH DEMENTIA

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Aims: Caring for dementia negatively affects the mental and physical aspects of the caregiver**s**. Most people with dementia living in the community are cared for by family members. This study aimed to investigate whether group-based psychosocial interventions can reduce the care burden and depressive symptoms of family caregivers and improve positive attitudes toward dementia.
Methods: We recruited family caregivers of dementia patients indwelling in the community registered with the Municipal Dementia Center. Group-based psychosocial interventions have been implemented for them. Components of the psychosocial interventions were general education on dementia, social skills training, problem-solving skills, social support, and mindfulness. It consisted of 12 sessions of 90 minutes per session. The primary outcome measure was the Zarit Burden Interview-short form (S-ZBI). The secondary outcome measures were the Dementia Attitude Scale (DAS), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Medical Outcomes Study Social Support Survey (MOS-SSS).
Results: Sixty-three family caregivers participated in this study, and forty-seven data were suitable for analysis. The age of subjects was 70.15±8.94 years, and 68.1% were female. The S-ZBI score significantly decreased from 23.64±7.68 to 20.47±7.62 ($p=0.009$). The DAS score increased from 86.34 ± 20.44 to 103.32 ± 14.64 ($p<0.001$), the CES-D score decreased (from 20.87 ± 11.67 to 14.28 ± 10.44, $p<0.001$), and the MOS-SSS score increased(from 64.23 ± 17.68 to 71.15 ± 16.71, $p=0.002$).
Conclusions: Psychosocial interventions had beneficial effects on alleviating care burden, attitudes toward dementia, and depressive symptoms and promoting social support of family caregivers caring for dementia patients. This study proposed that implementing group psychosocial interventions may improve the well-being of family caregivers.

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P1107 / #2293

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

THE TASK OF CARING FOR A DEMENTIA PATIENT IS INFLUENCED BY THE HEALTH OF THE FAMILY CAREGIVER

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Aims: The study was to analyze how the health status of the caregiver influences the task of caring, the burden, emotional state, and experiences and sensations that influence their quality of life
Methods: Retrospective study, unicenter, including 254 family caregivers of people with degenerative dementia (Alzheimer's 180 – non-Alzheimer's 74). Demographic data of caregivers: sex, kinship, age, schooling, health status (good or poor). The burden (Zarit), stress (CSI), anxiety (HAD-A), depression (HAD-D) and questionnaire of experiences and sensations – dichotomous response (true/false) indicative of quality of life were assessed.
Results: Good health status was considered in 131 (51.6 %) and poor health in 123 (48.4%) caregivers. These in poor health had significantly higher values in all the parameters evaluated: Zarit-burden (22.08 vs 32.46; $p<0.0001$); global score of Zarit (1.71 vs 2.28; $p<0.0001$); HAD-Anxiety (7.16 vs 9.71; $p<0.0001$) ; HAD-Depression (4.25 vs 7.87; $p<0.0001$) ; CSI-stress (4.26 vs 7.31; $p=0.04$) and DSQL (10.08 vs 16.29; $p> 0.0001$). In the Questionnaire (true/false), there was higher difference between groups ($p<0.0001$). There was a trend towards a worsening situation in female caregiver with poor health, which only reached a significant difference in the DSQL (14.26 vs 17.35; $p=0.023$) related to the emotional state and fatigue that were more marked in them.
Conclusions: Family caregivers with poor health have a much higher burden in their tasks of care, with greater depression, anxiety, stress, and worse quality of life. These caregivers need more support and care and even a period of substitution. Caregiver genre has relatively little influence in these caring tasks.

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P1108 / #2008

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

A VIRTUAL REALITY-BASED INTERVENTION TO TRAIN COGNITIVE EMPATHY AND PREVENT EMOTIONAL DISTRESS IN INFORMAL CAREGIVERS OF PEOPLE WITH DEMENTIA

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Aims: Empathy is defined as a complex bio-psycho-social concept, consisting of two distinct components, i.e., the cognitive and the affective component, mapped by two distinct neural systems. Recent evidence shows that experiential learning through virtual reality (VR) may be an appropriate and effective method for eliciting empathic behaviour. This study will implement an intervention for informal caregivers (CGs) of persons with dementia (PWD) that combines psycho-educational programme with VR to train cognitive empathy and decreasing the emotional distress.
Methods: 100 CGs will be randomised into two arms: i)the control group will participate in a validated psycho-educational intervention; ii)the experimental group will participate in the same psycho-educational intervention integrated with VR. VR consists of 360-degree videos and allows to experience dementia symptoms. Before and after intervention, all participants will complete validated scales for emotional distress. A subsample will also undergo fMRI task, modified from Ashar (2017), to investigate the effect of the intervention on the neural circuits that underlie empathy components.
Results: The 6-weeks psycho-education intervention is modelled on the Savvy Caregiver paradigm and aims to support the CGs in empathically managing PWD. During each session, CGs will be exposed to an empathy training based on i)reading autobiographical texts of CGs or ii)VR. Emotional activation will be normalised by a psychotherapist. The intervention is expected to result in deeper disease comprehension, thereby reducing the CGs affective empathy. At the network level, we expect to observe a greater activation of cognitive empathy circuits and a lower activation of affective empathy circuits in the experimental group.
Conclusions: To our knowledge, this will be the first randomized controlled trial that will combine psycho-education with VR and that will test its efficacy with both clinical and imaging markers.

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P1109 / #774

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

BUILDING COMPETENCES AND FAMILY RESILIENCE WITH CARERS OF PERSONS WITH DEMENTIA

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Aims: The number of families that provide care for persons with dementia is increasing and is going to rise accordingly to the predictions. There is a growing need to educate and empower carers about approaches, useful techniques, care processes and tips to take care for themselves in new roles, and also to facilitate the care role.
Methods: We carried out observational studies and interventions within ERASMUS KA2+ projects SINCALA and ADadHOME. Through surveys and consultations with end-users, educational materials were co-created and tested with carers, further guidance and materials for the interventions have been produced.
Results: The intervention with narrative-based workshops were well accepted and developed guidelines were found useful in Slovenia. Carers were discussing several topics that were different according to the patient-carer relation. The carers of people with dementia in late stage, provided feedback that they would like to build their knowledge about self-care, detection of pain and illness, music and snozelen therapy, among others. We found that usage of assistive technology is still rare to moderate within this group.
Conclusions: The narrative-based approach is a good strategy to facilitate the awareness of feelings and experiences of carers. However, there is also a need to provide them a safe non-judgmental space where they can express their inner thoughts and feelings, discuss and get support. There is also a need to develop the right approaches to empower carers about their role, and also to engage them in different (also on-line) activities, to strengthen the individual, but also prevent potential poverty for families that are living with dementia.

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P1110 / #224

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

FILIAL MATURITY, RESOLUTION OF A PARENT`S DIAGNOSIS, AND WELL-BEING IN ADULT CHILDREN OF PARENTS DIAGNOSED WITH ALZHEIMER'S DISEASE

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Aims: Alzheimer's Disease (AD) is one of the most common forms of dementia. There is vast research focusing on the spouse`s or adult children`s experience as primary caregivers. However, research dealing with the experience of adult children of a parent diagnosed with AD, regardless of whether the offspring is a caregiver, is not well developed, despite the offspring experiencing predeath grief and loss. The objective of the current research was to examine the associations between filial maturity, offspring's coming to terms with their parent's AD, and the well-being of the offspring.
Methods: Seventy Israeli adult children of parents with AD participated in the study and completed self-report questionnaires assessing their filial maturity, resolution of their parent`s diagnosis with AD, the adult children's well-being, and the severity of the parent's AD per their last MMSE neurologist's report.

Results: showed that higher resolution of the parent's disease was positively associated with well-being. In addition, filial maturity was negatively associated with resolution of the parent's disease, and resolution of the parent's disease mediated the association between filial maturity and well-being.
Conclusions: Resolution of a parent`s AD is highly challenging for offspring with high filial maturity, and the lack of resolution affects their well-being. Offering prolonged emotional support for offspring of parents diagnosed with AD during their ambiguous grief process may improve their ability to integrate the new reality into their lives and foster their well-being.

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P1111 / #2630

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

PATIENTS' EXPERIENCE OF A MOBILE HEALTH PROMOTING PHYSICAL ACTIVITY AMONG OLDER PEOPLE WITH DEMENTIA OR PARKINSON DISEASE: PILOT STUDY RESULTS

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Aims: Objectives: To report about the patients' experience regarding the pilot phase of developing a mobile health recommendation system that aims to promote physical activity (PA) among older people with Dementia or Parkinson disease (PD), within the context of the EU project PROCare4Life. This phase incorporates 40 days of daily notifications delivered to the patients via the PROCare4Life mobile application, providing general information and practical tips and videos about PA. Following a user-centered design approach, collected data shall provide inputs for the further deployment of the PA recommendations.
Methods: A mixed methods approach was applied. Data were collected through a Likert item questionnaire embedded in the mobile app. In addition, semi-structured interviews were carried out with the patients at the end of the pilot phase. Descriptive analysis was utilized.
Results: 77 patients answered the questionnaire, coming from Italy, Portugal, and Spain. Mean age 76 years, 59.7% males and 38.9% females, with around 86% diagnosed with PD and 13% with Dementia. More than half of the answers show that patients strongly agree or agree that the 40 days notifications are understandable; easy to apply; meet their PA needs; and motivating to be more active. From the 40 patients who took part in the interviews, more than the half (n=21) were positive about notification, mostly valuing its informative content. While, technical problems (n=10) and lack of personalization (n=10) were the least valued.
Conclusions: Conclusion: Mobile health PA recommendations in the form of daily notifications are acceptable and may be effective in motivating older people with Dementia or PD to be more active. For a better patient experience, overcoming the technical issues and including a goal-setting feature are need to be considered.

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P1112 / #1825

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

AUTOMATED SPEECH ANALYSIS USING PICTURE DESCRIPTION TASK IN ALZHEIMER´S DISEASE AND PARKINSON'S DISEASE

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Aims: Novel non-invasive screening methods to detect the early stages of Alzheimer´s disease (AD) and Parkinson's disease (PD) have been advanced. Automated analysis of speech is emerging as potentially useful, low cost and more objective method to assess language in individuals with neurodegenerative diseases.
Methods: Four tasks based on the picture description were collected from a large number of patients with AD (114), with PD (138), and more than a thousand healthy individuals from different regions of the Slovak Republic. Their spontaneous speech on the presented pictures was recorded using mobile application. Speech recordings were also transcribed, and linguistic and acoustic variables were extracted through natural language processing (NLP) and automated speech analysis (ASA). Obtained data were also correlated to the psychological and clinican assessment.
Results: summarize the main findings to summarize the potential of the mobile application to detect and differentiate the clinical groups from healthy participants included in the study.
Conclusions: The potential of the automated speech analysis using picture description tasks in the mobile application for the screening assessment would be discussed.

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P1113 / #687

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

RELATIONSHIP BETWEEN LONG-TERM CARE INSURANCE SERVICE UTILIZATION PATTERN AND CLINICAL FACTORS INCLUDING THE SEVERITY OF DEMENTIA

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Aims: In South Korea, the long-term care insurance system, introduced on July 1, 2008, has become an important social security system. We plan to produce basic data for establishing a strategy for providing long-term care benefits for dementia patients by analyzing the use of medical and long-term care services according to various clinical factors including the severity of Dementia.
Methods: Information on patients who received cognitive function tests was collected at Ilsan Hospital. Based on this patient group, the National Health Insurance service's customized DB and the elderly's long-term care DB information were joined to verify the patient's medical records and investigate the use of the elderly's long-term care benefits.
Results: A total of 1921 patients people were diagnosed with dementia at Ilsan Hospital from 2011 to 2020, and 391 patients (20.35 %) were classified as long-term care rating judges, 76 patients (3.96%) were undecided, and 1454 patients (75.69 %) were not applied. Statistically significantly, the number of patients diagnosed with dementia in Ilsan Hospital also increased from 2011 to 2018, and the number of dementia rating groups increased continuously, especially after the introduction of the special dementia grade in 2014. 75.69 % of the patients diagnosed with dementia at Ilsan Hospital are not applied for long-term care insurance for the elderly, and they are showing a relatively young age and high level of education.
Conclusions: It is necessary to identify the long-term care benefits required for each characteristic of dementia patients, to indirectly verify the validity of the current benefit system by current status, and to develop policies to establish long-term care benefit types and service strategies for individual characteristics of dementia patients

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P1114 / #416

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

FOR ONLINE COGNITIVE TRACKING, THE DATA OF THE DAILY LIVING ACTIVITIES OF THE USER IS AS VALUABLE AS THE COGNITIVE PERFORMANCE

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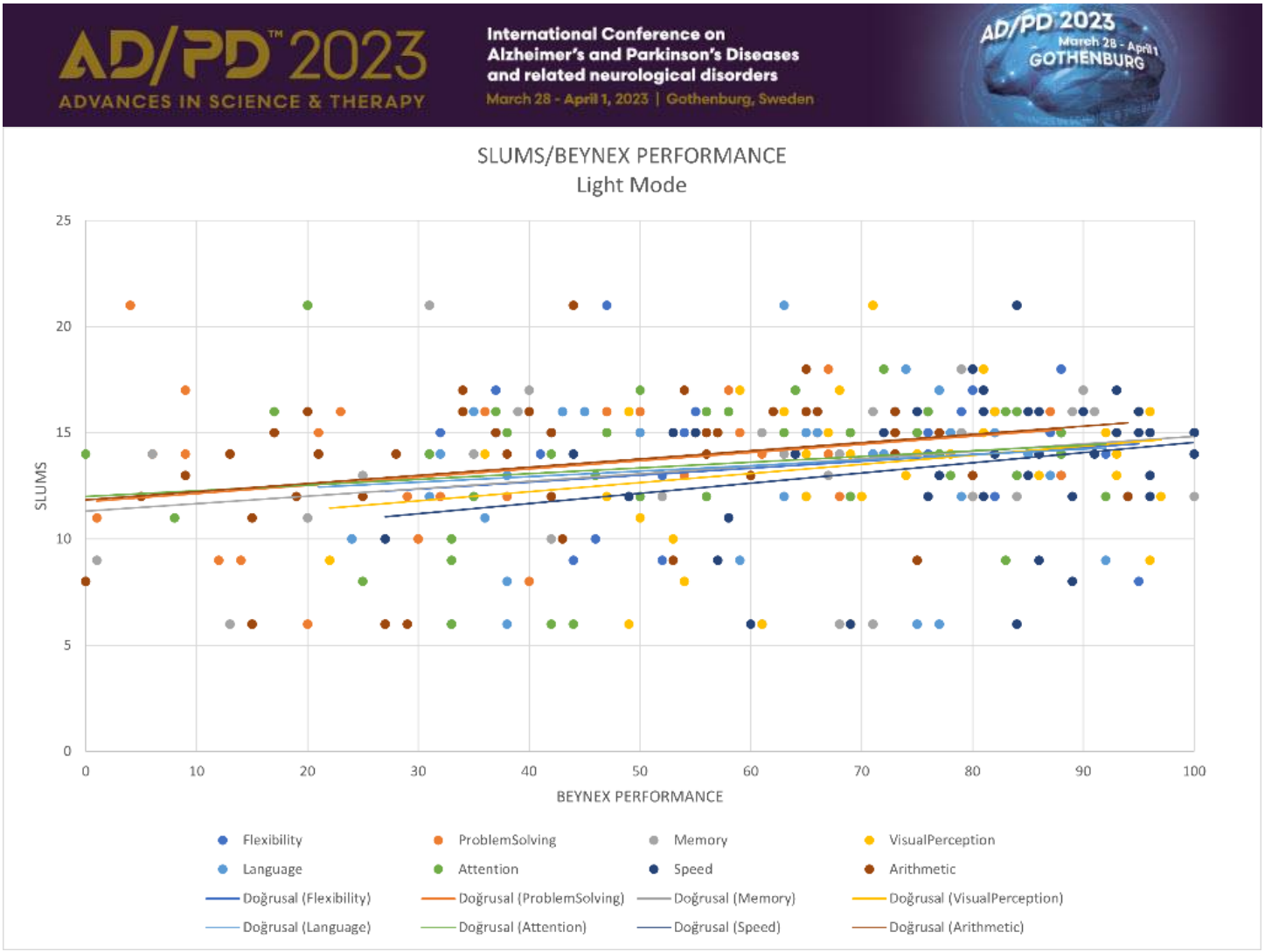
Aims: It is aimed to monitor the users with the data of the gamified online cognitive tests they have played for a year and to compare them with their answers to the questions of daily living activities.
Methods: The data of 331 people who applied to 38 centers with cognitive complaints for 1 year were collected. BEYNEX application (Online cognitive tracking) program, which is provided free of charge, was used in this research. No inquiries were made about his medical history and the treatment he received. Online SLUMS test applied within the application, users were divided into two groups as those below and above 17 points. While the normal mode is offered above 17 points , the light mode Beynex version is used for those below. Users who completed all cognitive domain games and answered daily life activity questions every 15 days were included for the study.
Results: Light and Normal mode (41 and 58 patient) groups were evaluated separately. Data from 8 different cognitive domains were not significantly different from each other in both groups. In normal mode group; **reading activity** is correlated with *Memory, Language, Problem Solving and Attention* domains and there is a negative correlation between **watching TV** and *Visual Perception and Memory* domains. In light mode group; there was a negative correlation between just for **watching TV** and the Problem solving domain.


SLUMS/BEYNEX PERFORMANCE
Light Mode
SLUMS
BEYNEX PERFORMANCE
0
5
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0
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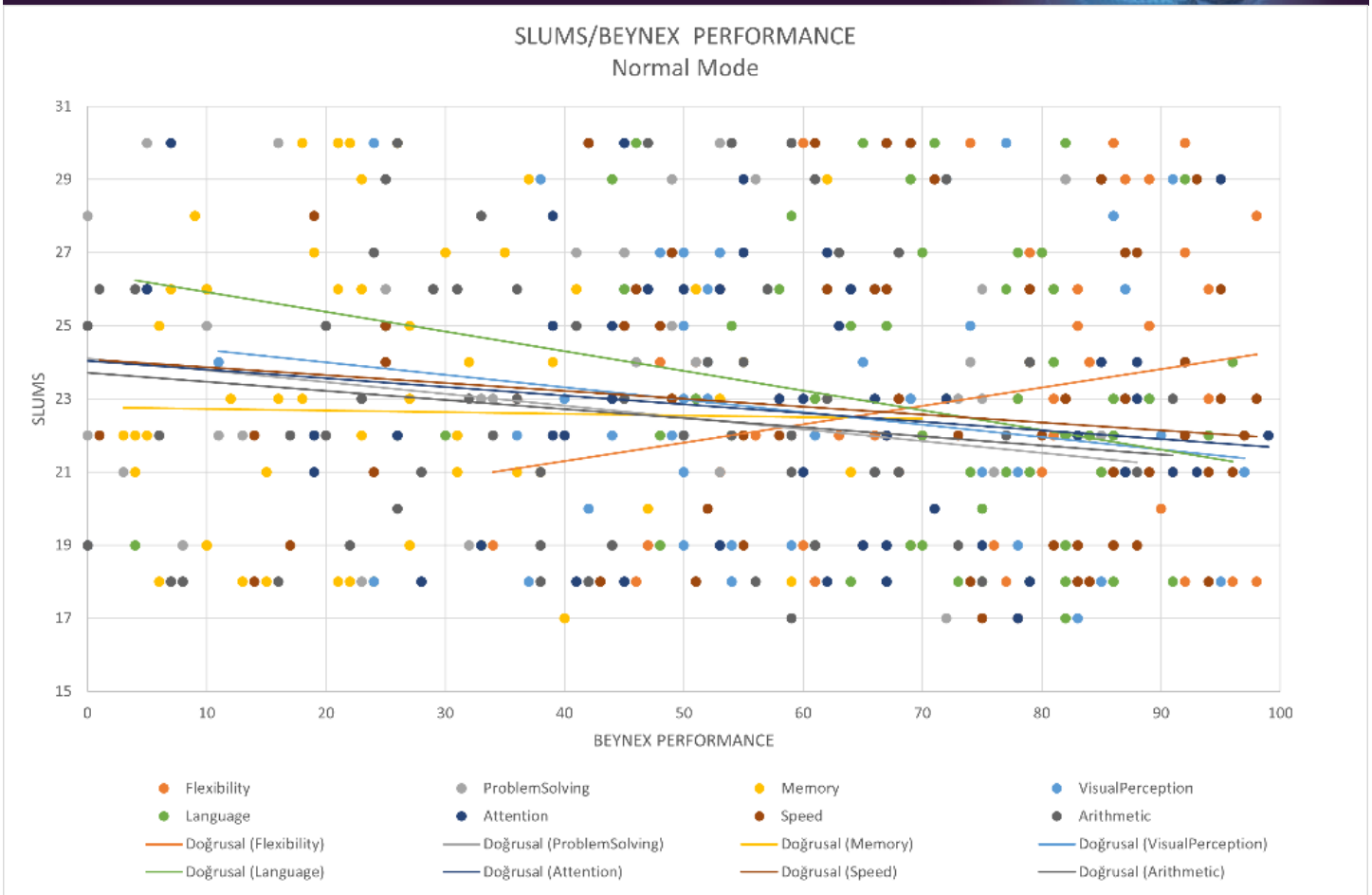
50
60
70
80
90
100
Flexibility
ProblemSolving
Memory
VisualPerception
Language
Attention
Speed
Arithmetic
Doğrusal (Flexibility)
Doğrusal (ProblemSolving)
Doğrusal (Memory)
Doğrusal (VisualPerception)
Doğrusal (Language)
Doğrusal (Attention)
Doğrusal (Speed)
Doğrusal (Arithmetic)



Conclusions: Generally, daily life activity data is neglected in online cognitive training/tracking applications. If activities of daily living can be well-monitored it can provide strong evidence to support early diagnosis for cognitive disorders. However, enriching the data and more sensitive analyzes will be possible in the near future with the development of wearable technologies and artificial intelligence softwares.

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P1115 / #895

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

EFFECT OF MULTIMODAL INTERVENTION IN COMPARISON TO HEALTH AWARENESS AMONG OLDER ADULTS WITH SUBJECTIVE COGNITIVE IMPAIRMENT (MISCI-TRIAL) – A PILOT RANDOMIZED CONTROL TRIAL

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Aims: This study was aimed to investigate the effect of multimodal non-pharmacological intervention on the cognitive functions of older adults with subjective cognitive impairment (SCI).
Methods: Sixty subjects were randomized 1:1:1:1 to receive either computer based cognitive therapy (CBCT) or CBCT+Mediterranean equivalent diet (MED) or CBCT+MED+ Exercise regime in comparison to the control group who received health awareness information. The intervention group received supervised CBCT twice a week to have 40 sessions, each of 40 minutes duration, and/ or supervised aerobic and resistive exercise for 24 weeks weekly 2 times and or MED at home supervised by dietician. The control group was provided with health awareness instructions for brain stimulating activities.
Results: Cognitive functions which was the primary outcome measure were assessed using the Post Graduate Institute Memory Scale (PGI-MS) battery, and Stroop Colour and Word Test at baseline and after 6 months of intervention. As assessed by the PGI-MS, there was significant improvement in domains such as mental balance, attention and concentration, delayed recall, immediate recall, verbal retention of dissimilar pairs, visual retention, and total score both in the unimodal and multimodal intervention groups. However, the improvement in terms of percentage change was observed to be the highest (16.71%, 67.52%, 9.97%, 16.33%, 22.95, 22.7%, 17.79% respectively) in the multimodal intervention group as compared to unimodal group. All the participants completed the trial.
Conclusions: This pilot randomized control trial indicated that CBCT +/- MED +/- exercise could be an effective non-pharmacological intervention in individuals with SCI for improving their cognitive status.

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P1116 / #1218

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

USABILITY AND EFFECTIVENESS OF A COGNITIVE TRAINING USING MOBILE APPLICATION IN MILD COGNITIVE IMPAIRMENT: A PRELIMINARY STUDY

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Aims: The use of mobile application has increased expanding its role in health care services. It can be hypothesized that older adults with mild cognitive impairment (MCI) can facilitate their cognitive function through experiences with mobile applications. This study explored the usability and effectiveness of a newly developed mobile application for computerized cognitive training (CCT).
Methods: Twenty-seven patients with MCI were randomly allocated into either CCT group (n=14) or book reading group (n=13). They underwent interventions for eight sessions for two months. Comprehensive neuropsychological function was evaluated at baseline and after intervention. People At the Center of Mobile Application Development (PACMAD) model was used for evaluation of usability of user and researcher: effectiveness, efficiency, satisfactory-text size, satisfactory-text type, learnability, memorability, and errors. Descriptive, comparative, and generalized linear model analyses were used.
Results: In CCT group, PACMAD model showed tolerable usability in all seven categories, with the highest score in the satisfaction text size (4.27 ± 0.88) and the lowest score in the errors occurred during the use of application (3.87 ± 0.74). In all categories, the participants evaluated the usability of the application better than researchers did. Additionally, CCT group showed improvements in in executive function ($p = 0.024$) and memory ($p = 0.020$) compared to control group after all interventions.
Conclusions: The newly developed mobile application for cognitive training was usable and effective in MCI patients. These results can suggest that CCT is a safe, effective, and user-friendly intervention method for cognitive decline. Future trials with larger sample size, various intervention method, and sophisticated design would find the usability and effectiveness of the CCT.

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P1117 / #2415

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

TRANSCUTANEOUS VAGUS NERVE STIMULATION IN MILD COGNITIVE IMPAIRMENT: PRELIMINARY COGNITIVE DATA FROM VINCI-AD TRIAL

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Aims: Objective: Transcutaneous vagus nerve stimulation (tVNS), delivered via a small handheld non-invasive device, is known to improve associative memory in cognitively unimpaired older adults, but little research has been done with mild cognitive impairment (MCI) patients. This study aimed to measure cognition at baseline, during active and sham tVNS in MCI patients. ClinicalTrials.gov identifier NCT05514756.
Methods: Persons with amnestic and non-amnestic MCI (Clinical Disease Rating Scale global score of 0.5) were recruited across three pseudorandomised visits. Stimulation was delivered to the cymba conchae of the left ear at 8Hz, 200 μs in 30-second bursts. Cognitive tests including Face-Name Association Task (FNAT), Sustained Attention Response Test (SART), Sea Hero Quest Navigation Test (SHQ), word list learning, semantic fluency, digit span, word list recall and recognition are undertaken with concurrent right frontal Near Infrared Spectroscopy (NIRS) oxygenation assessment. Acceptability and occupational utility of the device was also assessed.
Results: 12 participants (mean age 72.4, 8 male, RBANS DMI mean 81 ±19.2) were examined. Mean pre-testing tVNS stimulation time was 21.2 minutes, with mean amplitude setting during active stimulation of 2.2mA (1.7-4.5) and sham 2.1mA (0.9-3.2). During active stimulation recall accuracy of FNAT was significantly improved (68.2% ±10.8) compared to baseline (48.9% ±17.7) and sham (49.1% ±14.1). There was a small trend towards improved spatial navigation but no other changes in cognition was noted; no significant changes were noted in NIRS. Overall, participants found the device user friendly (58% agree) and the majority (66%) could operate the device independently.
Conclusions: Conclusion: tVNS may be a useful complementary therapeutic tool in managing MCI. Further larger studies are ongoing to delineate precise targets and settings in this population.

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P1118 / #2096

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

THE EFFECTIVENESS OF COMPUTERIZED COGNITIVE TRAINING PROGRAM FOR OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT AND EARLY STAGE OF ALZHEIMER'S DISEASE

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Aims: A computerized cognitive training program was conducted for patients with mild cognitive impairment(MCI) and early stage of Alzheimer's disease(AD) to confirm whether cognitive function was improved. It was also intended to be applied to the development of cognitive training contents in the future.
Methods: This study was conducted from April 2021 to April 2022 for those who visited the Dementia Clinic of IlsanPaik Hospital. Subjects were those diagnosed with MCI according to Peterson's criteria or early stage of major neurocognitive disorder due to AD according to DSM-5. A pre-test and a post-test was conducted before and after the computerized cognitive training program. The cognitive function of the subjects were assessed by SNSB, CDR, MoCA-K. Cognitive training was conducted twice a week, about 30 minutes per session, and 16 times for 8 weeks, and cognitive training contents consisted of five cognitive areas of attention, language, visuospatial function, memory, and executive function, and consisted of eight levels of difficulty for each training. Cognitive training was conducted using smartphones and tablets.
Results: Among the 17 subjects, 2 subjects were dropped(Mean age:76.13 years). There was a significant difference in the memory area. No significant changes were observed in the areas of attention, language, visuospatial function, and executive function in SNSB. In the 15 areas of the subtest, there were significant differences in the delayed recall test of auditory verbal learning test, delayed recall and recognition test of RCFT among the memory areas. The total CDR score was lower in the post-test compared to the pre-test, and the K-MOCA score was higher.
Conclusions: In this study,the computerized cognitive training programs were found to be a useful tool to improve memory in MCI and early stage of AD patients.

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P1119 / #2401

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

EFFECTS OF COGNITIVE TRAINING SYSTEM (CAVE) ON COGNITIVE FUNCTION IN PATIENTS WITH ALZHEIMER'S DEMENTIA

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Aims: The computerized cognitive training system could change the cognitive function of patients with Alzheimer's dementia. We newly developed CAVE system device with mixed reality in which the patients performed pre-designed cognitive and daily tasks in a simulated real-life environment within a virtual space.
Methods: Six AD patients were assigned to the CAVE system, and 5 AD patients were assigned to ComCog system. They received cognitive training through a total of 18 visits for 3 months. The Formal intensive neuropsychological test and and EEG were performed before and at the end of the training.
Results: Significant changes were observed only in the group of CAVE system which improved the K-MMSE, CDR, CDR's Sum of boxes, GDS, and I-ADL. Each patient was divided into responder/non-responder by the change of K-MMSE. Responder means a person whose personal score was maintained or improved before and after training. Five out of 6 AD patients in CAVE system were identified as Responder, and only 1 out of 5 AD patients in ComCog system were identified as responder. The EEG results showed the increased Theta Beta2 Ratio only in CAVE system.
Conclusions: AD patients trained with CAVE system compared to ComCog system showed the better cognitive function. This may be because the CAVE system is based on realistic physical space within the virtual environment. This study suggests that there is a possibility that the effect of cognitive function training may be observed under the conditions in which real life is implemented as a virtual environment.

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P1120 / #1681

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

PUPIL DILATIONS MARK THE EFFICACY OF A WORKING MEMORY INTERVENTION

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Aims: Studies show that baseline pupil size (bPS) is associated with cognitive performance.This study aims to assess the use of task-evoked PS(tPS) as a novel marker of the effectiveness of transcranial alternating current stimulation (tACS) on working memory(WM). In our previous analyses performed on this sample, we observed the largest effect on both, the WM N-back task performance and on changes in resting-state functional connectivity (rs-FC) of the frontoparietal network (FPN) during frontal stimulation.The current goal was to assess whether tPS responses to frontal stimulation are consistent.
Methods: We performed frontal, parietal, and frontoparietal in/out of phase tACS in a randomized within-subject sham-controlled design on 20 elderly subjects. Each stimulation targeted individualized coordinates of the FPN. PS was recorded with an eye-tracker concurrently with the stimulation and N-back task.
Results: The bPS correlated with education (r=.59, p=.013) and with the baseline FPN rs-FC (r=.59, p=.045). The mean tPS was largest during the frontal stimulation ($M_{2\text{-back}}$=1474.51;$M_{3\text{-back}}$=1483.46) followed by in-phase. In line with this, pairwise comparisons of the linear mixed model showed that the frontal target was the best predictor of the PS changes (tPS–bPS) during the 2-back [$F_{4,36}$=2.73, p =.044], and the 3-back task [$F_{4,40}$=3.08, p=.027]. The sessions did not predict PS. Finally, partial correlations (controlling for bPS) revealed an association between performance on 3-back and tPS during frontal stimulation (r=.51, p =.043).
Conclusions: Our results show that PS was associated with WM and varied in response to the most effective stimulation. Therefore, in the future, PS might serve as a marker of stimulation efficacy, particularly for highly demanding WM tasks, and bPS as a marker of FPN connectivity. The lack of prediction by the order of sessions suggests that pupils did not habituate to the task and environment.

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P1121 / #2190

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: EXERCISE

NEURAL SYNCHRONY DURING NATURALISTIC INFORMATION PROCESSING IS ASSOCIATED WITH AEROBICALLY ACTIVE LIFESTYLE: A NEUROIMAGING STUDY IN COGNITIVELY INTACT OLDER ADULTS

Yulia Lerner[1,2,3], Nir Giladi[1,2,4], Talma Hendler[1,2,3,5], Ofer Havakuk[1,6], Tamir Eisenstein[1,3]
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Aims: The functional neural mechanisms underlying the cognitive benefits of aerobic exercise is a subject of ongoing research. Cardiorespiratory fitness has previously been suggested to play a key role in the neuroprotective potential of aerobic exercise, However, while most neuroimaging studies to date which examined functional neural correlates of aerobic exercise have used simple stimuli in highly controlled experimental conditions, our everyday life requires a much more complex and dynamic neurocognitive processing. Therefore, to investigate the role of an aerobically active lifestyle in the processing of real-life cognitive-demanding situations, we have used a naturalistic complex information processing of story comprehension.
Methods: In an fMRI paradigm, by employing the inter-subject correlation (inter-SC) approach, we have identified differences in reliable stimulus-induced neural responses between groups of aerobically active (*n* = 27) and non-active (*n* = 22) cognitively intact older adults (age 65–80).
Results: We found that aerobically active lifestyle and cardiorespiratory fitness were associated with more synchronized inter-subject neural responses during story comprehension in higher order cognitive and linguistic brain regions in the prefrontal and temporo-parietal cortices. In addition, while higher regional inter-SC values were associated with higher performance on a post-listening memory task, this was not translated to a significant between-group difference in task performance.
Conclusions: We suggest that the modulatory potential of aerobic exercise and cardiorespiratory fitness on cognitive processing may extend beyond simple and highly controlled stimuli to situations in which the brain faces continuous real-life complex information. Additional studies incorporating other aspects of real-life situations such as naturalistic visual stimuli, everyday life decision making, and motor responses in these situations are desired to further validate the observed relationship between aerobic exercise, cardiorespiratory fitness, and complex information processing.

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P1122 / #2680

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

EARLY SCREENING OF MILD COGNITIVE IMPAIRMENT THROUGH HAND MOVEMENT ANALYSIS IN VIRTUAL REALITY BASED ON MACHINE LEARNING

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Aims: Mild cognitive impairment (MCI), an intermediate clinical stage between normal age-related cognitive decline and early dementia, is the last chance to stop the progression to dementia. Technology-activities of daily living (T-ADL), IADL that utilizes the latest information and communication technologies. Virtual reality (VR) technology can quantitatively evaluate T-ADL capabilities with behavioral data. This study developed a 'virtual kiosk test' in which both healthy controls and MCI patients were asked to order a hamburger set in an immersive virtual environment.
Methods: We recruited nine healthy controls and eight MCI patients. The neuropsychological tests were administered to enrolled subjects, the virtual kiosk test aims to evaluate the T-ADL in a virtual environment. The neuropsychological tests were conducted under the supervision of a neurologist, and the virtual kiosk test was guided and supervised by trained engineers. Before conducting the virtual kiosk test, all subjects had as much practice time as they wanted to become familiar with using the virtual kiosk.
Results: A chi-square test showed no significant effect of gender in each group. A Mann-Whitney U test showed no statistical difference in age and education level between each group. MCI patients showed significantly slower hand movement speed ($p = 0.014$) than healthy controls while conducting the virtual kiosk test. A Pearson correlation analysis was conducted to examine the relationship between neuropsychological tests and the virtual kiosk test, Digit Symbol Coding test and hand movement speed showed a positive correlation ($r = 0.65$, $p = 0.01$).
Conclusions: The virtual kiosk test used in this study has many limitations to replace the existing tests for dementia evaluation. However, it was possible to confirm the possibility that it could be easily used as a screening test before performing complex tests.

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P1123 / #2292

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

HEARING AID USE AND DEMENTIA: REVIEWING DIFFICULTIES AND BARRIERS FOR USERS AND NON-USERS

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Aims: Our recently published work in the journal of Alzheimer's & Dementia showed that hearing aid users were less likely to develop mild cognitive impairment than hearing-impaired users who did not use their hearing aids (53% reduced risk). Importantly, no difference in the risk of MCI was found between individuals with normal hearing and hearing-impaired adults using hearing aids. Our other work also showed that those with MCI and hearing impairment had reduced risk of progression to dementia if they used their hearing aids (19% vs 33%). However, with a significant proportion of elderly adults still reporting non-compliance with hearing aid use, there is a concern that this figure is even higher in those with MCI and dementia. There is a pressing need to understand compliance, difficulties, and barriers. Only when these are understood can intervention plans be implemented and the long-term effect on MCI and dementia progression can be understood, as previously suggested. The proposed project aimed to conduct a systematic review to assess difficulties and barriers for non-compliance of hearing aid use for the elderly and people with dementia.
Methods: Preliminary search was conducted to establish inclusion and exclusion criteria and protocol was registered with Prospero.We searched the PsycINFO, Embase and MEDLINE Databases up to June 2022 including keywords for the terms of 'cognitive impairment', 'dementia', 'hearing aid', 'outcomes - non-compliance', 'outcomes-refusal', 'population'.
Results: A total of 544 publications were available for initial screening, after which 483 were excluded for inappropriateness and duplication, leaving 61 available for full review and rating.
Conclusions: There is a pressing need to understand compliance, difficulties and barriers in people with dementia in order to address intervention work and to maintain later life brain health and prevent dementia progression.

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P1124 / #999

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

FEASIBILITY OF REMOTE EVALUATION OF SLEEP IN EARLY ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA

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Aims: To assess feasibility and acceptability of home-based research using technology for longitudinal sleep and circadian data collection in older adults with and without mild cognitive impairment (MCI) or early dementia due to probable Alzheimer's disease (AD) or Lewy body dementia (LBD).
Methods: Participants with MCI/early dementia due to AD or LBD and age-matched controls will undergo remotely-supported sleep monitoring from home across 8 weeks using sleep diaries on an app-based platform and wrist actigraphy. For 7 nights, a wireless electroencephalography (EEG) headband will be worn during sleep. Saliva samples for hormonally-derived circadian markers (melatonin, cortisol) will be collected. We will collect feasibility data on recruitment, retention, adherence, and data quality.
Results: Recruitment is ongoing. As of 18 September 2022, 19 of 21 consented participants met all screening criteria. Of the 19, majority are male (89%) with a mean age of 71.6 years (SD: 5.2, range: 60-78). Average MoCA score at baseline was 22.7 (SD: 3.2, range: 16-27) for patients with MCI/dementia and 27.8 (SD: 1.1, range: 26-29) for controls. 18 (86%) completed some remote study tasks. To date, 11 participants (AD=5, LBD=6) have completed the main study period. Of completers, actigraphy has been best tolerated with a mean of 48.5 (SD: 12.3, range: 14-55) out of 55 nights recorded per participant. Participants completed sleep diaries for an average of 47.5 nights (SD: 14.6, range: 11-56). EEG data was collected for an average of 6.3 nights (SD: 1.7, range: 1-7) per participant. 10 (91%) completed remote saliva samples.
Conclusions: Adherence to remote sleep tasks has been good overall. Using smartphones and wearables may offer cost-effective delivery of sleep research and interventions to enhance sleep, help delay dementia, and improve quality of life.

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POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

TOWARDS PATIENT-CENTRIC AUTOMATIC ADHERENCE EVALUATION IN VISUAL NEUROSTIMULATION TREATMENT PARADIGMS USING NOVEL INTEGRATED GAZE TRACKING

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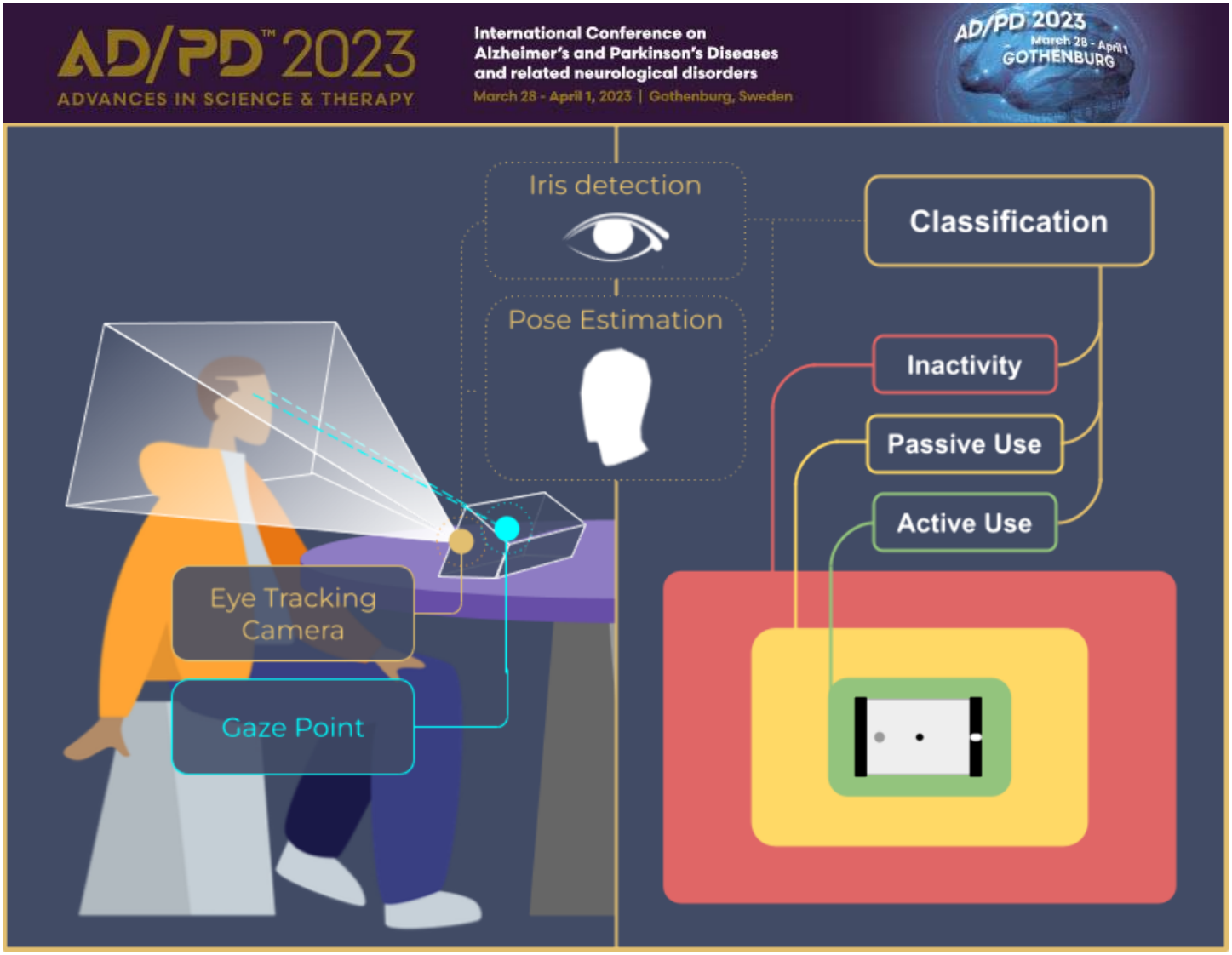
Aims: Accurate assessment of at-home neurostimulation in clinical trials is a challenge. The recently completed trial, ALZLIGHT Pilot (Clinicaltrials.gov Identifier: NCT04574921), investigated the safety and feasibility of visual gamma therapy with a Light Therapy System (Optoceutics ApS, Denmark). Built-in gaze tracking was deployed with the objective to fully quantify the nuances of light therapy adherence by automatic and accurate reports of the exposure level over time.
Methods: Throughout treatment sessions, adherence was automatically estimated without patient involvement. A camera (**figure 1**) captured images, and an on-board system-on-chip processed them real-time to extract and store gaze features, before deleting the image from memory, thus ensuring patient privacy. The extracted pitch and yaw angles of the head and the *x*- and *y*- angles of the eyes were continuously encrypted and uploaded to a secure cloud. A cascade discriminative model (AdaBoost followed by support-vector-machine) determined if the participant was looking towards the device from head pose and eye angles. Three categories of exposure were defined: *inactivity*, *passive use*, and *active use* (**figure 1**). The model was trained and evaluated in development using nested cross-validation on six volunteers.



Results: ALZLIGHT Pilot's deployed software reported adherence by 1) days with the device turned on, 2) time with the patient present (active or passive use) (balanced accuracy/precision of 0.93/0.95), and 3) time with direct exposure (active use) (0.70/0.73) (**figure 1**).

Conclusions: At-home light therapy adherence as function of time can be automatically and accurately quantified. Using patient-centric integrated gaze tracking provides nuanced insights about therapy feasibility at no nuisance to the patient.

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POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

A STUDY OF THE USEFULNESS OF SELF-ASSESSMENT MEMORY SCALE (SAMS) FOR THE ELDERLY IN THE COMMUNITY

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Aims: It is very important to detect a slight cognitive decline and start therapies at the very early stage as soon as possible. We have established a new method named the Self-Assessment Memory Scale (SAMS), consisting of 8-picture recall and 16-word recognition tests. This study examined the usefulness and validity of SAMS in older adults participating in a dementia prevention (J-MINT PRIME Tamba) study.
Methods: The subjects were 97 older adults aged 65 years or older (24 men). The subject was administered a test consisting of an 8-picture recall and a 16-word recognition test on a tablet twice on separate days. The SAMS index was calculated by adding up the ratio of correct responses to both tests (max point is two). The correlation with the WMS-R logical memory II (LMII) score was examined.
Results: The mean and standard deviation of SAMS for the subjects in this study by age groups 65-69, 70-74, 75-79 and 80- were 1.71 ± 0.24, 1.55 ± 0.25, 1.36 ± 0.29 and 1.36 ± 0.29, respectively. The first and second attempt of SAMS showed a significant correlation with the LMII score. ($R=0.56$ and $R=0.63$ respectively, both showed $p<0.001$). Comparing the first and the second score, the latter had better for more than 90% of the participants.
Conclusions: SAMS showed a good correlation with LMII in older people in this community-based study. The result that the second score of the SAMS was better and correlated better with the LMII compared to the first one suggests that it is important to provide some trial opportunities for this test administered on a tablet in order to accurately assess cognitive function in elderly subjects.

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P1127 / #607

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

LONGITUDINAL CHANGES OF COGNITION AND PHYSICAL FRAILTY IN ELDERS ASSOCIATED WITH ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY: A 13-YEAR CHINESE COMMUNITY-BASED COHORT

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Aims: To investigate the long-term simultaneous changing patterns of cognition and physical frailty among Chinese older population and their associations with the risk of mortality.
Methods: Using the Chinese Longitudinal Healthy Longevity Survey from 2005 to 2018, 7,452 adults aged 65 years and older who had a baseline and at least one follow-up assessment of cognition and physical frailty were included. Cognition (Mini-Mental State Examination) and physical frailty (FRAIL phenotype) were assessed. Group-based, joint trajectory modeling was used to fit the joint trajectories of cognition and physical frailty over time. Cox proportional hazards and linear mixed-effects models were used to evaluate the trajectories - mortality associations and the changing rates of cognition and physical frailty throughout ~45 years before death, respectively.
Results: The mean (SD) age of the 7,452 older adults was 81.5 (10.9) years and 4,104 (55%) were women. Three distinct joint trajectories were identified: *no cognitive frailty* (41.8%), *progressive cognitive frailty* (42.9%) and *cognitive frailty* (15.3%). During a median follow-up of 7.3 years, worse joint trajectories were associated with higher risk for mortality after fully adjustment, e.g., compared to *no cognitive frailty, cognitive frailty* had the highest risk estimates for all-cause mortality (adjusted HR, 3.11 [95% CI, 2.74-3.54]) and non-cardiovascular disease (non-CVD) mortality (HR, 3.23 [95% CI, 2.34-4.44]), respectively. Higher changing rates of cognition and frailty were observed among all-cause and non-CVD decedents compared to CVD decedents.
Conclusions: Three distinct joint trajectories of cognition and physical frailty were identified among Chinese older adults, and subjects with cognitive frailty were at the highest risk for all-cause and cause-specific mortality. Our findings could provide more insights on public and clinical decision making regarding this highly vulnerable subgroup of older

adults.

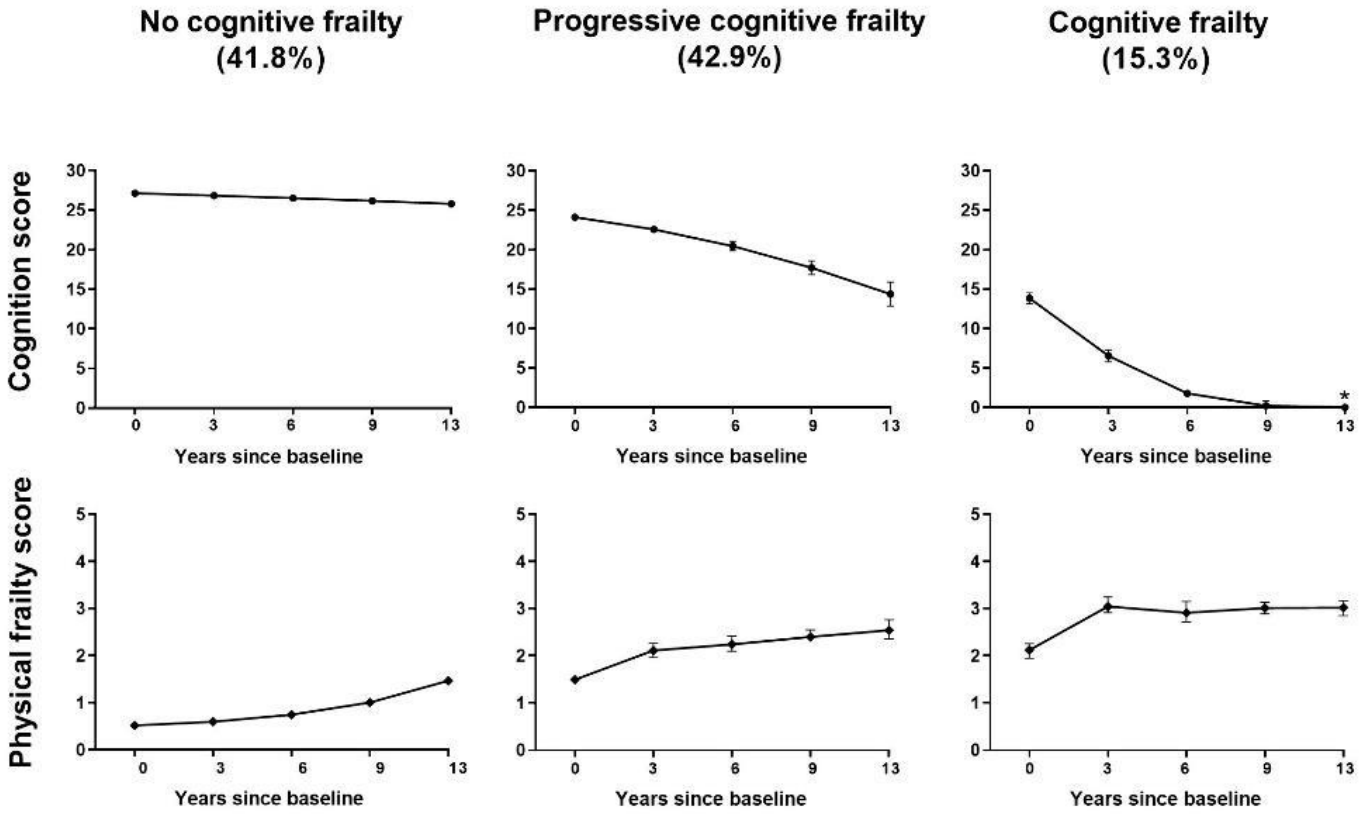

Fig. 1. Fitted joint trajectories of cognition and frailty across 13 years of follow-up among the CLHLS older adults (Waves 2005 to 2018). Cognition was assessed using the Mini-Mental State Examination (MMSE, score range: 0-30). Higher score indicates better cognition. Physical frailty was defined by the self-reported FRAIL phenotype with 5 components (fatigue, resistance, ambulation, illness, and weight loss). A higher score indicates worse frailty. ● ◆ and the error bars represent the predicted values and 95% confidence intervals (CIs) for MMSE score and physical frailty score, respectively. Three joint trajectories of cognition (top panel) and frailty (bottom panel) were identified as no cognitive frailty (n = 3,113), progressive cognitive frailty (n = 3,197) and cognitive frailty (n = 1,142).

* The predicted values and 95% CIs of MMSE in cognitive frailty group at 9 and 13 years of follow-up were 0.22 (0-0.79) and 0.01 (0-0.16), respectively.

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POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

PACEMAKER IMPLANTS AND THEIR INFLUENCE ON THE DAILY LIFE OF PATIENTS WITH DEMENTIA WITH LEWY BODIES: A QUALITATIVE CASE STUDY

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Aims: To explore how people with dementia with Lewy bodies (DLB) and their spouse carers experience daily life following a pacemaker implant to manage concurrent bradycardia.
Methods: Two men with DLB and their spouse carers were repeatedly interviewed as a dyad within one year following implant of a dual-chamber rate-adaptive (DDD-CLS) pacemaker to manage sinus node dysfunction in the men. Content analysis was used to assess the qualitative interview data collected.
Results: Three categories emerged: (1) *gaining control*, (2) *maintaining a social life*, and (3) *being influenced by concurrent diseases*. Less syncope and remote pacemaker monitoring increased a sense of control in everyday life of the dyads, while physical and/or cognitive relief increased social participation. The men were still affected by concurrent diseases, which continuously influenced each couple's daily life.
Conclusions: Identifying and managing concurrent bradycardia through a pacemaker implant could prove valuable for people with DLB and their spouse carers.

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POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

PROTECTIVE ROLE OF VITAMIN D AGAINST COGNITIVE IMPAIRMENT AMONG THE OLDEST OLD: A MENDELIAN RANDOMIZATION STUDY

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Aims: To investigate the observational association between serum 25(OH)D levels and cognitive impairment, and assess their causal relationship among the Chinese oldest old.
Methods: We conducted one-sample Mendelian randomization (MR) analyses based on Chinese Longitudinal Healthy Longevity Survey, which included 1560 community-based oldest old enrolled between 2012 to 2018. Cognitive impairment was determined at baseline by Mini-Mental State Examination with education-adjusted cut-offs. Logistic regression models were applied for observational association analysis. A 25(OH)D related genetic risk score (GRS) was constructed from 46 single-nucleotide polymorphisms (SNPs) strongly associated with serum 25(OH)D concentrations to derive causal estimates for subsequent MR models.
Results: The mean age of the participants was 93.0 years (SD 7.2), and 545 (34.9%) cases of cognitive impairment was recorded. Logistic regression models showed a reverse association between serum 25(OH)D concentrations and cognitive impairment after fully adjustment for age, sex, marital status, smoking, drinking, and history of chronic diseases. One unit of the 25(OH)D-GRS corresponded to a 0.42 nmol/L increase in serum 25(OH)D levels explaining 29.8% of its variance (P<2e-16). Linear MR revealed an inverse causal relationship between genetically predicted serum 25(OH)D levels and cognitive impairment. Each 1 nmol/L increment of predicted serum 25(OH)D led to 4.2% lower risk of cognitive impairment (2SLS model, hazard ratio, 0.958; 95% confidence interval, 0.944 to 0.972), and comparable results were presented by weighted median and inverse-variance-weighted. Subgroup analyses demonstrated a stable protective role of vitamin D against cognitive impairment.
Conclusions: Our findings support sufficient serum 25(OH)D as a causal protective factor for cognitive impairment among the oldest old, suggesting that elevating vitamin D level might serve as a way for protecting older people from cognition decline.

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P1130 / #191

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

RESILIENCE AND ITS RELATION TO NEUROCOGNITIVE DISORDERS

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Aims: Cognitive resilience has been associated with the maintenance of normal cognitive functioning despite neuropathological burden. It has been linked to socioeconomic status, education, cognitive activity, low neuroticism, and low depression. We wondered if overall resilience would be linked to maintenance of function.
Methods: We conducted life story interviews with older adults and administered the Brief Resilience Questionnaire (BRQ). Our format (the Maine Life Story Interview) was modified from the Northwestern University Life Story Interview of Dan McAdams for use with a less educated population. Part of the interview is an interactive determination of the major periods of a person's life. Using a modification of the BRQ designed for external raters, three independent coders searched for evidence of resilience in the life story and rated the level of resilience demonstrated in each of the life periods. We measured inter-rater reliability in identifying and rating moments of resilience. Interviewees and family members rated the interviewees level of memory difficulty. We asked if overall resilience across a level was associated with ratings of memory.
Results: Twenty-two people were interviewed ranging in age from 51 to 80. The independent coders identified the same examples of resilience 60% of the time. Their agreement on ratings of resilience in each life period averaged 68%. Their overall rating of resilience for interviewees agreed 76% of the time. The episodes of resilience comprised times when the interviewee "bounced back" quickly from times of adversity, met challenges with determination and resolve, and overcame setbacks quickly. Resilience was associated with higher ratings of memory function with a correlation coefficient of 0.81.
Conclusions: Resilience can be reliably measured in a life story and appears to be associated with higher cognitive functioning later in life.

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POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN DIFFERENT STAGES OF DEMENTIA DUE TO ALZHEIMER'S DISEASE

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Aims: The deficit in instrumental activities of daily living (IADL) is the main criterion for distinguishing dementia from mild cognitive impairment in Alzheimer's disease. The decline in IADL continues in the further course of the disease. The aim of our study was to analyze IADLs in mild, moderate, and severe stages of dementia.
Methods: Our sample included 53 patients with probable or possible dementia due to Alzheimer's disease, divided into three groups with different severity of dementia syndrome: mild (5 patients), moderate (33 patients), and severe (15 patients). Cognitive impairment was assessed using the Mini-mental state examination (MMSE), while IADLs were measured using the Amsterdam IADL Questionnaire (A-IADL-Q) - a short version that was completed by the informants (friends or relatives of patients). The analysis of variance and chi-square test were used to analyze intergroup differences.
Results: There was no significant difference between the three groups in age ($F=1.34$, $p=0.27$) , gender distribution (chi-square = 2.86; $p=0.24$), and level of education (chi-square = 7.77; $p=0.10$). Also, the informant's age, gender distribution, and level of education were not significantly different between the groups. The mean MMSE score was significantly different ($F=99.06$; $p<0.001$) between mild (MMSE 20.4±1.67), moderate (MMSE 14.7±1.96), and severe dementia (MMSE 8.0±1.93). A-IADL-Q score showed a significant difference ($F=4.55$; $p=0.015$) between the three groups: (43.18±12.62 vs. 31.92±9.02 vs. 28.39±9.52). After the post hoc analysis, significant differences in A-IADL-Q scores were detected between mild and moderate ($p=0.02$), and mild and severe dementia ($p=0.004$) but not between moderate and severe dementia ($p=0.24$).
Conclusions: IADL performance declines during the progression of dementia due to Alzheimer's disease. However, the measure of IADL performance does not discriminate between moderate and severe stages of dementia in our sample.

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P1132 / #1294

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: FUNCTIONAL FOODS

EFFECT OF MATCHA GREEN TEA ON COGNITIVE FUNCTIONS AND SLEEP QUALITY IN SCD AND MCI IN A RANDOMIZED CONTROLLED STUDY OVER 12 MONTHS

Kazuhiko Uchida[1], Kohji Meno[2], Hideaki Suzuki[2], Tatsumi Korenaga[2], Makoto Inoue[2], Shan Liu[2], Miho Ota[3], Yoshitake Baba[4], Chika Tagata[4], Yoshiharu Araki[4], Shuto Tsunemi[4], Kenta Aso[4], Shun Inagaki[4], Sae Nakagawa[4], Makoto Kobayashi[4], Takashi Asada[5], Tetsuaki Arai[3], Takanobu Takihara[4]
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Aims: Matcha green teacan exert effects on psychological functions, and the beneficial effects of green tea on cognitive functions and mood. In this study, we performed a randomized, double-blinded, placebo-controlled, clinical trial, conducted over 12 months, to investigate the effect of Matcha green tea powder on cognitive functions and sleep quality with biomarker analysis. The effect of Matcha intervention on blood and neuroimaging biomarkers was investigated.
Methods: We recruited 939 community-dwelling older adults aged 60–75 years and enrolled subjects with a diagnosis of subjective cognitive decline (SCD) and mild cognitive impairment (MCI). A total of 99 subjects (64 SCD, 35 MCI) were randomized, with 49 receiving Matcha (2 g/day) and 50 receiving placebo (male 20, female 30). The groups were adjusted for age, sex, and *APOE*4 genotype. Cognitive functions and sleep quality were were assessed. Plasma cytokines and biomarkers including amyloid beta and neuroimaging were also assessed.
Results: Compared to the placebo, the consumption of Matcha induced a significant improvement in perception of emotion (P=0.034) in facial recognition, and continuous performance showed a trend towards improvement. The PSQI differed by 0.86 between the groups, indicating an improvement in sleep quality in the Matcha group compared to the placebo group (P=0.087), and among the subjects with PSQI score over 5, there is significant improvement in the Matcha group compared to the placebo group (P=0.007). The MMSE score showed a slight increase in the Matcha group. Amyloid PET SUVR showed no change between baseline and at 12 months in either group, while the plasma Aβ42 was reduced in the Matcha intervention group.
Conclusions: This long-term Matcha intervention improved a part of cognitive functions and sleep quality along with changes of blood biomarker in elderly adults.

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P1133 / #2278

POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

EARLY ADVERSITY AND LATER LIFE POOR MENTAL HEALTH, COGNITIVE DECLINE AND DEMENTIA

Sarah Bauermeister
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Aims: Early adversity is a broad construct, encompassing adverse experiences during child and young adulthood which lead to higher risk of poor psychosocial, neurobiological and health outcomes in later life. Early adversity may include sexual, physical and emotional abuse, deprivation, and family dysfunction. Multiple early adversity experiences bring increased risk of multiple adverse outcomes. Impact on brain health is indicated by poorer cognition, greater brain atrophy and greater risk of dementia. Longitudinal studies are sparse, we are not aware of large-scale longitudinal cross-cohort approaches to understanding the impact of early adversity on dementia. The aim of this study was to determine a core mechanistic concept that could be attributed to longitudinal associations between self-report early adversity and later life depression and cognition.
Methods: The study was conducted using the MRC National Study of Health & Development (NSHD) birth cohort, analysing four waves of data on the Dementias Platform UK (DPUK) Data Portal. Data from waves 1989, 1999, 2009 and 2015 were used across 5,362 participants aged 43, 53, 63 and 69 years respectively. Two items from the Parental Bonding Instrument were used to represent the construct of self-report childhood 'rejection', 'Made me feel I wasn't wanted' for both Father and Mother. These items formed a latent constructed of rejected and were regressed onto longitudinal mental health (GHQ12) and cognition (letter search).
Results: Early adversity, measured as the underlying construct of self-reported childhood 'rejection' had a significant negative longitudinal association at three time points, 10 years apart. Early adversity was significantly ($p < .05$-$.00$) associated with higher depression and poorer cognition across all timepoints.
Conclusions: Results suggest experiencing early adversity is associated with longitudinal poor mental health and cognition. Both have implications for early clinical awareness and intervention.

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POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

PREDOMINANT OBJECTIVE COGNITIVE FUNCTION GROUPS AND THEIR ASSOCIATION WITH RISK FACTORS IN OLDER ADULTS: CROSS-SECTIONAL STUDY

Jessica Camacho Ruíz, Rosalinda Sánchez Arenas
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Aims: To analyze if there are association among predominant cognitive function gropus and lifestyle factors, comorbidity and motor function in older adults (OA).
Methods: Cross-sectional study with a probabilistic sample of insured OA, >60 years old of either sex, with one or more risk factors for dementia; were excluded those with complete data. Sociodemographic, habits, comorbidities and subjective and objective cognitive function, sex and academic level. Cognitive function from population gropus were defined accoording to DSM-5, and their association with risk factors.
Results: A sample of 350 OA, 65±7.4 years old with 9.5±5 years of education were recruited. Cluster analysis grouped four groups by age, sex, academic level and objective and subjective cognitive function. With DSM-5 criteria, they were identified as: i) without Neurocognitive Disorder (NCD), or normal cognitive function, ii) with major NCD, or dementia, iii and iv) with minor NCD, or mild cognitive decline in OA ≥70 years and <70 years. The sociodemographic factors associated with NCD were showed unqualified work and living alone. Regarding comorbidity the factors were high blood pressure, while type 2 diabetes mellitus (DM2) was present only in major and mild NCD >70 years, that was the group with more comorbidity. Motor functionality was frailty and altered activities of daily life (ADL); for major-NCD and minor NCD >70 years, grip strength was preserved in major-NCD and minor NCD≤70. Physical activity was protection for the three groups. The truth of the models for major NCD had lower values (65 to 91) than the models of the minor NCD groups.
Conclusions: There are association among lifestyle factors, comorbidity, motor function for protection and risk for the predominant cognitive function groups.

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P1135 / #1396

POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

IMPACT OF AMYLOID POSITIVITY ON SOCIAL COGNITION PERFORMANCE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND MILD DEMENTIA

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Aims: The DSM-V suggests social cognition as a distinct domain in neurocognitive disorders. However, data on social cognition in mild cognitive impairment (MCI) and dementia are still controversial. So far, only few studies have assessed social cognition in relation to amyloid-beta status. Here, we examined the impact of amyloid-beta positivity on social cognition performance in patients with MCI and mild dementia.
Methods: Included were 42 patients with MCI and 30 with mild dementia. Amyloid status was assessed either by cerebral spinal fluid or PET applying standard cut-off values for dichotomous classification (positive or negative). All patients performed two social cognition tasks: facial emotion recognition and cognitive theory of mind (TOM) picture stories. Additionally, all patients conducted a standard neuropsychological test battery. Statistical group comparisons were conducted applying nonparametric methods with post-hoc Bonferroni correction.
Results: Amyloid-beta analyses revealed that 27 (64%) MCI patients and all patients with mild dementia were amyloid positive resulting in three groups (A-MCI/A+MCI/A+Dem). A-MCI patients were significantly younger, more depressed and contained more males than A+MCI patients. Concerning emotion recognition, A+Dem patients were significantly more impaired than both MCI groups. Cognitive ToM performance was significantly worse in A+Dem patients, but also worse in A+MCI patients compared to A-MCI patients. The results were most pronounced in tasks which required highest cognitive load where all three groups differed significantly from each other. As expected general neuropsychological performance was most impaired in A+Dem, while both MCI groups did not differ significantly from each other.
Conclusions: Social cognition seems to be affected early in the course of the Alzheimer's disease spectrum with already A+MCI patients suffering from impairments. The results support the approach to implement social cognition in standard test batteries.

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P1136 / #391

POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

INCREASED RISK OF APATHY AND IRRITABILITY ASSOCIATED WITH FEMALE SEX AND APOE ALLELE CARRIER STATUS IN COGNITIVELY IMPAIRED

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Aims: A recent meta-analysis showed significant sex differences in Neuropsychiatric Symptoms (NPS). However, a better understanding of factors underlying these differences are required. While the Apolipoprotein E (APOE) ε4 allele is a known predictor of Alzheimer's disease, its impact on the clinical manifestation of NPS remains unclear. This study examined impact of sex and APOE ε4 allele carrier status on NPS manifestation in a population-based cohort of cognitively impaired older Australians.
Methods: 1417 participants (52% female; aged 72-79; 640 cognitively impaired) completed the NPS PATH Through Life Substudy. APOE ε4 allele carrier status was available for 1318 participants. Participants were classified as APOE positive if they were a carrier of at least one ε4 allele (APOE ε4/ε4, ε2/ε4, ε3/ε4). NPS were assessed using the Neuropsychiatric Inventory. Cognitive impairment was determined according to DSM-V criteria.
Results: Of the 570 cognitively impaired participants (53% female), 290 reported at least one NPS (57% female) and 152 were APOE ε4 allele carriers. At least one NPS was present in 46 female APOE carriers (61%) and 29 male APOE carriers (39%). Compared to male APOE carriers, female carriers were significantly more likely to report apathy (χ^2=5.137; p=.023) and irritability (χ^2=10.576; p=.001), and experience more severe symptomatology of apathy (F=4,421, p=.037) and irritability (F=5.137, p=.025).
Conclusions: Cognitively impaired, APOE allele carriers had a higher likelihood of experiencing apathy and irritability, and more sever clinical manifestation of these symptoms. A better understanding of the interaction between sex and the APOE allele is required to better target early risk diagnostic and interventions.

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P1137 / #626

POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

DEVELOPMENT OF A BPSD(BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS) APP

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Aims: Previous qualitative audits at Wyong hospital which is a 300 bed teaching and regional hospital and part of the Central Coast local health district (CCLHD) showed that local BPSD guidelines found on the intranet were often not adhered to and it was suggested that guidelines should be readily accessible. Interviews with staff who participated in clinical aggression response teams (CART) calls showed that many were not sure of what medications to prescribe and what was the most appropriate intervention to provide. These audits plus evidence about implementing practice change suggests that mobile apps are used frequently and are more effective than providing intranet documentation. Our aim was to develop a BPSD App with the potential to make local evidence based guidelines and recommendations accessible to the user at the bedside on a mobile device to enable to user to manage BPSD with ease particularly during CART calls.
Methods: Content of the app was based on BPSD guidelines published on the CCLHD intranet geriatric medicine web pages. A prototype of the app was developed on Marvel designs and provided to local IT and e- health who assisted with the integration and operations of the app. Training was provided on usage of the app which can be accessed 24 hours a day and posters placed on all the wards with instructions and a QR code for usage and download of the app. Ethics approval was obtained
Results: We aim to audit medical officers opinions as to the usability, effectiveness, barriers and facilitators in managing BPSD after introduction of the app.
Conclusions: The development of the app allows ease of access to concise evidence based information and supports clinicians in their role in managing BPSD

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P1138 / #187

POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

NON PHARMACOLOGICAL FRENCH STUDY AT HOME : CAN PSYCHOLOGISTS REDUCE BEHAVIORAL SYMPTOMS IN DEMENTIA?

Anne-Julie Vaillant-Ciszewicz, Alice Cuni, Laura Lantermino, Oriane Said, Olivier Guerin
CHU DE NICE, Pole Rav, NICE, France

Aims: Today in Europe, Alzheimer's disease and other related disorders affect 9 780 678 people. The major part of them live at home and are often supported by family's members who can often be overload by the burden of caring for their beloved. Their burden is particularly influenced by the Behavioral and Psychological Symptoms of dementia (BPSD) that appears in in 97% of patients with dementia. The better way to support BPSD is to provide non drugs approaches combined with psychoeducation
Methods: Psydoma is a non randomised monocentric phase II feasability study (n=20 caregivers/patients). Adults over 65 years old who lived with Alzheimer's diseases and carers are involved in this 7 months study. 3 times/week psychologist comes at home to administred a non drug customized interventions Carers participed to a psychoeducation program (3 modules : ininformation about the disease ; emotion's regulation, communication). A nurse coordinator and an occupational therapist are also part of the program. The french fondation (Mederic Alzheimer) carries out an external evaluation.
Results: The most used interventions are: cognitive stimulation and reminiscence therapy according to therapeutic indications for each patient. 4 couples over 20 stopped the study, 16/20 psychoeducations programmes have been completed and the caregiver's satisfaction rate was 9.6/10. Our main significant results are a decrease in delusions scores for 7/8 patients (12%, p=0.03, McNemar) and agitation frequency (decrease of 20% at the end of the study).
Conclusions: PsyDoMa is an innovative project in supporting helping patients and carers, who showed its efficacity for BPSD. All the results will be presented at the AD-PD congress.

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POSTERS: K01.H. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

CLINICAL CHARACTERISTICS OF BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN PATIENTS WITH DRUG-NAÏVE ALZHEIMER'S DISEASE

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Aims: Behavioral and psychological symptoms of dementia (BPSD) are less well-defined aspects of Alzheimer's disease (AD). We designed this study to explore the followings: 1) the clinical profiles of BPSD 2) the clustered-groups domains of the Korean-Neuropsychiatric Inventory (K-NPI) assessment of BPSD 3) the clinical characteristics of the clustered-groups of BPSD in patients with drug-naïve probable AD
Methods: Descriptive and cluster analyses of the 12 K-NPI domains were done in 220 patients with drug-naïve probable AD. After clustering these domains, characteristics of these positive symptoms clustered-group of patients were compared with the negative symptoms groups of patients.
Results: The mean Korean-Mini Mental Status Examination (K-MMSE), Clinical Dementia Rating (CDR) scale, and K-NPI scores were 15.0, 1.6, and 14.2, respectively. The CDR and K-MMSE scores correlated with total K- NPI scores, and depression was the most common symptom. According to cluster analysis, five major clusters were identified. Using the associated neuropsychological dysfunctions, characteristics of each group were defined
Conclusions: This study identified the clustered-domains for K-NPI, and suggested the possible anatomical substrates for these groups in drug-naïve AD patients. These attempts may clarify the complex and bizarre behavioral and psychological symptoms as more neurologically relevant symptoms

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POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

KNOWLEDGE, ATTITUDE AND PRACTICE OF DOCTORS REGARDING TO DETECTION AND TREATMENT OF MILD COGNITIVE IMPAIRMENT IN THE REPUBLIC OF KAZAKHSTAN

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Aims: Assessment of Knowledge, Attitudes and Practices (KAP) related to MCI among general practitioners and neurologists in the Republic of Kazakhstan. Detection of mild cognitive impairment (MCI) is necessary to slow down the progression of dementia.
Methods: An online survey of 100 general practitioners, neurologists from the cities of the Republic of Kazakhstan was conducted. Knowledge (13 questions), attitude (11 questions) and practice (19 questions) were assessed using a structured questionnaire previously approved by a group of experts. The questionnaire was specially designed for this study.
Results: Adequate knowledge regarding MCI was found only in 46.3% of participants. A higher level of knowledge was associated with a more favorable attitude to MCI management. Higher compliance with practical recommendations was associated with both a higher level of knowledge and a more favorable attitude. In general, 65.6% of participants admitted that cognitive impairments are difficult for them to control in the workplace or reported numerous difficulties in managing individual patients requiring special knowledge in cognitive neurology to make professional, legal decisions.
The connection between knowledge and practice is partly mediated by personal attitudes. Training was associated with a higher level of knowledge, while past MCI experience was associated with a more favorable attitude and higher compliance with practical recommendations. MCI screening tests were associated with higher compliance with practical recommendations, but with a less favorable attitude.
Conclusions: The knowledge of general practitioners in the Republic of Kazakhstan about HCV is low and is associated with a less favorable attitude to the management of HCV and low compliance with practical recommendations. Knowledge, Attitude and Practice are interrelated domains that must be taken into account in a comprehensive manner to preserve the cognitive health of patients.

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POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

DYSPHASIA AFTER STROKE AND LEGAL CAPACITY

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Aims: Although after stroke dysphasia or aphasia is not equal to incapacity, the legal capacity of patients can be doubted. The patients' ability to fully comprehend the given information and make decisions may be impaired. Stroke is sudden, life threatening and likely to affect capacity even in the absence of dysphasia. There are currently no published guidelines in the management of legal issues for patients and professionals.
Methods: A literature review in the Pubmed database has been made, using the key-words: stroke, legal capacity, decision-making.
Results: Brain injury after stroke may impair appreciation of decisions' consequences and/or communicating decisions effectively, while the capacity to reason remains. Stroke may affect various brain areas, i.e. prefrontal cortex involved in decision-making (ventromedial prefrontal cortex damage may lead to impulsive decision-making). A right-brain stroke may cause poor executive function, lack of initiation or neglect. Left-hemisphere strokes may lead to aphasia and reduced capacity evaluation. The dysphasic may understand more than he can express, or vice versa. Difficulties further compounding communication problems include: reading and writing; numeracy; inattention/concentration; fatigue; emotional control (lability); perseveration; intellectual functioning. Receptive aphasia can impair understanding medical options, while expressive aphasia may prevent communicating relative decisions. Patients may also be susceptible to undue influence regarding testamentary and financial capacity due to communication deficits and varying levels of dependence. Depression following stroke can further impair capacity.
Conclusions: The patient may have a communication rather than a capacity deficit. Judging a patient's ability to weigh information is often the most difficult aspect of legal capacity assessment. There is little literature or high court jurisdiction regarding whether dysphasia after stroke impairs patients' capacity. Evaluation of the prerequisites for legal capacity requires an multi-professional cooperation.

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POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

NATIONAL SURVEY OF CENTERS FOR COGNITIVE DISORDERS AND DEMENTIAS, NURSING HOME AND DEMENTIA DAY CENTERS IN ITALY

Ilaria Bacigalupo[1], Giulia Carnevale[1], Francesco Giaquinto[2], Patrizia Lorenzini[1], Fabio Matascioli[1,3], Giulia Remoli[4], Emanuela Salvi[5], Roberta Vaccaro[1,6], Nicola Vanacore[1]
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Aims: The Italian Fund for Alzheimer's and other dementias was approved in December 2020, in order to provide new strategies in the field of dementia. Three surveys will be carried out in the Italian health facilities for dementia care: Centers for Cognitive Disorders and Dementias (CCDDs), Nursing Homes (NHs), and Dementia Day Centers (DDCs). The surveys aim at: reporting the administrative features and the professional competencies; detecting discrepancies by geographic area; describing the markers of high quality in the provision of care; highlighting the impact of the Covid-19 pandemic on the services.
Methods: A list of all national CCDDs, NH and DDCs was requested to designed delegates from each Italian region.Three online questionnaires, approved by the National Permanent Table on Dementia, focuses on location, access, organization, services and treatments, activities and any discontinuation of the services due to the Covid-19 outbreak.
Results: The survey, will last from September to December 2022. To date, 174 out of the 540 listed CCDDs completed the questionnaire, 70 (40.2%) from Northern Italy, 36 (20.6%) from Central Italy, and 68 (39.8%) from Southern-Islands Italy. More than a third of CCDDs was open only once or twice weekly. A median of 632 patients regularly attended these services. About half of CCDDs were closed (1-3 months) during 2020 and 18% were closed (1-3 months) during 2021. NH and DDCs will begin the survey in December and February, respectively
Conclusions: The results from these surveys will allow an update of structural and human resources highlighting the disparities between different Italian regions in prevention, diagnosis, management and pharmacological, cognitive, and psychosocial treatments for dementia. Project carried out with the technical and financial support of the Ministry of Health chapter-2302

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POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENTS IN A SAMPLE OF OLDER ADULT COMMUNITY DWELLERS FROM NIGERIA

Valentine Ucheagwu
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Aims: 1) To determine the prevalence of cognitive impairment in older adults Nigeria using cumulative cognitive domain index. 2) To identify patterns of cognitive performance based upon five domains of cognitive assessments. 3) To elucidate the roles of modifiable risk factors and demographics on cognition.
Methods: Participants: 441 older adults (271 females) between the ages of 68-75 with mean age of 72.5 and SD age of 3.57 were studied using the door to door knocking approach. Instrument: Adapted version of Unified Data Set for AD study was used to assess cognition in the participants. The domains of cognition assessed were; attention/concentration, processing speed, memory, executive function and visual spatial abilitiy. Other variables like modifiable risk factors were further collected.
Results: Prevalence: Using 1.5 SD (and mean scores as well) from the mean of the group scores, we showed in descending order that 13% (41.40%) of the participants were impaired on visual-spatial index; 6.8% (48.7%) on memory index; 5.2% on attention/concentration index (49.2%); 2.7% (56.50%) were impaired on executive function index and 34.80% (mean only) of the participants were impaired on processing speed index. . We classified their performance into normal cognition (NC), borderline cognition (BC), mild cognitive impairment (MCI) and dementia. Our results showed that 49.7% had NC, 34% had BC, 12.9% had MCI (2.72% with amnesic MCI) and 3.4% had dementia.
Conclusions: Our findings demonstrated relative prevalence of cognitive impairments in our population with visual-spatial impairment being most prevalent and relative high number of participants on borderline cognition. Modifiable risk factors were further demonstrated to play significant role on cognitive impairment in the sample.

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P1144 / #2623

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

COMMUNICATING ABOUT RISK OF DEMENTIA IN THE EARLY STAGE OF THE NEURODEGENERATIVE DISEASE PROCESS: A LONGITUDINAL COHORT STUDY

Stina Saunders[1,2], Joyce Gomes-Osman[1,3], Alvaro Pascual-Leone[1,4]
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Aims: To understand patients' and clinicians' perspectives in receiving and giving information about dementia risk in early neurodegenerative disease.
Methods: Participants were individuals from memory clinics in Scotland who presented with mild cognitive concerns. Participants underwent baseline assessments, disclosure of dementia risk, and three follow-up visits over an average of two years after diagnostic disclosures. The explanatory variable was the self-reported rating of the experience surrounding the disclosure of their dementia risk ("good" or "not good"). A subset of participants was included in a longitudinal qualitative study and separately, clinicians were interviewed about their views on early detection of neurodegenerative disease.
Results: The main study included n=63 participants (n=38 [60.32%] women). There was a statistically significant association between negative experiences associated with dementia risk disclosure and [1] worse psychological adjustment to illness scores; and [2] better cognitive performance at baseline. The main findings from the longitudinal qualitative interviews were that over time, diagnostic disclosure of dementia risk caused uncertainty, compounded by the perceived lack of information of "what one could do about it". Clinicians noted mixed positions and degrees of confidence on how to communicate risk of dementia in a valuable manner to their patients.
Conclusions: Our findings indicate that worry after risk disclosure was related to a perceived lack of agency and that individuals referred to memory assessment services seek not only treatments, but also actionable information on how to reduce risk and the effects of dementia. We also revealed that clinicians need better information on how to convey risk of dementia in a way that empowers patients and promotes autonomy and agency. Risk reduction advice must be personally meaningful and incorporate outcomes that matter to the individual.

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P1145 / #2659

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ARE MEMORY SERVICES READY TO PRESCRIBE DRUG MODIFYING TREATMENT FOR ALZHEIMER'S DISEASE?

Ramin Nilforooshan
SABP, University of Surrey, R&d, Chertsey, United Kingdom

Aims: In this double presentation, we are discussing the challenges ahead of many clinicians around the world when the first effective DMT for Alzheimer's disesae is approved by FDA, EMA and NICE. We will discuss how the current memory services need to change to be able to adapt to start using a DMT. Many older adults with diagnosis of dementia will never seek help as they believe nothing can be done for them, this belief is somehow extended to some clinicians. By the arrival of the first effective DMT in the market, and the explosion in the media, memory services will be inundated with patients. Hardly any of the current clinical services (not the research centre) are ready and have the capacity to accomodate those patients. In this talk, we will discuss the steps necessary for clinicians, managers, funders and all the other relevant services (MRI, Infusion centres, Labs, LP clinics, On call systems,....) to take to be able to deliver a new model of care. I (psychogeriatrics) will present challenges and opportunities ahead of us.
Methods: I have been PIs and CIs for many clinical trials. We are clinical leads for two different memory services.
Results: This is a opinion session
Conclusions: We will present how the future memory services will look like

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POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

SWEDISH FTD INITIATIVE A PLATFORM FOR CLINICIANS, RESEARCHERS, PATIENTS, FAMILIES AND OTHER ADVOCACY GROUPS

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Aims: Purpose: To facilitate powerful research on FTD in Sweden and reach out to patients and relatives with the latest knowledge. Aims: ·Build a database and biobank on FTD ·Provide information and knowledge to patients with FTD and their relatives. ·Collaborate closely with interest groups such as patient organizations

Methods: Information about SWEFTDI is available on the website frontallobsdemens.se: - working group with clinicians at the 8 University hospitals to harmonize and standardize diagnostic criteria, discuss cases and share current research findings. - working group with care scientists and health care professionals to discuss person centered care and generate common examples from real-life experiences. Researchers in SweFTDI are represented in several international research consortia e.g. Genetic FTD Initiative (genfi.org), FTD Prevention Initiative (thefpi.org), FRONTIERS and NIC-FTD. Researchers in SweFTDI are also involved in recruiting 2 clinical treatment trials for genetic FTD to Sweden.
Results: Clinical guidelines for diagnosing FTD published online at frontallobsdemens.se The clinial trial unit at Karolinska University Hospital in Stockholm is recruiting people with FTD caused by progranulin or C9orf72 mutations to clinical treatment trials. The Stockholm site has been part of the GENFI-study since 2012 and adult family-members with C9orf72, progranulin, TBK1 and MAPT mutations are enrolled. Starting next year, the Lund/Ängelholm site will start to

enrol families in the GENFI-study.

Conclusions: A unique interdisciplinary consortium SweFTDI, founded by researchers at KI, KTH and SciLifeLab and supported by the Schörling Foundation, serves as a national infrastructure for clinical and experimental researchers, health care providers as well as people with FTD and their families. The network is open to anyone interested in FTD, please email <FTDemens@nvs.ki.se> and visit our website frontallobsdemens.se to contact us.

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P1147 / #1538

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

BLOOD TESTS OF VITAMIN B12 AND THYROTROPIN AS RULE-OUT PROCEDURES TO ASSESS ALZHEIMER'S DISEASE IN VETERANS AFFAIRS HEALTHCARE SYSTEM

Byron J Aguilar[1,2], Peter Morin[3], Dan Berlowitz[4], Donald R Miller[4], Raymond Zhang[5], Amir Abbas Tahami Monfared[5,6], Quanwu Zhang[5], Weiming Xia[1,2]
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Aims: We aim to assess documentation of Vitamin B12 and Thyrotropin (TSH) tests to rule out other causes of cognitive decline in suspected Alzheimer's Disease (AD) patients in the Veteran's Affairs Healthcare System (VA).
Methods: An AD cohort of 203,651 Veterans derived from clinical notes between 2010 and 2020 were studied. B12 and TSH test orders and results within ±1 year of first clinical notation for AD were extracted based on Logical Observation Identifiers Names and Codes (LOINC).
Results: About 57% and 80% of the cohort had B12 and TSH test results, respectively. Of the B12 tests, 58% patients did the test before and 70% did on or after their first AD note. Approximately 50% of the B12 tests results showed deficiency (<500 pg/mL) and 20% were normal (>900 pg/mL). More women (21%) had normal B12 levels than men (17%). About 70% of patients had a TSH result before and 80% had a result on or after their first AD note. Approximately 90% of patients had a normal TSH (0.4-4), and 3% and 10% of patients had a low (<0.4) and high (>4) TSH result, respectively. More women (4%) had low TSH levels than men (1.7%).
Conclusions: B12 and TSH are routinely tested to rule out other, 'reversible' causes of cognitive decline before an AD diagnosis is made. A majority of the Veterans had B12 and TSH test results within a year of their first AD clinical note, suggesting a standard rule-out process for AD diagnosis in VA.

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P1148 / #1499

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

IDENTIFICATION OF PATIENTS WITH ALZHEIMER'S DISEASE IN THE US VETERAN'S AFFAIRS HEALTHCARE SYSTEM FROM CLINICAL NOTES

Byron J Aguilar[1,2], Dan Berlowitz[3], Donald R Miller[3], Peter Morin[4], Raymond Zhang[5], Amir Abbas Tahami Monfared[5,6], Quanwu Zhang[5], Weiming Xia[1,2]
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Aims: To identify patients with Alzheimer's disease (AD) from clinical notes in the Veteran's Affairs Healthcare System.
Methods: Clinical notes were evaluated via Text Integration Utilities for AD keywords ("Alzheimer" or "AD"). Veterans at least 50 years old at the time of note between 2010-2020 were included in the study.
Results: 203,651 patients with 3,175,238 clinical notes fulfilled the search criteria. The cohort comprised of Veterans that were 96% male and 76% White with a mean age of 82. Overall, 43% of patients had an AD note from Primary Care Providers (PCP) while 15% of the cohort had an AD note from a Neurologist. Other notes included psychiatry (14%), mental health (18%), geriatric medicine (12%), and neuropsychology (12%). Among patients' first notes that mentioned AD, 11.0% and 8.5% were documented by a PCP and Neurologist, respectively. First AD notes from psychiatry, mental health, geriatric medicine, and neuropsychology were 4.6%, 1.7%, 2.6%, and 10.7%, respectively. About 53% of the cohort had at least one AD ICD-9 or ICD-10 code contained in the VA administrative database. A review of 200 randomly selected notes revealed an error rate of 24% with inter-rater Kappa of 0.86.
Conclusions: This study finds that clinical notes on AD assessments or diagnosis are more often documented by primary care or other healthcare personnel instead of AD specialists, especially for the first medical notes for AD. Nearly half of individuals identified as having an AD note had no ICD-9 or ICD-10 code for AD in the VA administrative data.

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P1149 / #173

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

PROGNOSIS IN DEMENTIA PATIENTS, TEN-YEAR MORTALITY, AND COMORBIDITY-BASED PREDICTIVE MODEL

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Aims: To describe the ten-year survival probability of dementia patients in Thailand and identify associated co-morbidities with ten-year overall survival
Methods: The retrospective study was conducted using secondary data from dementia patients who had visited the OPD at Maharaj Nakorn Chiang Mai Hospital between 2006 and 2012. The Thai Clinical Practice Guidelines for Dementia were used to confirm the dementia diagnosis. Overall survival analysis and Kaplan-Meier survival plot were performed to describe the ten-year survival probability. The association between co-comorbidities and overall survival time was analyzed using a multivariable Cox proportional hazard model adjusted for age, gender, and types of dementia.
Results: Of 702 patients who were diagnosed with dementia, 56.9% were female. The median overall survival was about six years (95% CI 5-7). Alzheimer's disease (39.6%) and vascular dementia (28.8%) were the most prevalent types of dementia. The comorbidity associated with poor prognosis included AIDS (HR 7.08, 95% CI 1.86-26.88), liver disease (HR 2.72, 95% CI 1.47-5.03), atrial fibrillation (HR 2.16, 95% CI 1.30-3.60), myocardial infarction (HR 1.56, 95% CI 1.07-2.27), and type 2 diabetes (HR 1.40, 95% CI 1.13-1.74). Hypertension was associated with a better overall prognosis (HR 0.80, 95% CI 0.66-0.97).
Conclusions: Overall survival in dementia patients was similar to previous studies. Several comorbidities were associated with ten-year survival, while some comorbidities increased the risk of overall mortality in dementia patients. The prognosis of dementia patients may be improved by the appropriate care of comorbidities.

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P1150 / #1116

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

PRIMARY PROGRESSIVE APHASIA (PPA) COHORT IN CENTRAL NEW YORK: ADVANTAGE OF THE ELECTRONIC MEDICAL RECORDS (EMR) FOR RETROSPECTIVE AND PROSPECTIVE STUDIES

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Aims: PPA is an umbrella of neurodegenerative syndromes with different clinical presentations and underlying pathologies. The goal of this retrospective study was to characterize PPA cohort and demonstrate that the EMR is effective at creating cohorts of patients for review of incidence, epidemiology, risk factors, and diagnostic criteria of various PPA disorders which can help better characterize accurate diagnosis, serve in designing future clinical studies and improve patient recruitment in clinical trials.
Methods: The EMR EPIC was used to identify a cohort of 72 patients diagnosed with PPA from 2012 to 2022 in a Central New York Major Academic Medical Center. Microsoft Excel was used to compile data for analysis.
Results: Our cohort yielded diagnoses of PPA, not characterized (24 patients, 33.33%), Progressive Nonfluent Aphasia(PNFA) (17 patients, 23.61%), Logopenic PPA (8 patients-11.11%), Semantic variant PPA (3 patient, 4.16%), atypical Alzheimer's Disease (AD)(3 patients, 4.16%), AD (1 patient, 1.38%), anomic aphasia(2 patients, 2.77%) and frontotemporal dementia with speech apraxia(1 patient, 1.38%). Concurrent diagnoses of AD and vascular dementia (VaD) (3 patients, 4.16%); PPA Logopenic +AD+VaD (2 patients, 2.77%), PPA uncharacterized and AD (4 patients, 5.55%), and Logopenic PPA and AD (4 patients, 5.55%) were additionally present. Those diagnosed with PPA not further characterized, PNFA, and PPA Logopenic were predominantly female at 54%, 58%, and 75% respectively and the one PPA semantic variant was also female. Average ages of diagnosis for PPA not further characterized, PNFA, and PPA Logopenic were 72.6, 74.7 and 75.87 years respectively.
Conclusions: The data acquired from the EMR can be used to create a representative database. Our dataset indicates that incidence and correlation of PPA subsets agree with reported literature and can be used in multicenter trials and research studies.

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P1151 / #1122

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

A DEEP-LEARNING NATURAL LANGUAGE PROCESSING ALGORITHM TO IMPROVE KEYWORD-BASED IDENTIFICATION OF PATIENTS WITH ALZHEIMER'S DISEASE FROM ELECTRONIC HEALTH RECORDS

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Aims: Keyword search to identify patients with Alzheimer's disease (AD) in electronic health records (EHRs) requires additional steps to process contextual information such as family history. We are developing a deep-learning natural language processing (NLP) algorithm to improve accuracy of keyword-based patient identification.
Methods: Our algorithm builds on RoBerta, a transformer-based deep-learning model pretrained on large biomedical and clinical text corpora. It classified sentences from EHR notes from the US Veterans Affairs Healthcare System that contained AD diagnosis (positive case) versus those that did not (negative case). We collected a dataset of 921 sentences (from 420 notes of 316 patients) labeled by domain-experts and randomly divided them (2:1:1) into training:development:test sets. We enlarged the training and development sets, using data augmentation techniques, to fine-tune the algorithm. We validated the algorithm on the test set (92 positive vs. 138 negative cases), comparing it with the keyword-based routine. The experiment was repeated 10 times using different random division of training/development/test data.
Results: Comparing with the keyword-based routine, the NLP algorithm achieved higher positive predictive value (0.89±0.04 vs. 0.79±0.01, P<0.001), area under ROC curve (0.99±0.01 vs. 0.91±0.004, P<0.001) and lower false positive rate (0.10±0.03 vs. 0.18±0.01, P<0.001). Sentences that likely lead to false positive AD identification were better flagged as negative, e.g., "her 95-year-old father has Alzheimer 's disease", "to assess Alzheimer's symptoms, med management", etc.
Conclusions: NLP is applicable to AD patient identification in EHR. Combined with keyword search, it is scalable to millions of EHR notes with enhanced accuracy and potentially adaptable for other diseases.

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P1152 / #1380

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ADEQUATE CARE FOR ELDER CITIZENS WITH A MIGRATION BACKGROUND LIVING IN GERMANY

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Aims: To demonstrate the needs of elderly people with immigration background living in Germany
Methods: We analysed the demographic change and development of eldere care in Germany
Results: The demographic change in Germany is one of the biggest challenges we have to face now and in the years to come. 24.1% of the German population is already over 60 years old Even in a global comparison, the average age in Germany is 45.7 years. As the population ages, so does the cost of caring for citizens
Conclusions: With regard to the care of people in Germany, with and without a migration background, our primary goal should be to strive for the best possible care that enables every citizen to shape their everyday life with dignity and the greatest possible independence.

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P1153 / #311

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ASSESSING KNOWLEDGE TOWARDS PEOPLE WITH ALZHEIMER DISEASE AMONG EMPLOYEES OF A PHARMACEUTICAL COMPANY IN ITALY, SPAIN AND PORTUGAL

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Aims: Assess Alzheimer's Disease (AD) knowledge of a pharmaceutical company employees in 3 countries (Italy, Portugal and Spain) by using the Alzheimer's Disease Knowledge Scale (ADKS). The results might help to understand the gaps in AD knowledge.
Methods: An anonymized web-based study/survey was conducted among Roche employees in Spain, Italy and Portugal. Participants answered sociodemographic questions and completed the ADKS.
Results: 447 subjects participated in Spain. 63% were between 30-50 years old, similar to Italian participants, 65% female. In Italy, 76 subjects participated, 68% were female. 86 subjects participated in Portugal. 72% were female. Overall knowledge about AD was moderate in all countries: mean ADKS score = 21.2 ± 2.8 [71% of correct answers] in Spain, 21.58 ± 3 [72% of correct answers] in Italy and 21.33 ± 3.09 [71% of correct answers] in Portugal. Risk factors and caregiving aspects were the lowest scores domains. The correct answers percentage were 59% and 63% in Spain, 58% and 61% in Italy and 64% and 55% in Portugal, respectively. Knowledge about treatment and management was the best-known domain in Spain and Portugal, and life impact for Italy. The scores did not show any significant association with sex or educational level in any country. Only age was correlated with better knowledge about AD.
Conclusions: There is a continuing need to improve the understanding of AD to fill the gaps in knowledge of the disease, even in a population working in a healthcare company and with an university degree.

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P1154 / #2200

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ACTIVE AGING FOR THE PREVENTION OF MILD COGNITIVE IMPAIRMENT AND DEMENTIA

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Aims: Introduction/Objective Healthy lifestyles and participation in cognitively stimulating activities during aging are considered protective factors against cognitive impairment and dementia by helping to preserve cognitive function through an increased cognitive reserve. Thus, active older people are likely to outperform non-active individuals on cognitive tests. Previous works developed specific normative data for people who attend university programs for Seniors (UPS). Scales such as the Scale of Cognitively Stimulating Activities (EACE) are used in neuropsychology to measure if a person is cognitively active. This work aims to explore the differences in the EACE between older people who attend UPS and same-age people from the general population (GO) and verify the need to use specific normative data to identify cognitive impairment in active older adults.
Methods: Method A linear regression model was built with age, sex, educational level and group as predictors of total EACE scores. The frequency of cognitively stimulating activities was compared between both groups (T-Student).
Results: Results There was no impact of sociodemographic characteristics on the differences between groups. The frequency of total cognitively active activities was significantly different between both groups ($t(df=172) = -3.04$; $p = .003$). Statistically significantly differences were also found in different items, such as attending class and courses ($t(df=172) = -9.16$; $p = .000$) and going to the cinema and theater ($t(df=172) = -2.60$; $p = .010$).
Conclusions: Conclusions Older people who attend UPS are involved in more cognitively stimulating activities than people from the GP. This might increase cognitive reserve as wells as performance in the neuropsychological assessment. The use of specific normative data for active older adults might reduce the number of diagnostic errors of cognitive impairment.

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P1155 / #2176

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

CUT-OFF SCORES OF FRONTAL ASSESSMENT BATTERY

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Aims: Dementia is a chronic syndrome characterized by progressive cognitive decline. Executive dysfunction is a typical symptom, which appears from the early stage of dementia. Frontal Assessment Battery (FAB) is a brief neuropsychological examination which is sensitive to the frontal dysfunction and suitable for clinical use. However, there is no consensus made on the cut-off score of FAB for screening dementia. The goal of the present study is to suggest a potential cut-off score of FAB for screening mild cognitive impairment (MCI) and dementia, by analyzing over 200 clinical data stored in our hospital.
Methods: We have collected clinical records of 239 patients who visited our outpatient section of the department of dementia and underwent FAB. The patients were diagnosed by a neurosurgeon, as 21 healthy individuals, 48 with MCI, and 170 with dementia. For the comparisons between healthy individuals vs. MCI and healthy individuals vs. dementia, the classification accuracies were evaluated by drawing receiver operator curves, and optimal thresholds were determined.
Results: For healthy individuals vs. MCI, the AUC was 0.66 and an optimal cut-off score was 14/15 with the sensitivity of 0.429 and the specificity of 0.875. For healthy individuals vs. dementia, the AUC was 0.86 and an optimal threshold was 11/12 with the sensitivity of 0.810 and the specificity of 0.771.
Conclusions: Present study suggested a potential cut-off score that screen patients with MCI and dementia from healthy individuals most effectively. The results encourage us to use FAB for screening dementia-related disorders at their earlier stages.

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P1156 / #2343

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

LIFETIME DISTRIBUTION OF MEDICAL COST AND ESTIMATION OF LONG-TERM CARE UTILIZATION FOR DEMENTIA IN REPUBLIC OF KOREA

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Aims: To investigate the current status of long-term care services for patients with dementia and lifetime medical costs for dementia in Republic of Korea.

Methods: This study utilized the National Health Insurance Service-National Health Information Database (NHIS-NHID) from January 2013 to December 2017. The prevalence and incidence of dementia was estimated by extracting people who were diagnosed and treated with dementia (age ?45 years) from the database. The use of long-term care services for the elderly with newly diagnosed dementia was also investigated. Additionally, the lifetime medical expenses for dementia were estimated using data on single year's medical costs, population data, and a life table from Statistics Korea.

Results: The prevalence of dementia increased over three years from 2015 to 2017, while the incidence of dementia gradually decreased. Among the patients with newly diagnosed dementia, approximately 30% used the long-term care services, while 4th graders accounted for the highest proportion every year. The older the age and the lower the income quartile, the shorter the time it took to apply for long-term care services after diagnosis of dementia. The total medical expenses per capita increased steadily every year, and the lifetime medical expenses were higher for females than males. Half of the lifetime medical costs of dementia occurred after 67 years of age for males and 83 years for females.

Conclusions: This study suggests that medical, social, and political measures are needed to effectively manage long-term care service recipients and prepare for rising medical costs for dementia.

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P1157 / #871

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

EXPECTED VS DIAGNOSED RATES OF MILD COGNITIVE IMPAIRMENT AND DEMENTIA IN THE US MEDICARE POPULATION

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Aims: Cognitive impairment is common in elderly populations, but remains underdiagnosed. We sought to derive contemporary population-level diagnosis rates of mild cognitive impairment (MCI) and dementia from US Medicare data and compared those rates to expected rates based on a predictive model.
Methods: We analyzed data from 2017-2019 100% samples for Medicare fee-for-service and Medicare Advantage; diagnoses were identified based on ICD-10 codes. To estimate the expected prevalence of MCI and dementia, we used the Health and Retirement Study, a nationally representative, longitudinal survey of older US adults, which includes formal cognitive assessments. We predicted MCI, dementia, and any cognitive impairment based on age, sex, race/ethnicity, dual eligibility status (ie, individuals covered by both Medicare and Medicaid), and a continuous linear trend account for the secular decline in dementia incidence with a probit model. The model was calibrated using 2000-2014 data, validated using 2016 data, and applied to 2017-2019 Medicare data to generate expected diagnosis rates.
Results: The prediction model performed well, with areas under the curve of 0.7128 (MCI), 0.8156 (dementia) and 0.7449 (any cognitive impairment). Predicted and observed rates are summarized below.

	MCI	Dementia	MCI or Dementia
Predicted rate	0.2175	0.121	0.2708
Diagnosed rate	0.0162	0.106	0.1221
Difference	0.2013	0.015	0.1487
Undiagnosed cases (n)	7,291,008	483,649	7,774,657

Conclusions: Dementia is diagnosed in the US Medicare population at approximately the expected rate; however, MCI remains substantially underdiagnosed. If failure to diagnose is not addressed, it will have negative implications for timely access to a disease-modifying treatment for Alzheimer's disease.

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P1158 / #419

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

QUANTITATIVE COMPARISONS OF TWO THEORETICAL MODELS OF COGNITIVE DECLINE

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Aims: Several cognitive aging theories aim to explain the mechanisms underlying cognitive decline. Although these theories have received considerable attention, they are not comprehensive enough to fully explain the complex mechanism involved in cognitive aging. In contrast, the revisited Scaffolding Theory of Aging and Cognition and the theory of Cognitive Reserve present important viewpoints on the underpinnings of healthy cognitive aging by taking a multifaceted approach.
Methods: We designed a system's dynamics computer simulation model of both the Cognitive Reserve model and the Scaffolding Model. We used longitudinal data across the life span of 10 patients to “train” the model to predict cognitive functioning. This data was obtained through life story interviews. Three separated raters assessed the variables of interest that were psychosocial or lifestyle related. Other medical data was obtained from patients. We then tested the two models on 8 additional patients. to predict the onset of cognitive impairment given data across the person's entire life. Systems dynamics computer models allow the study of multiple, interacting variables over time and represent a quantitative way to assess the efficacy of theoretical models. The simulation model aims to portray the time course for a person to develop cognitive impairment and to progress to major neurocognitive disorder. We defined success as a prediction of onset of cognitive decline within 10% of the actual date.
Results: The Scaffolding Model achieved better predictions than the Cognitive Reserve Model. It achieved an accurate prediction 56% of the time compared to 23% of the time for the Cognitive Reserve Model.
Conclusions: The Scaffolding model better serves theorizing about cognitive function and cognitive decline. Factors are missing from this model. We theorize about what additional factors could improve this theoretical model.

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P1159 / #921

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

IMPACT OF PERCEPTUAL STRENGTH ON LEXICAL PROCESSING IN ALZHEIMER'S DISEASE

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Aims: While the impact of the sensorimotor system in lexico-semantic processing has already been demonstrated in young adults, very few studies have investigated this question in healthy aging and Alzheimer's Disease (AD). Recently, the effect of perceptual strength (PS) has been investigated and has demonstrated the importance of sensorimotor information in conceptual representations. It has also been shown that PS impacts lexical processing identically in young adults and older adults (i.e., faster processing for words with high PS), demonstrating that the sensorimotor embodiment of concepts remains significant in aging (Miceli et al., submitted). However, we do not yet know how this one evolves in AD. The aim of this study is to explorate the effect of PS in lexical processing in order to question the embodiment of concepts in AD.
Methods: 22 early AD individuals (mean age 73.78±7.26) and 36 healthy elderly individuals (77.5±6.85) took part in a lexical decision task in which 28 words of interest have high PS (multisensory words) vs. low PS (uni or bi sensory words).
Results: An ANOVA with repeated measures (2 groups X 2 conditions) showed an effect of condition (p=.006), interaction (p=.03) and group (p=.001) indicating that words with high PS are processed faster in both groups and that this effect is more important in AD (post hoc test, p = .010).
Conclusions: This study being exploratory, it provides a first insight on the involvement of perceptual systems in lexical processing in AD. The processing of PS in AD seems to evolve towards a strengthening of the facilitation of the most embodied concepts with, on the contrary, a slowing down of the less embodied ones. The results are discussed in the light of embodied cognition theories.

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P1160 / #1186

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

MENTAL HEALTH CONDITIONS IN VETERANS WITH DEMENTIA AS A BARRIER TO EARLY DETECTION OF ALZHEIMER'S DISEASE

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Aims: The presence of mental health conditions (MHCs) in Veterans may obscure new onset dementia symptoms, with providers misattributing new symptoms to preexisting psychiatric disorders, delaying diagnosis of Alzheimer's disease (AD). We identified Veterans diagnosed with AD and unspecified dementia (UD) to determine the relative presence of MHCs. We hypothesized that Veterans with UD would have higher rates of MHCs compared to Veterans with AD.
Methods: International classification of diseases (ICD) 10 codes were used to identify Veterans diagnosed with AD or UD. ICD10 codes were used to identify select MHCs in this study population.
Results: Our study population had 31.4% of Veterans diagnosed with AD (n= 30,740) and 34.9% diagnosed with UD (n= 34,140). Approximately 40.9% of AD patients had comorbid MHC that included depression (17.6%), post-traumatic stress disorder (PTSD, 16.9%), anxiety (15.0%), bipolar disorder (1.7%), and schizophrenia (1.2%). In contrast, approximately 53.8% of UD patients had comorbid MHC, including higher rates of depression (24.3%), PTSD (24.6%), anxiety (21.5%), bipolar disorder (4.0%), and schizophrenia (3.7%). Only 1% of the study population received amyloid (PET), structural (MRI/CT) or functional (SPECT) neuroimaging, or cerebrospinal fluid analysis.
Conclusions: Veterans with diagnoses of UD are more likely to have comorbid MHC compared to Veterans with clear diagnoses of AD, suggesting that the presence of MHC may contribute to delayed AD diagnosis. Overall, few Veterans have biomarker data that could help improve diagnosis. Referrals for additional biomarker testing may be particularly important for Veterans with comorbid MHCs that confound diagnosis of dementia.

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P1161 / #136

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

EVALUATION OF INTER-INSTITUTIONAL COOPERATION ON DEMENTIA-RELATED ISSUES BASED ON A SURVEY OF RELATED SPECIALISTS IN LITHUANIA

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Aims: Effective communication is imperative to ensure quality of care for people living with dementia. The aim of the present study is to evaluate the cooperation of different institutions on the topic of dementia in Lithuania.
Methods: An anonymous questionnaire of 13 questions related to dementia mannagement was used to survey the experience about cooperation between different institutions. It was send via email to professionals of health care, social care and policy institution in Lithuania in 2022. Data from 93 respondents were collected and analysed.Statistical significance of the data was confirmed by the $\chi 2$ criterion, the number of degrees of freedom and the statistical significance $p < 0.05$.
Results: The most active response was from health care professionals (42.5%). Many respondents had not dealt with dementia-related issues in the last year (58.7%), but the majority of respondents indicated that would like to participate in the training on dementia-related issues (78.4%) ($p < 0.001$). The majority of respondents who faced issues related to dementia do not cooperate directly with professionals in other fields (63.1%), but a large proportion of respondents say that it would be useful (65.9%) ($p < 0.01$). Respondents who cooperate with institutions stated that there are problems in dealing with dementia issues (51.6%) ($p < 0.001$), and the most common problems were the lack of clear roles and responsibilities of institutions in the field of dementia (32.4%), the need of a convenient way of sharing information (27.0%) and difficulties to find a liable person (25.7%).
Conclusions: Interinstitutional cooperation in dementia-related issues is limited in Lithuania and should be encouraged. There is a need to raise awareness, clarify the responsibilities of professionals and improve the sharing of relevant information.

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P1162 / #253

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

WORD READING PROFILE IN ALZHEIMER'S DISEASE IN FRENCH

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Aims: To date, little is known about the specific reading profile of French-speaking Alzheimer patients and the type of errors they make as the disease progresses. Studies conducted in English report difficulties in reading irregular words (words that have exceptional grapheme-to-phoneme correspondences) leading to regularization errors (reading pint to rhyme with mint). Given that French has also many irregular words, our study aims at investigating word reading abilities in Alzheimer's disease (AD) in French.
Methods: A word reading aloud task developed for the study was administered to 42 participants (age= 77.6 +/- 6.2): 25 healthy elderly (MMSE 29 +/- 0.7), 8 Mild AD (MiAD) (MMSE 22.7 +/- 1.3) and 9 moderate AD (MoAD) (MMSE 16.4 +/- 1.6). The task consists of 4x32 words: high frequency regular words (HFRw), low frequency regular words (LFRw), high frequency irregular words (HFIw) and low frequency irregular words (LFIw). Word groups are matched for word frequency, initial phoneme, length, age of acquisition, imageability and orthographic neighborhood size (all p-values at least >.275).
Results: A repeated-measures ANOVA showed a significant group*type of word interaction effect ($F=11.289$; $p<.001$). MiAD perform similarly as the control group on the whole task. MoAD perform significantly worse than the other groups on HFIw and LFIw (mostly producing regularization errors) and LFRw ($p<.001$) (producing visual and phonological errors). However, they perform similarly to MiAD and controls on HFR words ($p>.1$).
Conclusions: MiAD show preserved reading abilities while MoAD exhibit reading difficulties for HFIw, LFIw and LFRw but preserved reading abilities for HFRw. The next step will be to investigate these errors by studying the underlying processes of reading in AD.

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P1163 / #929

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

DEVELOPMENT OF A SWEDISH ANTICHOLINERGIC BURDEN SCALE

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Aims: To develop a Swedish anticholinergic burden scale to be used in healthcare and research.
Methods: A method initiated by Duran et al. 2013 was followed. Using PubMed and Ovid Embase, a systematic literature review was performed to identify previously published tools that quantify anticholinergic burden. Drugs and grading scores 0-3 (0=no activity, 3=high activity) were extracted from the identified lists. The variance between scores was appraised. Drugs with conflicting anticholinergic scores in pre-existing lists were re-evaluated by an expert group consisting of four physicians and one pharmacist. In the assessment the mechanism of action, contraindications, affinity to muscarinic receptors and adverse effects were included.
Results: The systematic literature review resulted in nine anticholinergic burden scales that met the inclusion criteria: German Anticholinergic Burden Scale, Korean Anticholinergic Burden Scale, Anticholinergic Drug Scale, Anticholinergic Burden Classification, updated Clinician-rated Anticholinergic Scale, Anticholinergic Activity Scale, Anticholinergic Load Scale, updated Anticholinergic Burden Scale and Anticholinergic Risk Scale. Drugs with strong anticholinergic effects described in a list provided by The Swedish National Board of Health and Welfare were also included. A total of 234 drugs and their grading scores were extracted from the identified lists. Drugs not approved in Sweden were excluded as well as superfluous routes of administration other than enteral or parenteral (n=117). Six drugs were added to the list. 59 drugs were re-evaluated by the expert group.
Conclusions: Anticholinergic burden is an important factor that may contribute to cognitive impairment. This scale adapted to the Swedish healthcare system might be a valuable tool for physicians in estimating anticholinergic burden in vulnerable patients. Further research is needed to validate the scale and evaluate anticholinergic exposure versus clinically significant outcomes.

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P1164 / #2131

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ALZHEIMER'S DISEASE LINKAGE TO EVIDENCE (AD-LINE) STUDY EARLY RESULTS: LINKING REAL-WORLD CLAIMS DATA TO PHASE III GRADUATE STUDY OF GANTENERUMAB

Sheila Seleri Assunção[1], Christopher Wallick[1], Howard Fillit[2], Oleg Tcheremissine[3], Ibrahim Abbass[1], Carmen Ng[1], Tu My To[1]
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Aims: A holistic understanding of healthcare resource utilization (HCRU) in early Alzheimer's disease is lacking. Medicare claims data from Centers for Medicare and Medicaid Services were linked to data from the phase III GRADUATE I/II studies evaluating gantenerumab in participants with early symptomatic AD, to understand HCRU patterns.
Methods: AD-LINE is a non-interventional cohort study of Medicare patients with early symptomatic AD who were enrolled in the GRADUATE pivotal trials. Participants consented to combine existing (including year preceding GRADUATE entry) and future medical claims with clinical trial data. HCRU was examined for the year preceding their baseline trial visit.
Results: In total, 111 GRADUATE participants were included in AD-LINE. Mean age was 75.1 years (SD: 5.5); 67 participants (60.4%) were female. At baseline, 55 participants (49.5%) had MCI-AD and 56 (50.5%) had mild AD dementia. This early proof-of-concept linkage analysis includes data from the GRADUATE baseline visit and Medicare claims through December 2019 (latest currently available). Excluding 2020 clinical trial entrants, there were 79 patients; of those, 78 were continuously enrolled in Medicare Parts A/B and 46 were not in a health maintenance organization (HMO) in the preceding year. Sample size and data availability will increase as more Medicare claims and GRADUATE study data become available. Initial results show that in the 1 year preceding GRADUATE trial entry, these 46 AD-LINE patients had an average of 4.09 outpatient visits.
Conclusions: AD-LINE is the first study to successfully link large phase III clinical trial and real-world claims data. Linking trial data with HCRU data may provide critical information for payers and population health decision makers.

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P1165 / #2133

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

EMPOWER AD: A NOVEL, PATIENT-CENTRIC, LONGITUDINAL, CLINICAL DATASET IN THE UNITED STATES

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Aims: Electronic medical records (EMR) can provide real-world insights into Alzheimer's disease (AD); however, they are not readily accessible to all patients. EMPOWER AD is a US ongoing observational study utilizing patient-centered EMR data retrieval. EMR are abstracted into a structured dataset with the aim of providing a longitudinal view of the disease course of people with AD. Obtaining access to their digitized records may empower patients and support shared decision-making with their healthcare providers.
Methods: After informed consent, EMR data (eg, detailed diagnoses, resources utilized, prescriptions ordered, laboratory results, imaging) are retrospectively collected for approximately 7 years; medical records and observer (ie, care partner)-reported outcomes (eg, ADCS-ADL, RUD-Lite, and the AD-SPGI-S) are prospectively collected for ≤2 years. Eligibility criteria include diagnoses of mild cognitive impairment or dementia with or without reference to AD; participants without reference to AD must have a reported progressive cognitive decline or be taking ≥1 indicated AD treatment. Planned enrollment is 2500 (first participant enrolled January 2022). Our intention is to recruit a patient sample representative of US AD epidemiology.
Results: This interim cohort included 453 participants with mean age of 72.5 (SD: 8.8) years; 55% were female; 52.8% were care-partner enrolled and 47.2% were self-enrolled. Approximately 84% identified as White, 8% Black/African American, 1% Asian American, 1% American Indian/Alaska Native, 2% multiple races, and 3% unknown. Roughly 6% identified as Hispanic/Latinx.
Conclusions: EMPOWER AD uses an innovative, longitudinal approach to data collection and patient empowerment. EMPOWER AD findings may deepen our understanding of the AD clinical trajectory and improve the standard of care for persons living with AD in the US.

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P1166 / #298

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

MRT-TRACKED TRANSCRANIAL PULSE STIMULATION – A NEW METHOD OF BRAIN STIMULATION TO AMELIORATE DEFICITS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: TPS (Transcranial Pulse Stimulation) which can be individually tracked by MRT-scans offers new perspectives to ameliorate deficits caused by Alzheimer's disease. Pilot studies show beneficial effects on learning and memory of TPS. There are also reports of restorative structural changes in the thickness of the cerebral cortex due to the stimulation. The aim of the application observation was to document behavioral benefits after treatment.
Methods: 21 out-patients with Alzheimer's disease (with light to moderate symptoms) received 6.000 pulses of TPS (0.2 mJ/mm^2 per single pulse, with a frequency of 4 Hz) per session. The application of the pulses with Neurolith by Storz Medical was inividually navigated by use of current MRT-images of the patients. TPS-pulses were administered bilaterally into the frontal, parietal and temporal cortex. Pulses were applicated over a period of 2 weeks (3 sessions per week). Cognitive capabilities (especially executive functions) of the patients were tested using the Stroop-Test (colour-word-interference-test) and CERAD. The Stroop-Test is a standardized test for executive functions. Patients were tested using a pre – post design (t_0 pre stimulation : t_1 after 6 sessions, two weeks later).
Results: TPS-stimulation over a period of two weeks (6 sessions) showed ameliorating effects on performance in the Stroop-Test. The mean-score was diminished significantly (pre vs. post ; $p < 0.05$ – paired T-test). Single patients showed extraordinary improvements by shortening completer times in the Stroop-Test by halve. No significant side-effects occured during all the sessions in none of the patients.
Conclusions: The results of this pilot-trial show that cognitive impairments of executive functions in Alzheimer's disease may be ameliorated using TPS as a noninvasive brain stimulation method. No severe side-effects were observed.

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P1167 / #950

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

ONLINE EDUCATION YIELDS SIGNIFICANT GAINS IN PHYSICIANS' KNOWLEDGE OF STRATEGIES FOR TIMELY AND ACCURATE DIAGNOSIS OF ALZHEIMER'S DISEASE

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Aims: We developed an online continuing medical education (CME) activity titled: "*Challenging Cases in Alzheimer's Disease (AD): Applying Strategies to Inform Timely and Accurate Diagnosis*". We hypothesized that participation in this online CME education would lead to improved knowledge of the current strategies for diagnosis of AD.
Methods: An online 30 minutes video CME activity (www.medscape.org/viewarticle/969018) consisting of a series of 3 expert commentaries was developed. Educational effect was assessed using a repeated-pair design with pre-/post-assessment. A paired samples t-test was conducted for significance testing on overall average number of correct responses and for confidence rating, and a McNemar's test was conducted at the question level (5% significance level). Cohen's d with correction for paired samples estimated the effect size of the education (<.20 modest, .20-.49 small, .59-.79 moderate, ≥.80 large). Data were collected from 2/24/2022 to 5/23/2022.
Results: A total of 3,525 Primary Care Physicians (PCPs) and 1,792 neurologists participated, of whom 539 and 254, respectively, completed all the pre-/post-activity questions. Overall 39% improved their knowledge and competence related to the recogntion and evaluation of mild cognitive impairement (MCI) in clinical practice (P< .001, Cohen's d=0.35 and 0.37 for PCPs and neurologists, respectively), showing a 113% and 140% relative increase in correct responses pre-/post-CME. 42% PCPs and 33% neurologists had a measurable increase in their confidence in establishing that a patient with MCI is on the path to AD.
Conclusions: This online CME activity significantly improved PCPs and neurologists knowledge of the current strategies for timely and accurate diagnosis of AD.

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P1168 / #238

POSTERS: K01.J. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

CLINICAL RISK FACTORS ASSOCITED WITH INCREASED HOSPITALIZATION AND EMERGENCY ROOM VISITS IN EARLY-STAGE DEMENTIA WITH LEWY BODIES.

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Aims: Identify risk factors associated with healthcare utilization prior to diagnosis of dementia with Lewy bodies (DLB).
Methods: We analyzed electronic health record and claims data for member-patients from an integrated U.S. healthcare system between October 2015 and June 2022. Rates of hospitalizations and emergency department (ED) visits for DLB cases were compared to non-demented older adults randomly matched 3:1 on age/sex at index, defined as the first encounter with a DLB diagnosis. Random chart audits were conducted to confirm diagnosis. Negative binomial regression was used to evaluate the association between DLB and annual utilization rate, including adjustment for clinical factors (race, Charlson Comorbidity Index (CCI), current prescriptions), that differed between DLB and control cohorts. An offset was included to capture differences in length of enrollment.
Results: We identified 175 patients clinically diagnosed with DLB. The rate of pre-index ED visits was 59% higher (95% CI: 12% to 124%) among patients with DLB compared to non-demented patients after adjustment for covariates. Within the full model, CCI and falls were associated with increased rates of ED visits [IRR_{CCI} 1.15 (1.08, 1.23); IRR_{falls} 2.64 (1.20, 3.86)] and hospitalization [IRR_{CCI} 1.30 (1.24, 1.37); IRR_{falls} 2.59 (1.83, 3.69)]in DLB. As independent predictors, delirium and prescriptions for sleep or anticholinergic medications were associated with higher utilization in DLB.

Table 1. Participant Demographics and Medical Characteristics at Time of Index Visit

	DLB (N=175)	Non-Demented Older Adults (N=525)	*p*-value
Age	78.3 (8.2)	78.3 (8.2)	NA
Sex - Female	41.7%	41.9%	NA
White	90.3%	78.3%	<0.001[2]
Hispanic	1.1%	0.8%	0.636[2]
Charlson Comorbidity Index	2.4 (2.4)	1.5 (2.1)	<0.001[1]
Benzodiazepines* 0-1 Year Prior to Index	17.7%	8.0%	<0.001[2]
Anticholinergics* 0-1 Year Prior to Index	73.1%	44.8%	<0.001[2]
Sleep Medications* 0-1 Year Prior to Index	45.7%	15.0%	<0.001[2]
History of Delirium 0-1 Year Prior to Index	9.1%	0.2%	<0.001[2]
History of Falls 0-1 Year Prior to Index	28.0%	4.6%	<0.001[2]

Notes: DLB = Dementia with Lewy bodies; [1] Equal variance t-test; [2] Chi-square test; Values listed as mean (SD) or percentage; * Based on prescription claims data

Table 2. Rates of utilization in the year before index date

	DLB (N = 175)	Controls (N=525)
Percent with Full Year of Coverage	89.7%	84.2%
Enrollment Time in Years (Mean (SD))	0.95 (0.18)	0.89 (0.27)
Range	0.01, 1.0	0.01, 1.0
Number of Inpatient Admissions (Mean (SD))	0.45 (0.76)	0.21 (0.58)
Frequency		
0	68.6%	**84.2%**
1-2	28.6%	**14.5%**
3+	2.9%	**1.3%**
Number of ED Visits (Mean (SD))	0.74 (1.08)	**0.27 (0.69)**
Frequency		
0	56.0%	**82.1%**
1-2	36.0%	**15.8%**
3-5	7.4%	**2.1%**
6+	0.6%	**0**

Notes: DLB = Dementia with Lewy bodies; Bold values significantly differ ($p<0.05$) between groups; Comparison of means using equal variance t-test, Chi-square test for all others; Values listed as mean (SD) or percentage; Range (Minimum, maximum) presented only for descriptive purposes.

Table 3. Unadjusted and multivariable analysis of risk factors for health care utilization pre-index for all subjects

	Inpatient Admissions		Emergency Department	
Predictors	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Diagnosis – DLB	**1.98 (1.38, 2.83)**	0.95 (0.67, 1.35)	**2.57 (1.87, 3.55)**	**1.59 (1.12, 2.24)**
Race – Non-White	1.19 (0.75, 1.87)	1.43 (0.99, 2.09)	0.91 (0.59, 1.42)	0.99 (0.65, 1.51)
Charlson Score	**1.38 (1.31, 1.46)**	**1.30 (1.24, 1.37)**	**1.23 (1.15, 1.32)**	**1.15 (1.08, 1.23)**
Benzodiazepines	1.35 (0.91, 2.26)	1.11 (0.69, 1.79)	1.24 (0.76, 2.02)	0.73 (0.44, 1.22)
Anticholinergic	**2.08 (1.43. 3.01)**	1.34 (0.95, 1.89)	**1.75 (1.25, 2.43)**	1.10 (0.78, 1.56)
Sleep medication	**1.81 (1.25, 2.62)**	1.02 (0.69, 1.50)	**2.19 (1.57, 3.05)**	1.49 (0.99, 2.25)
History of Delirium	**4.84 (2.40. 9.77)**	1.54 (0.92, 2.55)	**2.30 (1.01, 5.29)**	0.66 (0.31. 1.40)
History of Falls	**4.29 (2.96, 6.21)**	**2.59 (1.83, 3.69)**	**4.23 (2.96, 6.04)**	**2.64 (1.20, 3.86)**

Notes: DLB = Dementia with Lewy bodies; IRR = Incident rate ratio; 95% CI = 95% Confidence Interval; Bold values indicate significant ($p<0.05$) association with utilization rate; Unadjusted IRR calculated from univariate regression, adjusted using all predictors in multivariate model.

Conclusions: In the year prior to a dementia diagnosis, patients with DLB had higher frequencies of ED visits and hospitalizations compared to non-demented older adults. Patients wtih DLB were also more likely to have medical claims for falls and delirium, in addition to prescription claims for benzodiazepines, anticholinergic medications, and sleep aids, The results of this study highlight potential targets for interventions designed to reduce healthcare utilization in this population.

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POSTERS: K02.A. MOVEMENT DISORDERS: CAREGIVER SUPPORT

DIFFERENCE OF DAILY DISABILITY REPORT BETWEEN PATIENT AND CAREGIVER IN PARKINSON'S DISEASE

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Aims: The aim of this study is to determine how much difference in ADL report between patient and caregiver exists and to study factors influencing the difference.
Methods: A total 217 couples of PD patients and caregivers were consecutively recruited. A survey on Parkinson's disease ADL questionnaire (ADLQ) were done, and patients were grouped based on difference of ADL report (dADL) and absolute value of the difference (δADL). Characteristics of each group were compared to investigate factors influencing those differences.
Results: There were significant differences in reporting between patients and caregivers (ranging -47~50 in total score of 200). Relationship between patient and caregiver was not associated with dADL and δADL. Group without difference showed younger age of patient, milder state of disease and lower caregiver burden than other groups. Negative dADL group (patient report<caregiver report) showed higher caregiver burden. dADL was correlated with patients' depression, cognition, sleepiness, quality of life and caregiver burden. Higher δADL group (lager difference in absolute value of dADL) showed severe motor and non-motor symptoms, depression and anxiety of patients and caregivers, and higher caregiver burden. δADL was correlated with age of patient, disease duration, HY stage, most of motor and non-motor symptom severity, patients' and caregivers' depression and anxiety, and caregiver burden.
Conclusions: There were significant differences in ADL report between patients and caregivers in PD. The difference was observed to increase as the motor and non-motor symptoms of PD became more severe, and was associated with depression of patient and caregiver. Clinicians should pay attention when interpreting the report of patient and caregiver about patient's daily disability.

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P1170 / #2682

POSTERS: K02.C. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

THE MUSICAL INSTRUMENTS-BASED INTERVENTION FOR THE UPPER-LIMB FUNCTIONAL MOVEMENT IN PATIENTS WITH PARKINSON'S DISEASE: A SCOPING REVIEW

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Aims: Parkinson's disease (PD) is a neurodegenerative disease affecting mainly the elderly population and the symptoms appear tremors, muscle rigidity, postural instability, akinesia, and bradykinesia. In particular, the difficulties in upper-limb motor function cause restrictions on daily life, and the typical rehabilitation of upper-limb and bimanual motor functions for PD is non-pharmacological therapies such as physical therapy, occupational therapy, and endurance exercise training.
Methods: Recently, the rehabilitation of the upper limb for PD used playing instrumental-based music neurology therapy and reported effectiveness through music intervention. Therefore, this review describes the focus of the intervention of playing instrumental-based music activity with PD for upper-limb rehabilitation. In this study, MEDLINE, PubMed, Google Scholar, Cochran Central Register of Controlled Trials (CENTRAL), MEDLINE, Academic Search Complete, and Music Index were searched.The search terms included 'Parkinson's disease' and ‘music’, ‘instrument playing’, ‘music activity, ‘music therapy’, and ‘music-based intervention’.
Results: The eight studies were included and research in the field include only experimental design and quantitative studies. As a result, 2 types of playing instrumental were divided into 'Acoustic/Live playing', and 'Virtual playing'. According to playing types, confirmed the differences use of music, music feature, and intervention type.
Conclusions: This analysis is expected to provide clinical evidence on the therapeutic aspect of playing instrumental-based music intervention and cause the application and expansion of the type of playing instrumental in digital healthcare.

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P1171 / #1779

POSTERS: K02.C. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

NEURO-EXERGAMING FOR PARKINSON'S DISEASE: PILOT OF 3-MONTH PEDAL-N-PLAY WITH THE INTERACTIVE PHYSICAL AND COGNITIVE EXERCISE SYSTEM (IPACES)

Cay Anderson-Hanley[1,2], Marie Lucey[3], Sean Clark[3], Kartik Nath[1], Irelee Ferguson[2], Valerie Needham[2], Nelson Roque[4], Josh Rogers[2], Tobi Saulnier[2,5], Stella Panos[2,6], Robert Gillen[2]
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Aims: Objectives: To evaluate the feasibility of longer-term use and potential cognitive benefit of neuro-exergaming for Parkinson's Disease. It is estimated that up to 40% of PD patients would meet criteria for a diagnosis of mild cognitive impairment and that up to 80% will develop dementia over the course of the disease (Kenney et al, 2022). There has been a call for lifestyle interventions for older adults to prevent, delay or ameliorate cognitive decline via non-pharmacological interventions such as exercise (Camisul et al, 2019).
Methods: Methods: Parkinson's patients (n=6) began participation in a pilot, 3-month 45-min class, in which they would pedal-n-play the tablet-based interactive Physical and Cognitive Exercise System (iPACES). Physical therapists and PT assistants were available to assist with the iPACES technology as well as ergonomic and strategic issues. One participant dropped out part-way due to transportation issues and another due to health concerns. Four participants completed the class. Everyone was invited to participate in the electronic test of executive function (Stroop task; eStroop) available on the tablet.
Results: Results: Despite some technical glitches in this unfunded pilot, some eStroop data was successfully captured. A trend was noted over three months in the eStroop data points that were collected from three of the participants, with about a 10% reduction in the interference phenomenon of the eStroop task from baseline to class wrap-up.
Conclusions: Conclusions: This pilot provided a promising preliminary peek at how the iPACES neuro-exergame might be implemented as well as what might be the potential impact on cognition. Our team is thus pursuing options for expanding use and data collection with iPACES in a follow-up study to examine whether this promising preliminary indication is confirmed in a larger sample.

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P1172 / #1015

POSTERS: K02.C. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

RELATIONSHIPS BETWEEN ADVANCED DYNAMIC BALANCE AND PHYSICAL ACTIVITY/QUALITY OF LIFE IN INDIVIDUALS WITH PARKINSON'S DISEASE

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Aims: Balance problems commonly occur in Parkinson's disease (PD). However, balance tasks with only one performance objective may not be sufficient to be applied to the assessments and interventions which are designed to promote PD patients' balance functioning, physical activity (PA) and health-related quality of life (HQoL). Therefore, this study aimed to determine whether a demanding motor-motor dual task is a significant predictor of PA/HQoL in adults with and without PD.
Methods: Participants with (n = 22) and without (n = 23) PD were assessed using the Berg Balance Scale (BBS), the single leg hop and stick series (SLHS) task, the Physical Activity Scale for the Elderly (PASE), and the Parkinson's Disease Questionnaire–39 (PDQ39). We compared the multiple linear regression models determined both before and after adding the scores on the BBS and SLHS by calculating the change in the value of R^2, namely the incremental validity.
Results: While controlling for biological and socioeconomic covariates, competence at the SLHS task provided moderate and large levels of incremental validity to PA (ΔR^2 = .08, Cohen's f^2 = 0.25, p = .035) and HQoL (ΔR^2 = .16, Cohen's f^2 = 0.79, p < .001), respectively. In particular for participants with PD, the SLHS explained significantly more variance in HQoL in relation to psychosocial functioning (ΔR^2 = .26, Cohen's f^2 = 0.46, p = .024) compared to the BBS (p = .337).
Conclusions: Assessing advanced dynamic balance by means of a highly demanding dual-task training paradigm was not only strongly associated with PA but also covered a wider spectrum of HQoL components. This approach is recommended for use in evaluations and interventions carried out in clinical and research settings in order to promote healthy living.

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P1174 / #1471

POSTERS: K02.D. MOVEMENT DISORDERS: SUPPORT DEVICES & MONITORING

LEVODOPA-CARBIDOPA INTESTINAL GEL EFFICACY ON FREEZING OF GAIT AND OTHER GAIT FEATURES AT 6-MONTHS: PRELIMINARY RESULTS FROM OBJECTIVE OUTCOME MEASURES

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Aims: Continuous levodopa-carbidopa intestinal gel (LCIG) infusion showed some benefit on Freezing of gait (FoG) and gait difficulties in advanced Parkinson's disease (PD), also in cases refractory to oral dopaminergic therapy. Our aim is to implement findings from clinical expert-delivered rating scales with an objective, rater-independent assessment of the LCIG efficacy on FoG and spatiotemporal gait parameters in advanced PD patients by means of APDM wearable motion sensors, confirming subjective improvement impression.
Methods: This is an observational open-label study enrolling patients screened as candidates for LCIG therapy, currently including 11 patients with several episodes of FoG a day in the month preceding the baseline evaluation, before percutaneous endoscopic gastrojejunostomy implant. Assessment is provided by means of New Freezing of Gait Questionnaire (NFoG-Q) for patient's subjective impression and with motion sensors at baseline, in the OFF and best-ON oral antiparkinsonian therapy condition, and repeated 3 and 6 months after starting LCIG therapy, during daily-ON condition.
Results: 7 of 11 patients have currently completed the 6-month follow-up, with a significant improvement at the NFOG-Q (from 16,1±4,5 to 10±7,1 p=0,001). Results from motion sensors indicate an improvement from baseline best-ON to 6 months daily-ON: a trend is valuable at the Two-minute walking test for gait speed, step duration and stride length (increase), at the Timed up and go test for total duration and turn duration (reduction), and at the 360 degrees Turn Test for Turn velocity (increase).
Conclusions: Preliminary results suggest an improvement of gait features after LCIG start at six months, confirmed by patients' subjective impression. The lack of response at three months could indicate the need for a longer time to induce synaptic plasticity processes within neuronal networks implicated in the genesis of the symptom.

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P1175 / #955

POSTERS: K02.D. MOVEMENT DISORDERS: SUPPORT DEVICES & MONITORING

USER EXPERIENCES OF LIMB-WORN WEARABLE DEVICES FOR MONITORING PARKINSON'S DISEASE MOTOR FUNCTION AND BLOOD PRESSURE

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Aims: Wearable devices offer a potential for reliable and objective assessment and monitoring of Parkinson's disease (PD) symptoms. The design phase of prototypes typically focuses on technical performance, accuracy and reliability, with less evaluation of the user-experience of wearing monitoring devices, either for short-term assessment, or for longer monitoring, which is essential for use and adherence. This study aimed to explore the user-experience of a novel prototype wearable device (wrist- and ankle-worn), which records limb accelerations and angular velocities, along with photoplethysmograph (blood pressure) and electrocardiogram information.
Methods: This qualitative study used online semi-structured interviews with people with PD, following their wearing of the prototype devices for 24 hours at home. Interviews were audio recorded and transcripts were analysed using an inductive thematic approach.
Results: Six people with PD, aged 52-83 years, with an average disease duration of 8 years, took part. All were overall positive toward the prototype. The prototype was comfortable, however comfort was less of a priority to them than robustness, the device not hindering their usual clothing choices, and adjustability for fit. Valuable insights included a need to change to an elasticated strap, and to reduce the size/outwards projection of the device. Discreet design was important; some would be self-conscious about the stigma of wearing condition-specific products. The ankle-worn device was perceived as unfamiliar and non-discrete; some referenced negative associations such as prisoner tracking devices. Additional desirable features were: user-feedback, symptom prediction, and supporting medication management. Overall, participants would be happy to wear PD-specific devices and believed they would support better management of their PD.
Conclusions: This study provides insights for the design of wearable devices to promote patient acceptance, comfortable use and adherence.

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P1176 / #1818

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

DO MOTOR AND COGNITIVE FUNCTION IN PARKINSON'S DISEASE (PD) CORRELATE WITH DIETARY PROTEIN INTAKE?

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Aims: To measure dietary protein's effect on motor and cognitive function in Parkinson's disease.
Methods: We enrolled 118 patients prospectively in our PD Comprehensive Clinic. Patients consented to the Harvard Food Frequency Questionnaire to measure dietary intake, part III of the Unified Parkinson's Disease Rating Scale (UPDRS) to measure motor function, and the Mini-Mental Status Exam (MMSE) to assess cognitive function. Multivariable linear regression and Spearman's rank correlation assessed the relationships. A p value of <0.05 was considered statistically significant.
Results: Mean protein intake was 82±33.1 g/day. Mean UPDRS Part III was 34.25±9.8 and average MMSE score was 28.71± 2.1. UPDRS motor scores were significantly correlated with protein intake (p=0.04). No correlation was seen between MMSE and protein intake (p=0.19). After adjusting for relevant confounders, protein significantly associated with UPDRS scores (beta=0.06; p=0.02; 95% CI: 0.009, 0.12). Results indicate that UPDRS motor scores increase by 0.063 points for each gram per day in protein intake.
Conclusions: Nutrition should not be overlooked in PD patients. Dietary protein significantly associates with increases in UPDRS III scores. More research is needed in this field.

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P1178 / #1963

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

SYSTEMATIC REVIEW OF THE EFFICACY OF TRADITIONAL CHINESE MEDICINE IN PARKINSON DISEASE

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Aims: Parkinson's disease is a multi-system neurodegenerative disorder characterized by motor and nonmotor symptoms. To slow disorder progression, different treatment options are now available but in most of the cases these therapeutic strategies also involve the presence of important side effects. This has led many patients to pursue complementary therapies, such as acupuncture, to alleviate PD symptoms. Therefore, an update on the efficacy of this treatment for patients of PD is of great value. This work presents a systematic review of the efficacy of acupuncture treatments in relieving PD symptoms;
Methods: EMBASE, Medline, Pubmed, Science Direct, The Cochrane Library, Cochrane Central Register of Controlled Trials (Central) and Scielo databases, were systematically searched 21 from January 2011 through July 2021. Randomized controlled trials (RCTs) published in English with all types of acupuncture treatment were included. The selection and analysis of the articles was conducted by two blinding authors through Rayyan application;
Results: 720 potentially relevant articles were identified; 52 RCTs met our inclusion criteria. After exclusion of 35, we found 17 eligible. The included RCTs reported positive effects for acupuncture plus conventional treatment compared with conventional treatment alone in the UPDRS score;
Conclusions: Additional evidence should be supported by rigorous methodological strategies. Although firm conclusions cannot be drawn, acupuncture treatment, in the framework of an interdisciplinary care team, appears to have positive effects in PD symptoms.

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P1179 / #752

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

DYSPHAGIA AS A POOR OUTCOME IN PARKINSON'S DISEASE PATIENTS TREATED WITH LEVODOPA-CARBIDOPA INTESTINAL GEL

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Aims: To analyze the impact of dysphagia in a large group of PD patients treated with LCIG, comparing clinical factors, disability, and mortality between patients with and without dysphagia.
Methods: We performed a retrospective observational study including all patients with a diagnosis of idiopathic PD and treated with LCIG for at least six months between 2012 to 2022. Patients who presented dysphagia, dementia, and H&Y>4 before LCIG implantation were excluded. Clinical-demographic features, including age, sex, disease duration, MDS-UPDRS in ON-condition at baseline before LCIG implantation and at the last reported visit, total LEDD, and presence of dementia or hallucinations were collected by electronic database of the two centers. Death was chosen as the primary outcome measure, and H&Y>4, the presence of hallucination, and a diagnosis of dementia were chosen as the secondary outcome measures to analyze mortality and the main disability milestones in all patients.
Results: A total of 86 patients were included. The mean age and disease duration at LCIG start were 67.7±7.1 years and 13.0±5.1 years, respectively. Forty-two patients (49%) developed dysphagia. During follow-up, 34.7% of LCIG patients died (n=37/86), 6 (14%) without dysphagia, and 21 (50%) with dysphagia (OR:1.85, p<.001). According to the COX regression analysis, we found that the development of dysphagia predicts mortality in LCIG patients (p:<0.001,95%CI 7.569-20.609). Age, disease duration, and H&Y at surgery did not significantly affect mortality. Linear regression showed a correlation between dysphagia and H&Y at the last evaluation (p: <0.001,95% CI 1.608-4.468) and dementia (p: 0.033,95% CI 0.162-0.924)
Conclusions: We collected for the first-time data regarding the impact of dysphagia in PD patients treated with LCIG, emphasizing the importance of prioritizing the management of dysphagia representing a poor outcome predictor in terms of death.

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P1180 / #1069

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

NON-MOTOR SYMPTOMS PREDICT REDUCED HEALTH-RELATED QUALITY OF LIFE (HRQOL) IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOR DISORDER (IRBD)

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Aims: When assessing a disease's impact on a patients´s life, health-related Quality of Life (hrQoL) is a key metric. In patients with Parkinson's disease (PD), a plethora of non-motor symptoms strongly impacts hrQoL in addition to motor symptoms. Isolated REM sleep behavior disorder (iRBD) is a prodromal stage of PD without relevant motor symptoms. We aimed at studying hrQoL in iRBD patients and its relation to emerging non-motor symptoms.
Methods: HrQoL was measured with the 36-Item Short Form Health Survey (SF-36) in 63 patients with polysomnography- confirmed iRBD, and 22 age- and sex-matched healthy controls as well as 29 PD patients. All subjects completed clinical work-up and questionnaires on non-motor symptom burden. Motor symptoms were quantified with the MDS-UPDRS III. HrQoL metrics were compared using Kruskall-Wallis tests. We studied correlations between hrQoL and non-motor symptoms as well as clinical and demographic data. We performed multiple linear regression to assess determinants of hrQoL in iRBD.
Results: iRBD patients showed significantly reduced hrQoL on the SF-36 domains *general health*, *energy/vitality* as well as *psychological wellbeing* in comparison to HC. PD patients reported significantly lower hrQol than iRBD patients and HC in all domains. Significant determinants of reduced hrQoL in patients with iRBD were more symptoms of fatigue and more severe depressive symptoms, as well reported sleep impairments. Incipient motor symptoms were not associated with reduced hrQoL in iRBD.
Conclusions: This study highlights reduced hrQoL in iRBD patients independent of motor symptoms. Non-motor symptoms, particularly depressive symptoms and fatigue, seem to be the most relevant non-motor therapeutic targets in this stage of disease to improve the patients´ quality of life.

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P1181 / #475

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

THE PRESENCE AND IMPACT OF VISUAL COMPLAINTS IN PEOPLE WITH PARKINSON'S DISEASE

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Aims: Visual complaints can have a vast impact on the quality of life of people with Parkinson's disease (PD). In clinical practice however, visual complaints often remain undetected. A better understanding of visual complaints is necessary to optimize care for people with PD and visual complaints. This study aims at determining the prevalence of visual complaints experienced by an outpatient cohort of people with PD compared to a control group. In addition, relations between visual complaints and demographic and disease-related variables and objectified ophthalmological conditions are investigated.
Methods: The Screening Visual Complaints questionnaire (SVCq) screened for 19 visual complaints in a large cohort of people with idiopathic PD (n = 581) and an age-matched control group (n = 583).
Results: People with PD experienced significantly more complaints than control subjects, even when there was no underlying ophthalmological condition present. In addition, they experienced a greater impact of visual complaints on their daily lives. Most common were complaints regarding reading, unclear vision, trouble focusing, reduced contrast, blinded by bright light, and needing more light. Age, disease duration, disease severity, and the amount of dopaminergic medication had a significant positive relationship with the prevalence and severity of visual complaints in people with PD. Most complaints did not differ between the sexes.
Conclusions: Visual complaints are highly prevalent in people with PD. These complaints progress with the disease and can only partially be explained by the presence of ophthalmological conditions. Standardized questioning is advised for timely recognition and treatment of these complaints.

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P1182 / #1445

POSTERS: K02.F. MOVEMENT DISORDERS: QUALITY OF LIFE

EFFECTS OF METABOLIC RISK FACTORS ON DBS TREATMENT FOR DEPRESSION AND SLEEP DISORDERS IN PARKINSON'S DISEASE

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Aims: Depressive disturbances and sleep disorders in patients with Parkinson's disease (PD) are widespread and affect many clinical features of the syndrome. Deep brain stimulation (DBS) uses stereotactically implanted electrodes to deliver persistent electrical stimulation to specific target locations in PD's brain. However, its efficacy in treating depression and sleep disorders has always been debated.
Methods: In this study, we investigated 757 PD patients (DBS: 267, non-DBS: 490) using electroencephalography (EEG) and one sleep quality assessment scale, and four depression rating scales for depression assessment.
Results: Compared with control, DBS significantly improved depression and sleep disturbance in PD. The patients with depression and sleep disorders showed much higher levels of body mass index (BMI), fasting blood glucose (FBG), blood cholesterol and blood triglycerides (TG). Clinically, BMI, FBG, blood cholesterol and blood TG have significant detrimental impacts on DBS for improving PD patients' depression, sleep disturbance, and slow-wave sleep. DBS treatment could significantly improve depression and sleep disturbance in patients, and this effect remains effective for 5-6 years. Outcomes deteriorated sharply after DBS treatment for 6-7 years. Besides, we also found gender, family history, and age were significant variables affecting depression and sleep disruption in PD. In our cohort study, we found the reduction of hyperglycemia and hyperlipidemia enhances the treatment efficiency of DBS on depression and sleep disturbance in PD patients.
Conclusions: In conclusion, DBS is an effective treatment for depression and sleep disturbance in PD patients, but this is primarily influenced by BMI, FBG, blood cholesterol and blood TG levels. Anti-hyperglycemia and Anti-hyperlipidemia can enhance the therapeutic effect of DBS on improving the symptoms of depression and sleep disturbance in PD patients.

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P1183 / #2656

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

EVALUATING THE EFFECT OF INTRANASAL ADMINISTRATION OF INSULIN ON METHAMPHETAMINE-INDUCED MOTOR IMPAIRMENTS IN MALE RAT

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Aims: Methamphetamine (MA), as an active psychostimulant drug, is widely abused for its stimulant, euphoric and empathogenic effects. MA at high doses causes persistent neurotoxic effects on central nervous system by inducing the neuronal cell death especially in dopaminergic neurons which may lead to motor deficits. Regarding the protective and pro-survival effects, insulin can be considered as a promising approach to attenuate MA-induced neurotoxicity. In this study, we investigated the effect of intranasal administration of insulin on MA-induced motor impairments.
Methods: Male Wistar rats received interperitoneal injections of MA, 4×12.5 mg/kg, every 2 hours. The next day, insulin was administered intranasally (0.5 IU; 0.25 µl in each nostril) for 15 consecutive days. Normal saline was injected in control group. Motor performance of rats were evaluated by locomotor activity, beam, pole, and rotarod tests on day 1, 5, 10 and 15 post MA injection.
Results: Statistical analysis showed that MA increased the time to start walking on the beam, time to turn and total time to reach the floor in pole test. It could also decrease latency to fall from rotarod, and insulin could improve all these motor impairments.
Conclusions: Taken together, our findings suggest that intranasal administration of insulin can attenuate MA-induced motor impairments in rats. However, further studies are needed to establish insulin influence on dopaminergic neurons function at behavioral and molecular levels following MA administration.

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P1184 / #2113

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

RESULTS OF A SURVEY IN PARKINSON'S DISEASE PSYCHOSIS – REMAINING UNMET NEEDS

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Aims: Parkinson's Disease Psychosis (PDP), characterized by psychotic symptoms of hallucinations and delusions, occurs in around 20-40% of PD patients. This study aimed to evaluate the current treatment landscape and the need for additional therapeutic options for PDP.
Methods: 20 qualitative interviews guided the development of a quantitative survey administered to 150 neurologists in the United States. Topics evaluated included the PDP diagnosis process, current treatment options, and unmet needs to be remedied by additional options.
Results: Data collected from this study show that approximately three quarters of the PDP population have symptoms severe enough to require interventional treatment. The data also indicated that when prescribing treatment, neurologists consider many factors, with most viewing efficacy (61%) and safety/side effects (45%) as the first and second most important considerations. Other factors include drug-drug interactions and access. Out of current options, no singular treatment is favorable in all factors. Individual comorbid diseases also influence treatment choice. A majority of neurologists prefer particular treatment depending on the comorbidity with PDP: comorbid dementia(50%), cardiac risks(49%), daytime sleepiness(59%), depression(45%), difficulty sleeping(71%), and agitation/aggression(45%). For future PDP treatment, most neurologists indicated high interest in one with minimal EPS(69%), sedation(66%), and QT prolongation(63%), proven history of reducing hallucinations in other disease states(62%), and flexible dosing strengths(53%).
Conclusions: Survey data across a variety of neurologist practices that treat PD psychosis patients indicate that despite one available, approved product, these neurologists are nonetheless seeking additional treatment options that have high efficacy, minimal side effects, and offer flexible dosing strengths. Given the lack of treatment options and complexities of individual treatment, more research into therapeutic options for this patient population are needed. This study was supported by Vanda Pharmaceuticals.

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P1185 / #415

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

ASSOCIATION OF DEPRESSION WITH EARLY OCCURRENCE OF POSTURAL INSTABILITY IN PARKINSON'S DISEASE

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Aims: Depression in Parkinson's disease (PD) significantly affect the quality of life of PD patients. Among motor symptoms of PD, postural instability and gait disturbance are associated with the disease severity and prognosis of PD. We aimed to investigate the association of depression with axial motor symptoms in early-stage PD patients.
Methods: This study investigated 95 PD patients unexposed to anti-parkinsonian drugs. After baseline assessment for depression, subjects were divided into depressed PD group, and non-depressed PD group. Analyses were conducted to identify the association of depression at baseline with the following outcome variables of PD: the progression to Hoehn and Yahr (H-Y) stage 3, the occurrence of freezing of gait (FOG), levodopa-induced dyskinesia, and wearing-off. The follow-up periods were 53.4 ± 16.8 months from baseline.
Results: Kaplan–Meier survival curves for H-Y stage 3 and FOG showed more prominent progression to H-Y stage 3 and occurrences of FOG in the depressed PD group than in the non-depressed PD group (Log-rank $p = 0.025$ and 0.003, respectively). Depression in drug-naïve, early-stage PD patients showed a significant association with the progression to H-Y stage 3 (HR = 2.55; 95% CI = 1.32 – 4.93; $p = 0.005$), analyzed by Cox regression analyses. In contrast, the occurrence of levodopa-induced dyskinesia and wearing-off did not differ between the two groups (Log-rank $p = 0.903$ and 0.351, respectively).
Conclusions: Depression of drug-naïve, early-stage PD patients is associated with the earlier occurrence of postural instability. This study results suggest the shared non-dopaminergic pathogenic mechanisms, and the potential prediction of early development of postural instability by assessment of depression in early-stage PD patients.

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P1186 / #2157

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

MINDFULNESS OR MEDITATION THERAPY FOR PARKINSON'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Aims: Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. Recently, mindfulness or meditation therapies have gained popularities, and have been demonstrated to serve as an effective alternative treatment for patients with neurological disorders. However, the effects of mindfulness or meditation therapies for PD patients remain unclear. This meta-analysis aims to investigate the effects of mindfulness or meditation therapies in PD patients.
Methods: A literature search was conducted in September in Pubmed, Embase and the Cochrane library for randomized controlled trials comparing mindfulness or meditation therapies and control treatments in PD patients. Primary outcomes were Unified Parkinson's Disease Rating Scale Subscale III (UPDRS III), gait velocity, cognitive function, PDQ-39 SI, and ADL, while secondary outcomes were depression, anxiety, pain and sleep disturbance.
Results: 8 articles extracted from 7 different trials were included, with a total of 307 patients. Our meta-analysis revealed that mindfulness or meditation therapies significantly improved UPDRS III (mean difference [MD] = -6.31, 95% confidence interval [95% CI]: -8.57 to -4.05), cognitive function (standard mean difference [SMD] = -0.62, 95% CI: -1.02 to -0.23), and anxiety (SMD = -0.62, 95% CI: -1.02 to -0.23). However, there were no significant differences between mindfulness or meditation therapies and control in terms of gait velocity (MD: -0.05, 95% CI: -0.34 to 0.23), PDQ-39 SI (MD: 0.51, 95% CI: -1.12 to 2.14), ADL (SMD = -1.65, 95% CI: -3.74 to 0.45), depression (SMD = -0.43, 95% CI: -0.97 to 0.11), pain (SMD = 0.79, 95% CI: -1.06 to 2.63), and sleep disturbance (SMD = -0.67, 95% CI: -1.59 to 0.24).
Conclusions: Mindfulness or meditation therapy may serve as an effective complementary and alternative treatment to a certain degree for PD patients.

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P1187 / #463

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE IN MEXICO : CASE SERIES.

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Aims: Describe the MNS of patients with PD treated at the Hospital Juárez de México
Methods: Retrospective, descriptive, cross-sectional study. Thirty-four patients who met inclusion, exclusion or elimination criteria in the period 2021-2022 were studied, using a 22-question questionnaire in search of MNS variables. Data were analyzed with IBM SPSS 25 for measures of central tendency for quantitative and qualitative variables.
Results: The demographic analysis showed a predominance of male gender (71%) with mean age 68 years (±10.7). The clinical study showed that the time of evolution was 6 years (±4.1), the scale to assess functionality was the Hoehn-Yahr scale where most patients (44%) were independent of the family (II) and only 3% had severe disability (V). NMS were present in the whole sample, since 60% had at least 10 symptoms, which in order of frequency were nocturia(55%), constipation(52%), unexplained pain(52%), sexual dysfunction(53%), insomnia(47%), depression(44%), anxiety (41%), vivid dreams(32%), salivation(32%), REM sleep disorders(29%), restless legs(26%), falls(23%), urinary urgency(20%), diaphoresis(17%), hallucinations(14%), apathy(11%), unexplained weight loss(11%), diaugesia/dyssomias (8%), dysphagia(8%) and fecal incontinence(5%).
Conclusions: Intentional search for NMS in PD is essential for care as only the minority do not present them and implies a continuous deterioration of quality of life that needs a multidisciplinary approach.

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P1188 / #162

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

THE EFFICACY OF DBS STIMULATION ON SUBTHALAMIC NUCLEUS AND MEDIAL GLOBUS PALLIDUS IN ADVANCED PARKINSON'S DISEASE:A META-ANALYSIS

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Aims: 目的：通过Meta分析系统评价深部脑刺激（DBS）对晚期帕金森病（APD）患者丘脑下核（STN）和苍白内球（GPi）在改善精神效应、运动症状、生活质量和减少多巴胺剂量方面的综合疗效。

Methods: Methods: The randomized controlled trials (RCT) about stimulation of STN and GPi targets in advanced Parkinson's disease patients were systematically searched in CNKI,Wanfang, VIP, China Biomedical Database (CBM), PubMed, Embase, Cochrane Library and Web of Science. The search time was until February 2022. The included literature was independently screened and extracted by two reviewers using the Cochrane manual, and the methodological quality of the included literature was evaluated combined with the criteria of physiotherapy evidence database scale (PEDro). Revman5.3 was used for Meta analysis.

Results: Results: A total of 834 patients with 10 randomized controlled trials were included in this study. Meta analysis showed that GPi-DBS could significantly reduce the scores of Parkinson's disease unified rating scale: ①UPDRS-III: [WMD=1.20,95%CI (0.16~2.25),P=0.02;②UPDRS-II: [WMD=1.01,95%CI (0.03~2.00),P=0.04];③UPDRS-I: [WMD=0.46,95%CI (0.14~0.77),P=0.005]；④Increased the score of quality of life scale (PDQ-39) [WMD=6.12,95%CI (2.50~9.75),P=0.0009]；⑤Improved the score of Baker Depression scale (BDI) [WMD=1.81,95%CI (0.73~2.89),P=0.001], while STN DBS was superior to GPi DBS in reducing postoperative drug dosage [WMD=-298.75,95%CI (-347.30~223.19), P<0.00001].

Conclusions: 结论： 根据目前的证据，GPi DBS在改善晚期帕金森病患者的抑郁症，改善生活质量和运动功能方面优于STN DBS。STN DBS在减少药物使用方面比GPi DBS更具优势。在临床应用中，可以根据患者的实际用药需求做出适当的选择。上述结论仍需通过更高质量的研究来验证。

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P1189 / #1843

POSTERS: K02.G. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

COMPARATIVE CHARACTERISTICS OF COGNITIVE AND AFFECTIVE DISORDERS IN PATIENTS WITH ESSENTIAL TREMOR AND ESSENTIAL TREMOR-PLUS SYNDROME

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Aims: To conduct a comparative clinical characterization of ET (ET «pure») and ET-plus syndrome(ETP)
Methods: The continuous prospective study of 68 patients with ET was carried out; the average age was 66.29±10.16, among them men - 17 (25.00%), women - 51 (75.00%). The patients were divided into 2 groups according to their movement disorders: patients with ET (tremor) and ETP (tremor + symptoms of dystonia, parkinsonism, tandem walking disorders). The affective disorders were assessed by Zung's Self-Rating Depression Scale (SDS) and Non-Motor Symptoms Scale for Parkinson's Disease (NMSS). The cognitive impairment were assesed by the Montreal Cognitive Assessment (MoCA). The severity of tremor was assessed by the Fahn-Tolosa- Marin tremor rating scale (FTM-TRS) scale.
Results: Table 1. Comparative clinical and epidemiological characteristics of patients with ET and ETP

Patient's groups\ Gender	ET			ETP		
	Total	Female	Male	Total	Female	Male, 11
Age, average mean±average deviation	63,00±12,58	62,00±12,92	64,00±17,67	67,00±9,58	68,00±8,07	67,00±13,92
Gender, absolute\ relative values%	26\38,24%	20\76,93%,	6\23,07%	42\61,76%	31\73,81%	11\26,19%
Family history+, absolute\ relative values%	20\76,93%	Not applicable	Not applicable	25\59,52%	Not applicable	Not applicable
Age of onset, average mean±average deviation	48,00±16,80	49,00±16,30	47,00±18,56	57,00±14,57	56,00±14,22	59,00±15,47
FTM-TRS, average mean±average deviation	54,96±12,12	54,1±10,12	57,83±16,89	53,40±21,08	51,03±19,90	60,10±24,10
NMSS-total, average mean±average deviation	32,76±25,21	26,10±19,81	49,50±39,83	37,81±25,96	41,58±25,99	22,55±21,79
NMSS – attention, average mean±average deviation	3,96±3,55	2,60±2,26	24,00±7,83	5,29±4,10	6,16±4,25	2,82±3,22
NMSS – mood, average mean±average deviation	5,40±5,50	3,25±4,48	11,67±8,00	6,98±7,35	7,94±7,79	4,27±5,31
MoCA, average mean±average deviation	28,81±4,56	28,25±4,28	26,33±5,56	24,43±3,61	25,06±3,95	22,64±2,35
SDS, average mean±average deviation	39,79±9,23	38,65±9,02	46,83±7,83	39,90±5,75	40,20±5,45	39,10±6,48

Conclusions: There were no significant differences in gender and age. A family history of tremor was not a risk factor for ETP. Patients with ETP have a later age of disease onset. The severity of tremor and affective disorders in patients of both groups did not show statistically significant differences. In patients with ETP, MoCA was significantly lower than in patients with ET ($p<0.05$).

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P1192 / #1833

POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

IMPROVING DIVERSE REPRESENTATION IN PARKINSON'S DISEASE (PD) CLINICAL TRIALS: A LITERATURE REVIEW OF RECRUITMENT STRATEGIES AND TACTICS IN UNDERREPRESENTED AND UNDERSERVED COMMUNITIES.

Tamiko Magee-Rodgers[1], Alyssa O'Grady[2], Leigh Zisko[1], Dawn Batchuluun[1], Lisa Thurman[1], John Dwyer[3]
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Aims: To present the findings of a comprehensive literature review focused on Parkinson's disease (PD) prevalence rates by race/ethnicity, diverse representation in PD trials, and recruitment of underrepresented populations (URPs). The review will also examine successful URP recruitment strategies in PD trials, and make recommendations on how to improve diverse enrollmentTo present the findings of a comprehensive literature review focused on Parkinson's disease (PD) prevalence rates by race/ethnicity, diverse representation in PD trials, and recruitment of URPs. The review will also examine successful URP recruitment strategies in PD trials, and make recommendations on how to improve diverse enrollments.
Methods: There is well-established data on prevalence rates for Alzheimer's disease (AD) in Black/African American and Hispanic/Latino communities, however, more information is needed for Parkinson's disease. This information is critical to better understand ways to improve education, awareness, treatment engagement, and access to PD trials. A comprehensive literature review is underway that includes articles published between 2002 to 2022 focused on: Parkinson's prevalence rates by race and ethnicity and enrollments and recruitment of URPs in PD trials. Observational and interventional trials will be included in the analysis.
Results: An initial review of the literature has revealed that very few PD trials report race/ethnicity. Researchers have previously advocated for improving representation and access of PD trials in URPs but previous studies have reported more than 90% of clinical trial participants identify as non-Hispanic White. Results from our extensive literature review will be shared during the 2023 AD/PD International Conference.
Conclusions: Results from this large-scale literature review will help to better inform GAP's Inclusive Research Initiative (IRI) in developing a solutions-oriented approach to increase diverse representation in PD trials, building upon previous recommendations and generalizability of study results.

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P1193 / #2093

POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

COMMUNITY-ACADEMIC PARTNERSHIPS TO UNDERSTAND BARRIERS AND PROMOTORS OF PARTICIPATION OF UNDERREPRESENTED POPULATIONS IN PARKINSON'S DISEASE RESEARCH

Sneha Mantri[1], Jennifer Adrissi[2], Emily Forbes[3], Danielle Larson[2], Caitlin Kelliher[4], Alyssa O'Grady[5], Maggie Kuhl[4], Maddie Kutler[4], Roseanne Dobkin[6]
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Aims: In its first decade, the Parkinson's Progression Markers Initiative (PPMI), a longitudinal observational study of people with Parkinson's disease enrolled fewer than 5% Black/African American or non-White Hispanic participants. PPMI is developing and implementing a multi-faceted strategy in its current enrollment period toward a more inclusive study population. A primary objective is to understand the barriers and facilitators of participation in PPMI for the Black/African American and Hispanic/Latino communities
Methods: A dedicated funding mechanism for diversity, equity and inclusion in PPMI selected two pilot projects to conduct a needs assessment in the Black community in the Chicagoland area and the Hispanic/Latino community across the Denver region. Both projects centered around community-academic partnerships (CAPs) and consisted of focus groups, individual interviews, and participant surveys to better understand the barriers and facilitators of participation in longitudinal observational studies such as PPMI.
Results: Interviews were conducted with 35 Black participants, 30 Hispanic/Latino participants, and 10 community providers. Through qualitative analysis, major barriers to and promotors of research engagement will be identified. Findings will inform PPMI outreach strategies—including through CAPs—and can benefit the broader clinical research community dedicated to equitable enrollment practices.
Conclusions: Community-academic partnerships are an effective way to gather data on research engagement barriers and promotors. Additionally, they may be an avenue to promote participation in research by underrepresented racial and ethnic populations. PPMI will implement varied recruitment strategies over the next year and track enrollments to measure the efficacy of methods and messages in recruiting a more equitable study population.

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P1194 / #1944

POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

CACNA1A VARIANT CAN BE ASSOCIATED WITH GENERALIZED DYSTONIA

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Aims: Mutations in the *CACNA1A* gene have been correlated with episodic ataxia type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine type 1. Dystonia is not enlisted among the typical clinical manifestations of *CACNA1A* mutations.We report the case of patient with a novel missense mutation of the *CACNA1A* gene presenting headache, head and arm tremor, slowly progressive dystonia associated with episodic painful focal dystonic attacks, and unexplained falls.
Methods: A 57-year-old woman was referred because of neck dystonia associated with head and arms tremor since the age of 15 years. At the age of 47, in 2012, she presented an increase in tremor amplitude led to suspect an essential tremor. In 2019 she showed mild dysarthria, right torticollis with dystonic head tremor and both arms, adiadochokinesia without limb ataxia, gait with dystonic head posture, and no cerebellar features. Moreover, she reported paroxysmal dystonia attacks (3-4 per week) of the left paravertebral muscles and lower extremity with intense pain occurring without apparent provoking factors. The BFMDRS score was 14, and she tried therapy with levodopa/benserazide up to 300 mg/die with no improvement.
Results: Dystonia genetic panel showed a heterozygous mutation in the *CACNA1A* gene (NM_023035.2:c.1630C>T p.(Arg544Trp). In 2020 due to worsening dystonia (BFMDRS score 29,5), she underwent evaluation for GPi-DBS surgery. However, brain MRI showed cortical atrophy, and she was excluded.
Conclusions: *CACNA1A* mutations are associated with a broad spectrum of neurological manifestations, with a frequent overlap of headache and neurological signs related to the involvement of the cerebellum. Few dystonic symptoms have been reported so far; however, the link between dystonia and *CACNA1A* mutations is increasingly evident, although the prevalence, incidence, and pathogenesis still need to be elucidated.

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P1195 / #1051

POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

LONGITUDINAL CLINICAL AND BIOMARKERS CHARACTERISTICS OF NON-MANIFEST GBA CARRIERS: THE PPMI COHORT

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Aims: To examine longitudinal change in clinical, dopamine transporter (DAT) imaging and biofluid biomarkers in *GBA1* non-manifesting carriers (NMCs) versus healthy controls (HCs) in PPMI.
Methods: We analyzed baseline and longitudinal (up to 5-year) data from the PPMI *GBA1* N409S heterozygous NMC (N=167) and HC (N=182) cohorts. Participants were assessed longitudinally with comprehensive motor and non-motor scales, DAT imaging and biofluid biomarkers. The latter included cerebrospinal fluid Abeta, total tau, phospho-tau, plasma sphingolipids, blood glucocerebrosidase activity, serum urate, neurofilament light chain and urine bis(monoacylglycerol) phosphate (BMP).
Results: We analyzed baseline and longitudinal (up to 5-year) data from the PPMI *GBA1* N409S heterozygous NMC (N=167) and HC (N=182) cohorts. Participants were assessed longitudinally with comprehensive motor and non-motor scales, DAT imaging and biofluid biomarkers. The latter included cerebrospinal fluid Abeta, total tau, phospho-tau, plasma sphingolipids, blood glucocerebrosidase activity, serum urate, neurofilament light chain and urine bis(monoacylglycerol) phosphate (BMP).
Conclusions: We present a comprehensive clinical and biomarker longitudinal characterization of the most common *GBA1* NMC variant. Our data highlight essential need to identify clinical and/or biological enrichment strategies that predict progression over a time period feasible for disease prevention trials. PPMI is now testing DAT imaging as an enrichment strategy for NMC recruitment.

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P1196 / #467

POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

UNDERSTANDING READING DIFFICULTIES IN PEOPLE WITH PARKINSON'S DISEASE - EXAMINING POSSIBLE UNDERLYING VISUAL AND COGNITIVE IMPAIRMENTS

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Aims: Reading problems are common in people with Parkinson's disease (PD). However, it is still unclear what factors contribute to these problems. To provide optimal care and rehabilitation, this study aimed to investigate underlying visual and cognitive impairments of people with PD and reading difficulties.
Methods: People with PD who were referred for visual rehabilitation at Royal Dutch Visio, Haren, underwent an extensive examination of visual and cognitive functions. In addition, their visual complaints were administered using the Cerebral Visual Disorders questionnaire.
Results: Of the 74 people with PD referred for visual rehabilitation, only 9 reported no reading difficulties. The 65 people with reading problems reported complaints as difficulty staying on the same line, experiencing moving letters, skipping letters or words, difficulty finding the beginning of a new line, experiencing double vision, experiencing the text as too small or unclear, and experiencing reading as tiring. Half of the people (53%) had an ophthalmological disorder that might cause visual complaints (e.g., cataract or macular degeneration). Seventeen percent of people had abnormal visual acuity (<0.5), 14% abnormal contrast sensitivity, and higher percentages were found for impaired eye alignment (37%) and ocular motility (88% had at least one of the following: impaired stereopsis, convergence, smooth pursuit or saccades). In addition, all but one person (98%) had an abnormal score on at least one cognitive domain.
Conclusions: Prevalence of reading problems is high in people with PD with visual complaints. Looking at visual functions, there is not one visual function that can explain these problems. Although, impairments in ocular motility were highly prevalent and might contribute to reading difficulties. The same accounts for cognitive dysfunction. Future research might explore interventions to alleviate reading difficulties in daily life.

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POSTERS: K02.H. MOVEMENT DISORDERS: OTHER

ASSOCIATION BETWEEN CORONARY ARTERY DISEASE AND PARKINSON'S DISEASE IN KOREA: A NATIONWIDE POPULATION-BASED COHORT STUDY USING CLAIMS DATA

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Aims: The relationship between coronary artery disease (CAD) and Parkinson's disease (PD) still remains unclear considering that the epidemiological studies present conflicting evidence. The aim of our study was to evaluate the association of PD with the risk of CAD in the elderly.
Methods: A retrospective population-based cohort study was conducted using claims data from the Korean National Health Insurance Service-Senior Cohort database, which comprised 558,147 (10% random sample of adults 60 years or older) health insurance beneficiaries from 2002 to 2015. We compared PD patients with exactly matched controls for age, sex, hypertension, and diabetes mellitus (DM) at a ratio of 1:10. We calculated the incidence rate of CAD and compared the risk of CAD between the PD and the control groups. A stratified Cox-proportional hazard regression model was used to estimate the effect of PD on the subsequent occurrence of CAD.
Results: After exclusion, a total of 101,838 participants (9,258 PD and 92,580 controls) were included in the analysis. The incidence rate was 66 per 1000 person-years in the PD group while 47 per 1000 person-years in the non-PD control group. The adjusted hazard ratio of CAD in the PD group was 1.390 (95% CI 1.335-1.448) after adjusting for age, sex, hypertension, and DM compared to the control group. In the subgroup analyses, regardless of the stratification like age group, sex, and the presence of comorbidities, the risk of CAD among PD patients was significantly higher than in the non-PD control groups.
Conclusions: The study suggests that PD increases the risk of CAD in Koreans regardless of age, gender, or comorbidities. This association between PD and CAD suggests that PD could be an independent risk factor for CAD.

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P1198 / #1070

POSTERS: L01A. NEUROPATHOLOGY OF COVID-19

SARS-COV-2 INDUCES DOPAMINERGIC NEURON LOSS IN MIDBRAIN ORGANOIDS

Javier Jarazo[1,2], Eveline Santos Da Silva[3], Enrico Glaab[4], Danielle Perez Bercoff[3], Jens Schwamborn[1,2]
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Aims: COVID-19 presents numerous symptoms mostly associated with the respiratory tract. However, recent evidence showed that the SARS-CoV-2 virus affects the nervous system. We evaluated the effect of the infection in midbrain organoids to determine if cells and pathways related to the onset of Parkinson's disease (PD) are affected.
Methods: The effect of the virus after short- and long-term cultures (4 days, and 1 month) post-infection was analyzed. Features measured included the degree of dopaminergic differentiation (TH), neurite fragmentation, and the level of activated astrocytes (GFAP and S100beta). Bulk RNAseq was performed to determine the effects of the infection on gene expression.
Results: After infection with SARS-CoV-2, the levels of dopaminergic neurons were significantly reduced in both short and long-term culture. Moreover, neurite fragmentation of TH positive neurons in infected organoids significantly increased respective to controls in long-term cultures. Within the same infected organoid TH/SARS-CoV-2 double positive neurons presented an altered morphology and high degree of neurite fragmentation compared to uninfected TH positive neurons. Activation of astrocytes was significantly reduced after infection in the short-term culture. While the levels of S100beta recovered over time, they still remained lower in infected organoids. In both short- and long-term culture, SARS-CoV-2 colocalized more with certain types of cells showing a marked preference for GFAP positive and TH positive cells when normalized to their respective abundance in the organoid. Gene expression analysis revealed a disruption in gene pathways related to vesicle transport, endosomal and autophagy pathways following infection with SARS-CoV-2.
Conclusions: Infection of midbrain organoids with SARS-CoV-2 induced a clear neurodegenerative process of TH positive neurons, while disrupting main pathways known to be involved in Parkinson's disease.

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P1199 / #1626

POSTERS: L01A. NEUROPATHOLOGY OF COVID-19

SARS-COV-2 SPIKE PROTEIN INDUCING IRF3 ANTIVIRAL SIGNALING PATHWAY MEDIATED BY TOLL-LIKE RECEPTORS 2/4 IN A HUMAN MINI-BRAIN

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Aims: Recent analyses on post-mortem severe COVID19 patients have detected SARS-CoV-2 RNA and protein components in brain tissues, of which the roles of astrocytes on viral invasion have been mainly focused. However, it remains unclear how SARS-CoV-2 proteins trigger immune responses in astrocytes, furthermore, the role of microglia, the primary innate immune cells, in COVID19 pathogenesis is not yet recognized; therefore, we aim to unravel those questions.
Methods: In this study, we used a human mini-brain model to investigate how SARS-CoV-2 spike (S) protein triggers antiviral responses in astrocytes and microglia, as well as validate the underlying mechanisms.
Results: We found that S protein triggered antiviral signaling pathway – IRF3 transcriptional factor in astrocytes (by 6-fold), which was mediated by both Toll-like receptor (TLR) 2 and TLR4. Interestingly, we observed that S protein suppressed IRF3 level in microglia (by 2-fold), while upregulating ACE2, the virus entry receptor (by 1.5-fold) via TLRs 2/4. We also discovered that S protein induced iNOS, the enzyme involved in NO production, in astrocytes (by 1.5-fold) in an IRF3-dependent manner and inhibiting this signaling pathway in microglia.
Conclusions: Taken together, our study has provided the mechanisms of how SARs-CoV-2 interacts with the brain immunity and triggers antiviral responses, which may contribute to long-term neurological symptoms on COVID19 patients.

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P1200 / #1156

POSTERS: L01A. NEUROPATHOLOGY OF COVID-19

BRAIN TRANSCRIPTIONAL AND CELLULAR PATTERNS FOLLOWING SARS-COV-2 INFECTION PARALLEL ALZHEIMER'S DISEASE CASES

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Aims: SARS-CoV-2 is a neuroinvasive pathogen with the potential to impact cognition as seen in current Post-acute sequelae of SARS-CoV-2 (PASC) cases. Previous studies have speculated about a potential similarity in Alzheimer's disease (AD) and COVID-19 disease states. We hypothesized that SARS-CoV-2 exacerbates neuroinflammatory pathways seen in AD cases and may lead to symptoms seen in neuro-PASC.
Methods: We examined sequencing data in the BA9 cortex (CTX) and hippocampus (HP) regions of samples from postmortem tissue from Alzheimer's disease (AD), COVID-19, and AD+COVID-19 cases and compared these to neurologically healthy controls. We then analyzed cellular morphology of these same cases using region matched samples.
Results: RNAseq data analyzed demonstrated differential regulation of pathways key to neuroinflammation, cellular senescence and neuronal function. Strikingly, AD and COVID-19 cases shared a strong overlap in gene expression suggesting a similar inflammatory process occurs in COVID-19 as seen in AD. Immunohistochemistry further highlighted this similarity where microgliosis and activation was statistically similar in AD and COVID-19 cases and showed a potential exacerbative effect in AD+COVID-19 as indicated by an increase in microglial nodules.
Conclusions: COVID-19 cases in elderly individuals activates many pathways that are considered hallmarks of AD, and thus, may be telling of the potential long-term progression of disease states in COVID-19 infected individuals. While our data cannot predict long term impacts of COVID-19, it does suggest mechanistically that COVID-19 may exacerbates cognitive deterioration, as seen in microgliosis and nodule formation, and that it shares similar neuroinflammatory processes observed in AD which may explain some neuro-PASC symptoms.

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P1201 / #516

POSTERS: L01B. NEUROIMAGING OF COVID-19

VOLUMETRIC CHANGES IN MEDIAL TEMPORAL LOBE SUBREGIONS AND THE OLFACTORY BULB OF COVID-19 PATIENTS – RESULTS FROM THE SAHLGRENSKA NEUROCOVID STUDY

Iris Bosch[1,2], David Berron[3,4], Fredrik Öhman[1,2], Alexis Moscoso[1,2], Hannah Baumeister[4], Erika Stentoft[5,6], Nelly Kanberg[5,6], Arvid Edén[5,6], Isabella Björkman-Burtscher[7,8], Anna Grahn[5,6], Magnus Gisslén[5,6], Michael Schöll[1,2,9]
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Aims: Neurological sequelae, including cognitive impairment and loss of smell, have been described in a large proportion of COVID-19 patients. Although the underlying pathogenesis remains largely unknown, volumetric brain changes have previously been reported. Our study aims to investigate volumetric changes in medial temporal lobe (MTL) subregions and the olfactory bulb (OB) of COVID-19 patients over time using state-of-the-art segmentation methods, along with complementary neuropsychological and olfactory testing.
Methods: We included nineteen COVID-19 patients recruited one month after hospitalisation (Group 1), nineteen patients with post-acute COVID syndrome (PACS) and remaining neurological symptoms recruited from outpatient clinics (Group 2), and twenty controls. Patient Group 1 underwent structural 3T-MRI scans as well as neuropsychological and olfactory testing at baseline and at 3-, 6-, and 12-month follow-up, patient Group 2 at baseline and at 12-month follow-up, and the control group only at baseline. MTL subregion and OB volumes were obtained using ASHS and a fully automated OB segmentation pipeline, respectively.
Results: Both COVID-19 patient groups show subjective and objectively assessed cognitive impairment compared to controls, but no impaired olfactory functioning. Preliminary results did not indicate significant changes in MTL subregion or OB volumes at baseline, nor over time for Group 1 compared to controls. For Group 2, preliminary cross-sectional analyses were indicative of increased volumes of the right subiculum, but no other regions, compared to controls at baseline.
Conclusions: These preliminary results provide first insights into MTL subregion and OB volumes in the context of cognitive and olfactory functioning in COVID-19 patients. We will present a complete dataset including longitudinal data for both patient groups, focusing on volumetric group comparisons, and the relationship between the volumes of interest and measures of cognition and olfactory functioning.

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P1202 / #171

POSTERS: L01B. NEUROIMAGING OF COVID-19

SPECTRUM OF AUTOIMMUNE ENCEPHALITIS/ENCEPHALOPATHY FOLLOWING SEVERE ACUTE RESPIRATORY SYNDROME CORONA VIRUS 2 (SARS- COV -2), INFECTION AND OR VACCINATION

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Aims: 18F-FDG PET/CT scan in the early diagnosis of patients with clinically suspected encephalitis associated with corona virus 2 (SARS- CoV -2) infection and or vaccination
Methods: A retrospective analysis of 45 patients of suspected autoimmune encephalitis was done. All the patients either gave a history of COVID-19 infection and or vaccination in the last 6-8 weeks. Besides clinical examination, all patients had undergone cerebrospinal fluid autoimmune assay, electroencephalograms, Magnetic Resonance Imaging and FDG-PET scans. The FDG uptake patterns were recorded and areas of hypermetabolism or hypometabolism that were two standard deviations from the mean were considered as abnormal.
Results: All the subjects were serologically and radiologically (MRI) analyzed and were further segregated into MRI positive (n=7) and negative (n=38) subjects. The subjects with positive MRI showed hyper intense and hypo intense lesions suggestive of neuroinflammatory process within the cortex and deep brain nuclei. All the subjects had foci of hypermetabolism in the pre frontal, dorso-lateral frontal, insular and cingulate cortices, subcortical regions and cerebellar regions in varying intensities on FDG PET scan without any obvious abnormality on the corresponding CT images. Antibodies to COVID-19 was found in the serum of 40 and CSF of 25 subjects.
Conclusions: FDG PET CT scan may help in the early identification and management of acute and sub acute Neuroinflammation associated with COVID-19 infection and or vaccination, especially with non contributory MRI, thereby expediting the subsequent clinical management.

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P1203 / #2613

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

NEUROLOGICAL ASPECTS OF COVID-19-RELATED OLFACTORY DYSFUNCTION WITH NEUROINVASION : A SYSTEMATIC REVIEW

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Aims: The purpose of this study is to determine the neurological aspects of the cerebrospinal fluid (CSF) of coronavirus infection-19 (COVID-19) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).
Methods: An observational study was conducted on patients with COVID-19 who searched the PubMed and EMBASE databases and performed CSF PCR analysis through March 26, 2021 and reported loss of smell due to neurological symptoms.
Results: Initially, 2,387 studies were identified. 167 studies performed SARS-CoV-2 CSF PCR analysis, of which 101 patients and 45 observational studies performed CSF PCR analysis of SARS-CoV-2 in 55 patients. Loss of smell has been reported. 101 patients. Central and peripheral nervous system symptoms observed in patients with COVID-19 varied. The most common neurological diagnosis was Guillain-Barré syndrome (GBS) and its variants (24%), followed by encephalopathy (21%). The SARS-CoV-2 PCR analysis was positive only in 4 CSF samples, of which 2 patients had olfactory dysfunction and the other did not.
Conclusions: The neurological spectrum of COVID-19 is diverse and direct neurological involvement of SARS-CoV-2 is rare. Neuroprotection against SARS-CoV-2 in COVID-19 patients with olfactory impairment is controversial because CSF PCR results for SARS-CoV-2 are positive in the same number of patients with and without olfactory dysfunction. , further research is needed on this.

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P1204 / #1230

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

THE SARS-COV-2 SPIKE GLYCOPROTEIN INTERACTS WITH MONOAMINE OXIDASE B (MAOB) AND ALTERS MITOCHONDRIAL METABOLISM

Miroslava Cuperlovic-Culf[1,2], Chantal Pileggi[3], Gaganvir Parmar[3], Irina Alecu[1], Steffany Bennett[1], Jagdeep Sandhu[4], Mary-Ellen Harper[3]
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Aims: Neurological symptoms are reported in up to 70-80% of COVID-19 hospitalized patients with some patients reporting persistent neurocognitive symptoms and continued post-COVID myalgia encephalomyelitis/chronic fatigue syndrome or "long-COVID" with underlying causes remaining largely unknown. Recently we have computationally shown high level of structural similarity between binding regions of Monoamine Oxidase B (MAOB), PD treatment target, and ACE2 for the SARS-CoV-2 Spike glycoprotein, as well as high binding energy for Spike protein and MAOB. With major role of MAOB in dementias we have investigated functional aspects *in vitro* and show here proof of hypothesized MAOB-Spike binding and its effect on metabolic characteristics of neurons.
Methods: Molecular modeling of protein-protein interactions in lipid membrane proximity and 3D structure comparisons were used for computational hypothesis development. Experimental analysis was performed in Spike protein transfected SH-SY5Y neuroblastoma and in Spike and MAOB protein transfected HEK293 cell lines. Protein-protein interaction and metabolic changes were assessed using number of complementary assays including co-immunoprecipitation, immunofluorescence, proximity ligation analysis, microscopy, radiometry, H2O2 emission, respirometry, mitochondrial membrane potentials and western blotting.
Results: Experimental and computational analyses show that that the SARS-CoV-2 spike glycoprotein can interact with MAOB and increase monoamine oxidation while impairing mitophagy, leading to increased content of aberrant mitochondria. Additionally, spike protein transfection increases oxidative stress in cells while additionally suppressing parkin expression, increasing susceptibility of neurons to cell death.
Conclusions: Together, these and additional findings that will be shown in the presentation highlight the mechanisms that may cause SARS-CoV-2-induced neurodegeneration and alterations in monoamine metabolism. Further research is needed to determine if MAOB inhibitors could be useful to prevent or mitigate SARS-CoV-2-induced neurodegeneration.

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P1205 / #422

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

COGNITIVE DYSFUNCTION IN LONG COVID LIMITS FUNCTION AND HEALTH STATUS, INDEPENDENTLY OF HOSPITAL ACUITY AND PREEXISTING CONDITIONS

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Aims: Post-COVID-19 condition (long COVID) causes significant debility. However, age and some other risk factors for more severe COVID-19 are not associated with increased risk of long COVID. Growing evidence implicates distinct SARS-CoV-2 neuropathologic consequences in the mounting cognitive and psychiatric symptoms of long COVID often known as "brain fog" (BF). We identify the prevalence and factors associated with BF one year after emergency room or hospitalization with COVID-19.
Methods: Adding to a retrospective observational cohort study (surveys and clinical data), we surveyed survivors of acute COVID-19 infection from spring 2020 regarding prevalence of BF (explained as slow thinking) and other factors in the past 7 days.
Results: 530 respondents had a mean age 59.2±16.3 years; 44.5% were female and 51.5% non-White. 31.9% of respondents (n=169) experienced BF in past 7 days. Sleep disturbance (63% vs. 29%), shortness of breath (46% vs. 18%) weakness (49% vs. 22%), and dysosmia/dysgeusia (12% vs. 5%) were associated with reported BF ($p<0.001$). Patients with respiratory symptoms had 54% higher risk of having BF. Acute COVID-19 medications and elevated inflammatory markers did not differ between the groups. Those with BF had more limitations in physical activity ($p<0.001$), decreased employment ($p<0.043$), lower perceived health ($p<0.001$) and more social isolation (Lubben Score) ($p<0.02$), despite no differences in premorbid medical conditions or age.
Conclusions: BF persisted for a year in roughly a third of acute unvaccinated COVID-19 patients from one large U.S. hospital cohort. BF is independent of COVID-19 acuity and is associated with insomnia, pulmonary symptoms and weakness, and smell/taste disturbances less commonly. Given that BF is associated with persistent debility, further investigation is needed into mechanisms including neuroinflammation, clearance and perfusion/metabolism.

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P1206 / #616

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

NEUROCOGNITIVE DISORDER IN POST-COVID-19 SYNDROME: A CROSS-SECTIONAL AND LONGITUDINAL STUDY IN PATIENTS EXPERIENCING SUBJECTIVE DECLINE OF COGNITION

Ann-Katrin Schild[1], Anton Regorius[1], Yasemin Goereci[2], Lukas Kirchner[1], Daniel Scharfenberg[3], Kim Klein[1], Dix Meiberth[1], Christiana Franke[4], Joachim Lülling[1], Finja Schweitzer[2], Stefanie Jost[2], Gereon R. Fink[2], Frank Jessen[1], Clemens Warnke[2], Franziska Maier[1]
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Aims: Some persons infected with SARS-CoV-2 report persisting neuropsychiatric symptoms beyond acute infection. Such symptoms persisting for more than three months after infection are classified as post-COVID-19 syndrome (PCS). Although PCS frequently occurs in patients with mild course of acute COVID-19 disease, detailed longitudinal neuropsychological characterization and prediction of performance is scarce in this group.
Methods: Here, N = 42 patients with asymptomatic or mild acute COVID-19 and persisting or newly emerging cognitive deficits were examined at two time points. Baseline assessment took place at least three months after infection, whereas follow-up was performed at least six months after baseline. Both assessments included comprehensive objective testing of five neurocognitive domains according to DSM-5. Potentially confounding variables such as sleep, anxiety, depression, general health status, fatigue, premorbid IQ, and time between infection and assessment were also analyzed.
Results: We noted a decrease of subjective cognitive deficits from 94.20% to 80.95% between assessments. Objectively assessed neurocognitive disorders (NCDs) decreased from 61.90% to 42.85%. Generally, global cognitive functioning improved over time with variable performance courses for single neurocognitive domains. Premorbid IQ and health status were identified to significantly predict the probability of classification with NCD at follow-up. Anxiety symptoms and language composite score served as predictors for global cognition at follow-up. Screening tests performed worse than comprehensive assessments in classification and prediction of neuropsychological variables.
Conclusions: This study provides important insights into understanding of long-term neuropsychological impairments in PCS and emphasizes the need for comprehensive neuropsychological assessment in research and clinical practice.

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P1207 / #2431

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

CONFUSIONAL MANIACAL EPISODE VERSUS POST-VACCINATION ENCEPHALITIS

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Aims: The coexistence of psychiatric and neurological symptoms is a medical clinical challenge. After the Covid-19 vaccination, numerous patients presented adverse reactions, some of them related to the vaccination, in the case of others, a causal link with the vaccine was not revealed. We present the clinical case of a patient who presented at the Emergency Room 48 hours after the first dose of the Pfizer vaccine for Covid-19. He presented for confusional state that started with a manic episode, temporal-spatial disorientation and euphoria.
Methods: The patient was admitted by transfer from a neurology department, where he had been investigated by: EEG, lumbar puncture, MRI, biological samples. During psychiatric admission, viral meningitis was suspected. Specific blood and CSF samples and blood antibodies were collected.
Results: The previously administered corticosteroids amplified the psychomotor agitation, so the patient was transferred to the psychiatric ward. Haloperidol was administered on the first day to clarify the field of consciousness. Later, because of the lack of reality testing, the patient refused any oral treatment so the current doctor decided to switch to intravenous Olanzapine, to which the response was favorable. The CSF analysis revealed exclusively antibodies to herpes simplex, which is why it was necessary to prolong the administration of Methylprednisolone and to consider the administration of Acyclovir additionally to the psychiatric treatment.
Conclusions: The case highlights the differential diagnosis for an altered field of consciousness: acute reaction to vaccination, the onset of a herpetic viral encephalitis or manic episode. Any medication should be administered with caution, as corticosteroids may potentiate the manic state.

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P1208 / #1661

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

PLASMA PROTEOMICS OF SARS-COV-2 INFECTION POINT TO CHANGES ON ALZHEIMER AND CORONARY DISEASE PATHWAYS

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Aims: Identification of the plasma proteomic changes of Coronavirus disease 2019 (COVID-19) can help to understand the pathophysiology of the disease and developing predictive models and novel therapeutics.
Methods: We performed plasma deep proteomic profiling from 332 COVID-19 patients and 150 controls and pursued replication in an independent cohort to identify biomarkers and causal proteins for COVID-19 infection, ventilation, and death.
Results: We identified 841, 833, and 253 proteins associated with infection, ventilation and death after infection respectively. Protein levels can be queried on a web portal (https://covid.proteomics.wustl.edu/). Machine learning approaches were used to create and validate specific prediction models for ventilation (AUC>0.91), death (AUC>0.95) and either outcome (AUC>0.80). Dysregulated proteins were enriched in immune and cytokine signaling (FDR≤3.72×10-14), Alzheimer's disease (FDR≤5.46×10-10) and coronary artery disease (FDR≤4.64×10-2). Mendelian randomization using pQTL data identified BCAT2 and GOLM1 as a causal proteins for COVID-19.
Conclusions: Here we provide distinctive prognostic biomarkers for COVID-19 outcomes, reveal their relationship to Alzheimer's disease and coronary artery disease, and identify potential therapeutic targets for COVID-19.

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P1209 / #2262

POSTERS: L01D. COMORBIDITY OF NEURODEGENERATION WITH COVID-19

BRAIN PATHOLOGY IN INDIVIDUALS WITH COVID-19 WITH AND WITHOUT DOWN SYNDROME OR ALZHEIMER'S DISEASE

Anah Gilmore[1], Hannah Saternos[1], Isaac Colvett[1], Katherine Lyman[1,2], Eric Hamlett[3], Steven Carroll[3], Elliott Mufson[4], Elizabeth Head[5,6], Elisabet Englund[7,8], Aurelie Ledreux[1], Ann-Charlotte Granholm[1]
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Aims: Prior research has shown that SARS-CoV-2 infection resulting in COVID-19 may activate inflammatory signaling and oxidative stress pathways in the brain. Those with Down Syndrome (DS) have an increased risk for AD at a younger age, and higher risk of hospitalization and death due to COVID-19. The objective is to investigate whether COVID-19 impacts AD pathology in *postmortem* brain tissue from AD, DS, and healthy controls confirmed to have severe COVID-19 compared to the same groups without COVID-19.
Methods: AD pathology including Bielschowky silver stain and immunohistochemical staining for astrocytes (GFAP), microglia (Iba1), amyloid, and phospho-tau (p-Tau) was examined in the hippocampus and frontal cortex *postmortem* tissues in the following groups: DS +/- COVID-19, AD +/- COVID-19, and Controls +/- COVID-19. COVID-19 spike protein 1 antibodies were used to confirm the presence of SARS-CoV-2 in brain tissue. Cases were staged using the CERAD/BRAAK scoring system for plaques and tangles. Sholl analysis was performed to characterize astrocytic arborization.
Results: Preliminary results show that COVID-19 spike protein is present intra-neuronally in the entorhinal cortex of patients with confirmed severe COVID-19. P-Tau staining was observed in neuronal layers of the parahippocampal gyrus and cerebellum/brainstem in DS+COVID-19 cases and to some extent also in the Ctrl and AD+COVID-19 cases compared to non-infected cases. Glial abnormalities were observed in DS+COVID-19 cases, especially in Layer I and II of the parahippocampal gyrus including increased perivascular astrocytic processes and reduced density of microglia.
Conclusions: Further studies are needed to explore whether COVID-19 impacts AD pathology in the brain, especially in populations that are currently suffering from AD and in the DS population, as these population groups suffer from increased mortality to a SARS-CoV-2 infection. Supported by BrightFocus Foundation grant CA2018010.

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P1210 / #903

POSTERS: L01D. COMORBIDITY OF NEURODEGENERATION WITH COVID-19

IS THERE A NEED TO INCREASE THE DOSE OF DOPAMINERGIC DRUGS IN PARKINSON'S DISEASE DURING COVID-19?

Athena Sharifi-Razavi[1], Elham Sharifi-Razavi[1], Mana Baziboroun[2]
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Aims: Implications of COVID-19 infection on Parkinson's disease, particularly worsening of motor and non-motor symptoms have been reported in several case series and observational studies. There is debate on the change of dopaminergic drug need during COVID-19. The theory has been proposed that dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19, as ACE2 and dopamine decarboxylase co-express and co-regulate in non-neuronal cell types, which may indicate dopamine depletion and the need for considering levodopa as treatment.: Implications of COVID-19 infection on Parkinson's disease, particularly worsening of motor and non-motor symptoms have been reported in several case series and observational studies. There is debate on the change of dopaminergic drug need during COVID-19. The theory has been proposed that dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19, as ACE2 and dopamine decarboxylase co-express and co-regulate in non-neuronal cell types, which may indicate dopamine depletion and the need for considering levodopa as treatment.
Methods: In this review summarized the impact of COVID-19 on Parkinson's disease symptoms and changes in levodopa daily dose requirements.
Results: Patients with Parkinson's disease may experience substantial worsening of motor and non-motor symptoms during COVID-19 and may need to increase the dose of dopaminergic drugs.
Conclusions: Clinicians should take pathophysiological changes of COVID-19 into consideration during adjusting therapy regimens in Parkinson’s disease.

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P1211 / #2327

POSTERS: L01E. IMPACT OF COVID-19 ON CLINICAL TRIALS

"IMPACT OF ORAL OMEGA-3 FATTY ACID SUPPLEMENTATION ON PROINFLAMMATORY MARKERS IN ADULTS WITH COVID-19"

Diana Rodriguez Vera[1], Marvin Antonio Soriano Ursúa[2]
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Aims: The present investigation evaluated the effect of oral supplementation with omega-3 fatty acids on biochemical-clinical parameters and markers of inflammation in patients diagnosed with COVID-19 in moderate and severe degrees who were treated at the Hospital Regional de Alta Especialidad de Ixtapaluca. (HRAEI), belonging to the Secretary of Health of the State of Mexico.
Methods: Sampling was performed for a total of 28 patients, considering a control group (n=14) and an experimental group (n=14); the latter with doses of 2.2 grams of omega-3/day for at least 14 days with monitoring by measuring biochemical-clinical parameters during hospital stay. A database was followed up that included clinical and metabolic parameters, markers of inflammation, complete blood count, percentage of recovered patients, those who required intubation and/or intensive care, as well as length of hospital stay and percentage of mortality.
Results: A beneficial effect was found associated with the supplementation of omega-3 fatty acids in some proinflammatory markers, as well as in metabolic parameters such as cholesterol and triglycerides compared to the control group. The results of the present study identified a difference in survival rate between patients.
Conclusions: Omega-3 fatty acid supplementation may have promising effects in improving clinical outcomes of COVID-19 patients. The possibility remains open for future research in population groups with chronic-degenerative diseases whose pattern is an exacerbated inflammatory response.

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P1212 / #2345

POSTERS: L01G. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

THE FAMILY CAREGIVER OF A DEMENTIA PATIENTS BEFORE AND DURING THE COVID PANDEMIC

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Aims: Caring for and living with dementia has a significant influence on the family caregivers. The objective of the study was to analyse if the covid pandemic period (March-2020/March-2022), modified their experiences, sensations, and workloads.
Methods: Retrospective study and comparative analysis of 138 family caregivers, grouped according to the time of evaluation: pre-covid (n=78) or covid-period (n=60). Patient data: gender, age, duration of the illness, schooling, clinical manifestations: cognition (MMSE), behavior (NPI), functionality (BRDS and RDRS-2), mood (Yesavage), dementia stage (GDS). Caregiver data: gender, kinship, age, schooling, health status, burden (Zarit), stress (ICS), anxiety (HAD-A), depression (HAD-D), impact of behavioral alteration (NPI-c) and experiences/sensations with Questionnaire-DSQL (true/false)
Results: The two groups of patients (pre-covid and covid-period) differed in MMSE (p=0.009), BDRS (p=0.006), Yesavage (p<0.05), GDS (p=0.003); not in the rest of the clinical parameters. Caregivers showed no difference when comparing the two periods (Zarit, HAD-A, HAD-D, NPI-c, DSQL). The 30 dichotomous responses of the DSQL showed in all: nervousness (81.9%), always thinking with the patient (71.7%), feeling very low in morale (69.6%). Percentages above 50% expressed physical and emotional exhaustion, lack of dialogue with the patient, loss of freedom and feelings of guilt. Sometimes they wanted to escape (42.8%). In 28 of the 30 responses there were no significant changes between both groups. In the two other responses there were significative differences: in the covid-period there was a positive increase in dialogue between caregiver and patient (60,3% vs 43,3%; p=0,049), but the mood of caregiver decreased (61,5% vs 80,0%; p=0,017).
Conclusions: The COVID period did not cause relevant changes in the task of caring or in the emotional state, experiences, and sensations of the family caregiver

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POSTERS: L01G. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

COVID-19 AND NEURODEGENERATIVE DISEASES: RECIPROCAL IMPACTS, MEDICAL CARE STRATEGIES AND UNDERLYING MECHANISMS

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Aims: Objectives: Recently, the impact of the COVID-19 pandemic on patients with neurodegenerative disease, as well as the specific neurological manifestations of COVID-19 have aroused great interests. However, there are still many issues of concern to us that need to be clarified.
Methods: Methods: We reviewed the current literature on the complex relationship between neurodegenerative diseases [including Parkinson's disease (PD) and Alzheimer's disease (AD)] and COVID-19. We summarized the impact of COVID-19 infection on symptom severity, disease progression and mortality of neurodegenerative disease, and discussed whether COVID-19 infection could trigger neurodegenerative disease. The vulnerability to COVID-19 infection and prognosis of COVID-19 positive individuals in patients with neurodegenerative disease were also included. Modification of care strategy, specific drug therapies and vaccines during the pandemic were also listed. At last, mechanisms underlying the link between COVID-19 and neurodegenerative disease were reviewed.
Results: Results: There is an interaction between COVID-19 infection and neurodegenerative diseases, including worsening symptomatic severity and accelerating neurodegeneration by COVID-19 infection in PD and AD patients, and vice versa, neurodegenerative diseases increasing the vulnerability to COVID-19 infection and enhancing the risks of hospitalization and death after virus infection. Many potential molecular and cellular pathways were hypothesized to be the link between COVID-19 infection and neurodegenerative diseases, but further studies are still needed to verify the mechanisms. COVID-19 pandemic has profoundly changed the way of medical care, telemedicine, vaccines and specific drug therapies are promising for the better management of PD and AD patients.
Conclusions: Conclusions: COVID-19 and neurodegenerative diseases have reciprocal impact on each other.

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POSTERS: L01G. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

THE EFFECTS OF COVID-19 LOCKDOWN ON BEHAVIOR AND EMOTIONAL OUTCOMES IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Aims: As social distancing has been widely implemented, a significant decrease in physical activity in both the elderly population and people with dementia is observed. Under the restriction, those living with dementia are at high risk of decreased physical activities, cognitive decline, and poor emotional well-being. The present study investigates whether social distancing throughout COVID-19 results in significant outcomes for people with dementia regarding their daily behaviors, cognitive abilities, and emotions.
Methods: The data was obtained retrospectively from the outpatients who visited dementia clinic in SMG-SNU Boramae Medical Center from January 2018 to October 2021. A total 62 participants with Mild Cognitive Impairment (MCI) and 184 patients with Alzheimer's Disease (AD) were recruited for this study. Participants completed the following measurements: Barthel Activity of Daily Living (Barthel ADL), Neuropsychiatric Inventory (NPI), Short version of Geriatric Depression Scale (SGDS). A series of *t*-test and multivariate analysis of covariance was used to verify the effect of the lockdown during the disease crisis, where the effect of COVID-19 was divided before and after 2020. Age, sex, and education level were adjusted for analysis.
Results: The level of daily living measured by Barthel ADL represents worse outcomes after the lockdown of COVID-19 ($t = 7.12$, $p < .001$). Especially, AD participants had more decrease in daily function than MCI participants ($F(239,1) = 5.90$, $p < .05$)). There were no significant differences in depression (SGDS) and neuropsychiatry symptoms (NPI) in all participants.
Conclusions: Our findings demonstrate that the social distancing announced by Korean government may affect the daily activities of people with dementia, especially AD patients. These results suggest the necessity of social recommendation which involves enough social interactions for people with AD and MCI in order to fully maintain their daily function.

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POSTERS: L01G. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

THE EFFECT OF COVID-19 LOCKDOWN IN COGNITION AND FUNCTIONALITY OF ALZHEIMER DISEASE PATIENTS

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Aims: Covid pandemic associated lockdown has been a great impact in aged populations, especially in patients with neurological and neurodegenerative diseases increasing their psychiatric symptoms. However, the impact of the lockdown in terms of cognitive and functional impairment has not been well described. The aim of this study is to evaluate the effect of covid-19 lockdown over cognitive impairment progression and functionality disability in early Alzheimer Disease (AD) patients.
Methods: Cognition and functionality were assessed in patients with mild cognitive impairment due to AD (MCI-AD, n=41) at baseline (T0) and in 2 years follow-up (T1), 21 patients with the covid lockdown between T0-T1 (case group) and 20 patients before covid pandemic (control group).
Results: All the patients (MCI-AD) showed cognitive impairment progression in the two-years period time. However, this progression was not different between case and control groups. Similarly, functionality showed a deterioration in that period time in both participants groups. However, its impairment showed differences between both participants groups. In fact, a lower deterioration was observed in the case group, suggesting not prejudicial effect of covid-19 lockdown in MCI-AD patients for disease progression.
Conclusions: Contrary to expectation, covid-19 lockdown could not produce a higher progression of AD at least in a 2 years evaluation period time. Therefore, the impairment observed could be considered as part of the normal disease progression. However more longitudinal studies on MCI-AD patients are required to evaluate long-term effects of covid-19 lockdown.