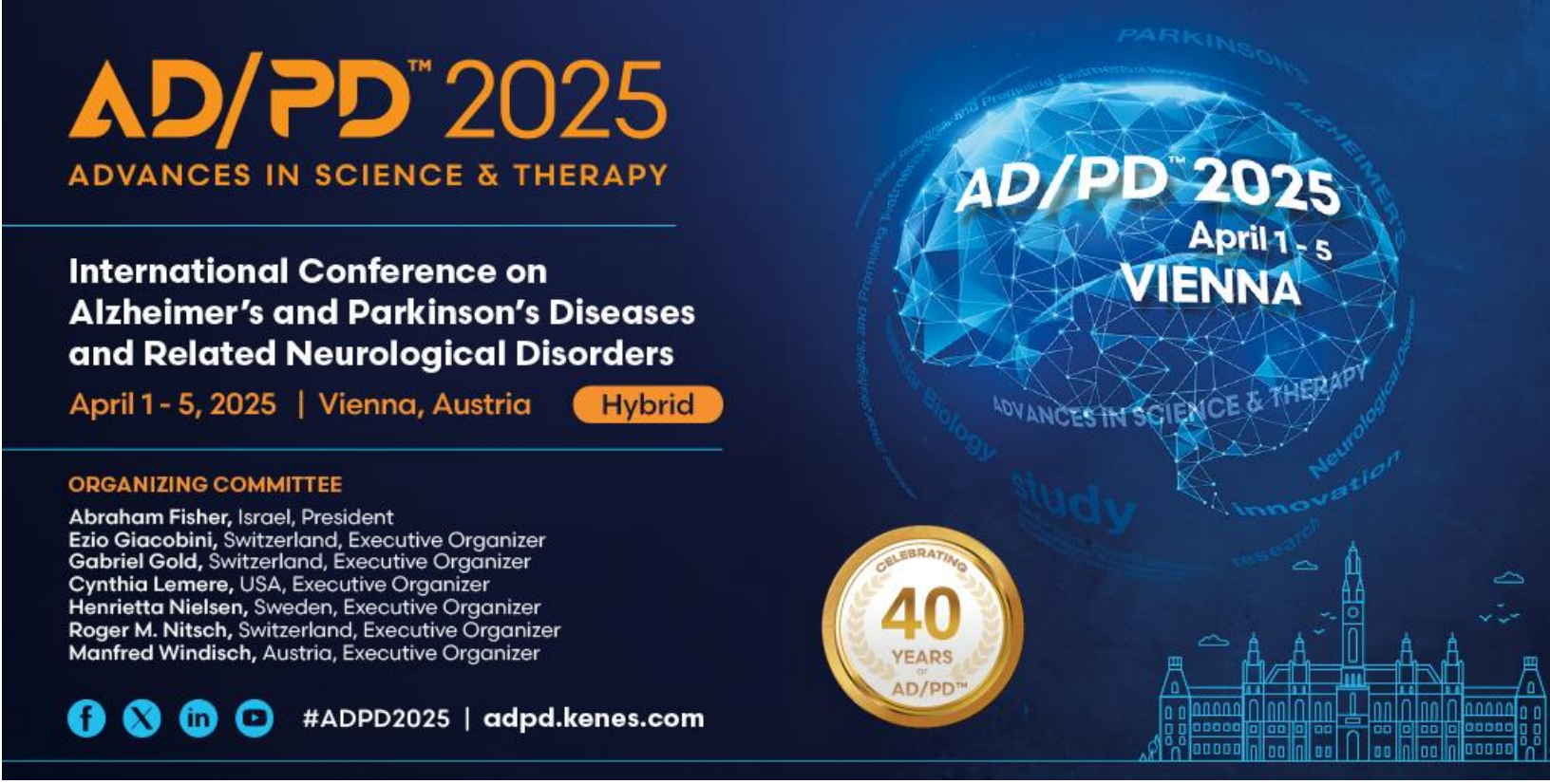

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Shift 1: April 2-3

- **Mounting time** April 1, during welcome reception, April 2 from 08:00 will 10:00
- **Dismounting time** April 3 from 17:30 till 18:30

Shift 2: April 4-5

- **Mounting time** April 3 from 17:30 till 18:30, April 4 from 08:00 till 10:00
- **Dismounting time** April 5, from 17:30 till 18:30

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On-Demand Orals Posters on Board

Shift 01

2 – 3 April 2025

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SHIFT 01-001

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / ANIMAL MODELS / RODENTS
2 - 3 April 2025

COMBINATION MODEL FOR PRECLINICAL PROOF OF CONCEPT STUDIES TARGETING HUMAN ALPHA-SYNUCLEIN PATHOLOGY

Eline Vonck[1], Sofie Carmans[2], Wannes Dejonckheere[2], Veerle Baekelandt[1], Tom Cornelissen[2]
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Aims: Parkinson's disease (PD) is characterized by the pathological accumulation of α-synuclein (αSyn), positioning this protein as a critical biomarker and therapeutic target. Existing αSyn rodent models have provided valuable insights into PD pathogenesis, but many fail to fully capture the complexity and robustness of the disease's pathology and behavior. Thus, a more comprehensive model that reflects a broader spectrum of PD pathology is needed to improve preclinical research. Here, we present an innovative approach that integrates two well-established methods to enhance the construct validity of αSyn-based models. Specifically, we combine AAV-mediated overexpression of human αSyn (hαSyn) with hαSyn preformed fibrils (hPFFs), targeting the human variant of αSyn to increase translatability for therapeutic interventions.
Methods: Young wild-type mice received unilateral stereotactic injections of either AAV2/7-CMVenhSyn-hαSyn, recombinant hPFFs (Stressmarq), or both. AAV2/7-mediated overexpression of hαSyn was localized to the right substantia nigra, while hPFFs were administered in the ipsi-lateral striatum 3 weeks after AAV injection. Motor function is currently being assessed and will be followed by detailed pathological evaluation.
Results: Preliminary findings from a pilot study indicate a 25% loss of tyrosine hydroxylase-positive (TH+) neurons in the substantia nigra and a 45% reduction in TH+ terminals in the striatum three months post-AAV injection. When hPFFs were co-administered, these effects were exacerbated, with TH+ cell loss increasing to 45% and striatal terminal loss reaching 90%. Notably, hPFFs alone did not cause dopaminergic degeneration, likely due to a species-specific barrier.
Conclusions: These results suggest that hPFFs do seed the monomeric hαSyn and aggravate the pathology induced by AAV-mediated overexpression of hαSyn. This combination model offers a promising platform for in vivo evaluation of therapeutic strategies aimed at mitigating hαSyn pathology, with a particular focus on human αSyn-targeted treatments.

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SHIFT 01-003

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / A-SYNUCLEIN
2 - 3 April 2025

CRYO-EM STRUCTURES OF A-SYNUCLEIN FILAMENTS DERIVED FROM THE CASE OF ATYPICAL MULTIPLE SYSTEM ATROPHY

Masahiro Enomoto[1], Ivan Martinez-Valbuena[2], Shelley Forrest[2], Xiaoxiao Xu[3], Jun Li[2], Helen Chasiotis[2], Renato Munhoz[4], Ekaterina Rogaeva[2], Anthony Lang[4], Gabor Kovacs[2]
[1]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, [2]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [3]University of Toronto, Medical Biophysics, Toronto, Canada, [4]University Health Network, Toronto, Canada

Aims: To determine the cryo-electron microscopy (cryo-EM) structures of α-synuclein filaments derived from different brain regions from one case with atypical MSA-type α-synuclein pathology.
Methods: Following clinical follow-up, a state-of-the-art neuropathology characterization, and genetic study to evaluate *SNCA* mutations including gene dosage, sarkosyl-insoluble material was extracted from fresh-frozen brain regions. Extracted α-synuclein filaments were applied to glow-discharged holey carbon gold grids covered with graphene oxide films and plunge-frozen in liquid ethane. Micrographs were acquired using a Thermo Fisher Titan-Krios microscope that was operated at 300 kV equipped with a Falcon 4i direct electron detector. All image-processing steps were performed using RELION 5.0. Filaments were picked using crYOLO 1.9.9. Atomic models were built *de novo* using ModelAngelo v1.0.12 and manually refined in Coot. Models were validated with MolProbity. In addition, we performed western blot examination of α-synuclein.
Results: Clinical history was typical of MSA but MRI unexpectedly showed very severe temporal lobe atrophy. Neuropathology revealed classical Papp-Lantos bodies in subcortical areas; however, the temporal lobe and hippocampus showed large amounts of eosinophilic and α-synuclein immunoreactive globular neuronal cytoplasmic inclusions as described in atypical MSA (or also called FTLD-synuclein), which is reminiscent of MSA-P. We did not detect any mutations, including copy number variations, in the *SNCA* gene. Cryo-EM revealed α-synuclein filament folds which were different from those identified in brain regions with the typical MSA-type α-synuclein pathology and reported in the literature.
Conclusions: Our study expands the spectrum of biochemical and ultrastructural findings of α-synucleinopathies and contributes to the characterization of a rare form of MSA.

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SHIFT 01-005

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
2 - 3 April 2025

MODULATION OF SERUM MICRORNA EXPRESSION IN PARKINSON'S DISEASE PATIETNS BY A MULTIDISCIPLINARY INTENSIVE OUTPATIENT REHABILITATION PROGRAM (MAC

Simone Agostini[1], Roberta Mancuso[1], Francesca Lea Saibene[2], Riccardo Nuzzi[1], Jorge Navarro[2], Mario Clerici[3]
[1]IRCCS Fondazione Don Carlo Gnocchi, Lammb, Milan, Italy, [2]IRCCS Fondazione Don Carlo Gnocchi, Neurology Unit, Milan, Italy, [3]University of Milan, Department Of Pathophysiology And Transplantation, Milan, Italy

Aims: Objectives: Parkinson's disease(PD) is one of the most common neurodegenerative diseases, characterized by misfolded α-synuclein (α-syn) accumulation. miR-223-3p and miR-7-1-5p are miRNAs that modulate the expression of α-syn. One of the most promising rehabilitation treatments for PD patients is a multidisciplinary intensive outpatient rehabilitation program ('MAC-Macroattività Ambulatoriale Complessa' setting), consisting in an intensive 160/180-minutes per day, five days/week, for a total of six weeks. The aim of this study is to verify if circulatory miR-223-3p and miR-7-1-5p can be used as biomarkers of PD and – together with α-syn – of MAC rehabilitative outcome.
Methods: Methods: Seventy-six patients were enrolled. All the enrolled patients underwent a rehabilitative program: 40 were allocated in EXP Group (i.e. MAC treatment), whereas 36 were allocated in Control Group (a home-based self-managed stretching treatment, CTRL). Blood samples were collected before the start of the treatment (T0), after six weeks (T1), and, after three months from the treatment (T2). Serum α-syn, miR-223-3p and miR-7-1-5p were analyzed for all the time points.
Results: Results: α-syn resulted increased in T1 in EXP Group (18.03±9.70ng/ml) compared to T0 (12.97±7.07 ng/ml;p=0.05), although its concentration decreases in T2 (12.19±7.74 ng/ml;p=0.02), whereas α-syn expression remained stable in all time points in patients allocated in CTRL Group. Regarding miRNAs expression, both treatments cause a decrease of miR-223-3p expression, even at T2; on the converse the miR-7-1-5p decreases at T1 in EXP group (T0=: 160.00c/ng; T1: 0.01 c/ng), although it returns to baseline levels in T2 (266.67 c/ng, p=0.02 for the comparison T1 vs. T2), whereas remains stable in CTRL group.
Conclusions: Conclusions: We found that the multidisciplinary intensive outpatient rehabilitation program MAC has a different effect on circulatory markers compared to a home-based self-managed stretching treatment.

SHIFT 01-007

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES
2 - 3 April 2025

UNRAVELLING THE ROLE OF ENSHEATHING GLIA IN A PINK1 DROSOPHILA PD MODEL

Lorenzo Ghezzi
VIB-Ku Leuven, Leuven, Belgium

Aims: Recently oligodendrocytes have been associated with Parkinson's disease (PD) at a stage prior to dopaminergic neuron loss, therefore we use ensheathing glia (EG), the most similar cell-type to oligodendrocyte in *Drosophila,* to understand the role of wrapping glia in PD pathogenesis. EG is the most deregulated cell type in a scRNA seq study performed in our lab on a *Pink1* loss of function *Drosophila* model. With our study, we first aim to understand how EG reacts to Pink1 loss of function in neurons and glia, and how *Pink1* loss of function in EG affects neuronal integrity. Finally, we want to understand the molecular mechanism affected in EG by the lack of *Pink1* and how this affects neuronal integrity.
Methods: In order to answer our question we used immunohistochemistry to assess activity of EG and dopaminergic synaptic integrity. We also used an electrophysiological recording to evaluate synaptic functionality. Finally, we optimized a cell-type-specific transcriptomic method to identify specifically in EG modifiers of the synaptic phenotypes.
Results: Immunohistochemistry experiments show that EG is active non-cell-autonomously triggered by neuronal *Pink1* deficiency. The finding that Pink1-KO neuronal injury elicits an EG activation response, suggested that this cell type might functionally modulate neuronal integrity. To test this hypothesis, we genetically manipulated EG, and performed electrophysiological recordings of photoreceptors and stained dopaminergic neuron afferents. Our results demonstrate that Pink1 in EG is necessary to protect neurons from synaptic loss and that healthy EG can deal with and maintain fragile neurons. Finally, through cell-type-specific transcriptomics we identified modifiers of neuronal integrity phenotypes in EG that suggest that imbalance at the contact points among mitochondria-ER-endosomes are central in EG to maintain neuronal integrity.
Conclusions: In conclusion, our study shows non-cell-autonomous activity of EG in response to neuronal damage, and *Pink1* in EG is fundamental to maintaining neuronal integrity.

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SHIFT 01-010

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2 - 3 April 2025

SPATIOTEMPORAL ANALYSIS OF DOPAMINERGIC ALDH1A1+/- SUBPOPULATIONS IN THE MIDBRAIN OF A MOUSE MODEL OF ALPHA-SYNUCLEIN OVEREXPRESSION

Carmen-Jeanette Stepek[1], Ayse Ulusoy[2], Donato Di Monte[2], Jochen Prehn[1], Niamh Connolly[1]
[1]RCSI University of Medicine and Health Sciences, Dublin, Ireland, [2]The German Centre for Neurodegenerative Diseases (DZNE), Bonn, Germany

Aims: Characteristics of Parkinson's Disease (PD) include progressive and preferential degeneration of dopaminergic neurons (DANs) in the substantia nigra (SN) and intraneuronal α-Synuclein (αSyn) inclusions known as Lewy bodies. DANs can be categorized into distinct subpopulations based on location, physiological functions and expression profiles. Over 60% of DANs in the SN express Aldehyde Dehydrogenase 1A1 (ALDH1A1), a subpopulation identified as selectively vulnerable in post-mortem PD tissue. Other findings suggest complex molecular mechanisms of vulnerability that have not yet been delineated. This study characterises the distribution and transcriptome of ALDH1A1$^+$ and ALDH1A1$^-$ DANs in a mouse model of αSyn pathology.
Methods: Mice received intra-nigral injections of AAV-expressing human-αSyn or GFP. Midbrain tissue was collected 3- and 8-weeks post-injection, corresponding with pre- and post-cell death. Neuroanatomical regions and DAN subtypes were identified using immunofluorescence, and spatial transcriptomics was performed using NanoString's GeoMx Digital Spatial Profiler. Bioinformatics analyses were performed in R.
Results: We observed diffuse αSyn pathology and increased Snca expression at both timepoints. At 8 weeks, significant DAN (TH$^+$) loss was observed in the SN, due to a selective loss of ALDH1A1$^-$ DANs. No DAN loss was detected in the ventral tegmental area. Spatial transcriptomics identified a robust transcriptomic signature distinguishing ALDH1A1$^+$ and ALDH1A1$^-$ DANs in naïve and αSyn-overexpressing conditions. αSyn over-expression induced greater transcriptional dysregulation in ALDH1A1$^-$ DANs, including downregulation of synaptic vesicle and metabolic pathways, particularly glycolysis. In contrast, ALDH1A1$^+$ DANs showed a stronger up-regulation of cholesterol biosynthesis and lipid metabolism, suggesting metabolic rewiring as a potential compensatory mechanism.
Conclusions: We provide a comprehensive spatial and temporal characterisation of murine midbrain ALDH1A1$^+$ and ALDH1A1$^-$ DANs, revealing cell type-specific transcriptomic and metabolic responses to αSyn over-expression.

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SHIFT 01-015

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2 - 3 April 2025

UNITING MICROFLUIDICS AND ELECTRON MICROSCOPY TO STUDY THE STRUCTURAL PROTEOME OF SYNUCLEINOPATHIES

Thomas Braun[1], Elaine Schneider[1], Andri Fränkl[1], Michael Zimmermann[1], Larissa Glass[1], Maryam Mohamadi[1], Sebastian Hiller[1], Luca Rima[1], Tetiana Serdiuk[2], Ronald Melki[3]
[1]University of Basel, Biozentrum, Basel, Switzerland, [2]ETH Zurich, Inst. F. Molekulare Systembiologie, Zurich, Switzerland, [3]Institut Francois Jacob (MIRCen), CEA and Laboratory of Neurodegenerative Diseases,, Fontenay-Aux-Roses, France

Aims: α-synuclein (α-syn), a natively unfolded protein, misfolds into a pathogenic structure that can induce healthy proteins to adopt the same abnormal configuration, leading to fibrillar α-syn aggregates and progression of synucleinopathies. Age-related decline in proteostasis, which maintains α-syn folding, increases the risk of spontaneous neurodegeneration. **We aim to study the structural proteome of α-syn, its interactome, and the processing of aggregated α-syn by the proteostatic system.**
Methods: Using the in-house developed cryoWriter system, which merges microfluidic technology with high-resolution imaging and single-molecule detection by electron microscopy (EM), we resolve protein structures from nL total volumes. A microfluidic protein extraction module allows the direct isolation of target proteins, and another module enables the processing of single adherent eukaryotic cells. Our approach includes (i) isolating diseased amyloids from patient brain homogenates to analyze fibril architecture, (ii) studying in-cell processing using cryoWriter's single-cell analysis infrastructure, (iii) investigating fibril processing through a microfluidic assay with structural readout; and (iv) "interaction labeling" to identify fibril modifications and biding partners.
Results: The integration of microfluidics and EM enabled the direct isolation of amyloid fibrils from patient brain homogenates using less than ten µg of total protein. We identified the energy-dependent processing of fibrils in brain homogenates from samples as small as 20 nL. Furthermore, we successfully investigated the processing of synthetic fibrils within individual cells using visual proteomics.
Conclusions: These results underscore the unique capability of combining microfluidics and EM to achieve detailed structural and functional analysis of α-synuclein and its aggregates. The integrated approach's visual readout advances our understanding of α-syn aggregation and its processing by the proteostasis system. It provides a robust tool for exploring the mechanisms underlying neurodegenerative diseases at a previously inaccessible resolution.

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SHIFT 01-016

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2 - 3 April 2025

PROXIMITY PROTEOMICS REVEALS A ROLE FOR RNA PROCESSING PATHWAYS IN ALPHA-SYNUCLEIN AGGREGATION

Analiese Fernandes[1,2], Abigail Owen[1], Ayman Faroqi[1,2], Jannifer Lee[1], Dmytro Morderer[1], Cody Hoffmann[3], Benjamin Madden[3], Shuwen Zhang[4], Yingxue Ren[5], Suelen Boschen[1,2], Akhilesh Pandey[6], Wilfried Rossoll[1,2], Pam Mclean[1,2]
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Aims: The aim of this project is to discover cellular cofactors associating with alpha-Synuclein (aSyn) during aggregation, with the goal of identifying novel proteins which initiate or modulate aSyn aggregation processes. Such cofactors will provide new understanding of mechanisms involved with aggregating aSyn prior to the development of late-stage Lewy pathology. This project will offer insights into the formation – and potential function – of Lewy pathology.
Methods: This study employed an *in vitro* proximity-dependent biotin identification (BioID) model, whereby a biotin ligase enzyme (BirA*) was fused to aSyn. Furthermore, utilization of a split BioID assay identified cofactors of multimeric aSyn. By comparing the proximal proteome of aSyn fused with full-length enzyme (Syn-BirA*) to that of the split model (split Syn-BirA*), cofactors associated with monomeric and multimeric aSyn were discerned. To mimic aggregation processes, cells expressing Syn-BirA* or split Syn-BirA* were treated with human pre-formed fibrils. Biotinylated proteins in treated and untreated groups were identified via biotin-based pulldown and LC-MS/MS.
Results: A total of 1005 biotinylated proximal proteins were identified, with 345 demonstrating significant preferential associations in one or more group comparisons. Notably, 136 proteins had increased association with aggregating aSyn compared to non-aggregated controls. Identified cofactors represent processes such as mRNA splicing, RNA binding, and ubiquitination and may represent disease-specific interactors. Analysis of aSyn in aggregated states uncovered 29 proteins increasingly associated with multimeric aSyn. These cofactors, related to chromosome organization and RNA processing, may respond to, or exacerbate, pathogenic oligomer formation.
Conclusions: This proteomics approach based on proximity-dependent biotinylation identified candidate molecular cofactors uniquely associated with monomeric, oligomeric, and aggregating aSyn. These could modulate early-stage aSyn aggregation or exacerbate oligomeric aSyn toxicity. Ongoing studies aim to validate the relationship of these proteins with aSyn.

SHIFT 01-025

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
2 - 3 April 2025

AUTOPHAGY AND CALCIUM HOMEOSTASIS DEFICITS IN DIFFERENTIALLY VULNERABLE IPSC-DERIVED CORTICAL AND DOPAMINERGIC NEURONS FROM AD AND PD PATIENTS

Ajantha Abey[1], Eden Mellor-Davis[1], Bryan Ng[2], Rachel Heon-Roberts[1], Becky Carlyle[1], Nora Bengoa-Vergniory[3], Richard Wade-Martins[1]
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Aims: Alzheimer's (AD) and Parkinson's disease (PD) feature progressive neurodegeneration in a regionally selective manner. *Post mortem* studies have posited a role for cell autonomous mechanisms driving this. Therefore, we aimed to examine live human induced pluripotent stem cell (iPSC)-derived neuronal models to see whether disease-related phenotypes were cell-type specific, reflecting selective neuronal vulnerability, so to better determine disease mechanisms and therapeutic targets.
Methods: iPSC-derived neurons offer a rare opportunity to examine cell autonomous vulnerability in live human cells. iPSCs from patients with AD-related presenilin-1 mutations (n=6), PD-related leucine rich repeat kinase 2 mutations (n=6), and isogenic corrected (n=4) and healthy controls (n=4) have been differentiated into both cortical and midbrain dopaminergic neurons to enable comparison of disease phenotypes in different neuronal subtypes from the same patient. We examined autophagic flux, lysosomal function calcium homeostasis, and mitochondrial morphology using live imaging assays and immunolabelling to understand underlying drivers of vulnerability in the specific cell types.
Results: PSEN1-Intron-4-Deletion cortical neurons displayed profound autophagic flux deficits, lysosomal perturbations, and calcium handling deficits, that were reversed in dopaminergic neurons. These lines displayed also hyperactivity on microelectrode arrays and increased pathology in response to alpha synuclein pre-formed fibrils. The AD cortical neurons also displayed impaired neurite outgrowth, while PD LRR2 cortical neurons strikingly remained resilient to neurite impairment.
Conclusions: These preliminary results show that some genotype-dependent phenotypes in AD and PD are also cell type dependent. Comparing a large number of cell lines across multiple diseases, these data suggest that the iPSC model reflects selective vulnerability to these diseases observed in the brain, and support the notion that cell intrinsic factors like autophagy drive vulnerability.

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SHIFT 01-030

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

NOVEL IN SITU RT-QUIC ASSAY FOR THE DIRECT VISUALISATION OF PRION-LIKE PROTEIN SEEDING IN CELLS AND TISSUES

Javier Alegre-Abarrategui[1], Maria Otero-Jimenez[1], David Miller[2], Simona Jogaudaite[1]
[1]Imperial College London, Department Of Brain Sciences, London, United Kingdom, [2]Imperial College London, Advanced Hackspace, London, United Kingdom

Aims: The aims were to i) develop a novel seeding amplification assay to visualise the prion-like protein seeding capacity of endogenous misfolded protein aggregates within their morphologically preserved cellular and histological setting (*in situ* RT-QuIC assay) and ii) to apply *in situ* RT-QuIC to a pilot cohort of alpha-synucleinopathies to determine any differential alpha-synuclein seeding capacity of neuronal and glial alpha-synuclein inclusions.
Methods: The *in situ* RT-QuIC assay was applied to a cohort of alpha-synucleinopathies, including MSA, PD, PDD and DLB samples, from The Multiple Sclerosis and Parkinson's Tissue Bank at Imperial College London. Immunohistochemistry was also used for assessment of alpha-synuclein pathology.
Results: The novel *in situ* RT-QuIC assay was applied to detect spatially resolved alpha-synuclein seeding in formalin-fixed paraffin embedded tissue sections with preservation of cell and tissue morphology. The *in situ* RT-QuIC assay successfully detected the alpha-synuclein seeding activity of pathological alpha-synuclein inclusions including Lewy bodies, Lewy neurites, oligodendrocytic and astrocytic alpha-synuclein inclusions. Furthermore, differences were found in the number of cell-type specific alpha-synuclein inclusions detected by immunohistochemistry and *in situ* RT-QuIC assay, suggesting that immunohistochemistry does not label all seeding-competent alpha-synuclein inclusions and sheds light into other potential key drivers of alpha-synuclein seeding.
Conclusions: Our newly developed *in situ* RT-QuIC assay provides spatially resolved and cell-type specific information on alpha-synuclein seeding capacity, differentially detecting seeding-competent alpha-synuclein pathology. This groundbreaking technique provides detailed information about seeding-competent cells and subcellular origin of the alpha-synuclein species. This pathomechanistic information can be exploited to understand the differences underlying alpha-synucleinopathies and be of use in other prion-like proteins with similar properties. Lastly, this can aid in the development of new therapeutic approaches tackling the alpha-synuclein species and cells most involved in alpha-synuclein seeding to halt disease progression.

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SHIFT 01-031

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

IMMUNE RECEPTOR FCΓRIIB FACILITATES PATHOLOGIC A-SYNUCLEIN PROPAGATION IN-VIVO

James Hennegan[1], Ali Roghanian[2], Jessica Teeling[1]
[1]University of Southampton, Clinical Neurosciences, Southampton, United Kingdom, [2]University of Southampton, Centre For Cancer Immunology, Southampton, United Kingdom

Aims: This project aims to elucidate the role of Fc gamma receptor IIb (FcγRIIb) in neuronal α-Synuclein (α-Syn) propagation using the pre-formed fibril (PFF) mouse model of Parkinson's disease. FcγRIIb is an inhibitory immune receptor that regulates cellular activation and interacts with misfolded α-Syn aggregates *in-vitro*. Key objectives include assessing whether FcγRIIb mediates α-Syn propagation *in-vivo* using transgenic (Tg) mice that lack FcγRIIb expression, or lack functional FcγRIIb (ITIM-mutant), and examining the role of FcγRIIb in α-Syn mediated neuroinflammation.
Methods: PFFs were generated by shaking and sonicating recombinant human α-Syn monomers. Full-sequence human (h) FcγRIIb Tg, ITIM-mutant hFcγRIIb Tg, and mouse (m) FcγRII knockout (KO) mice of mixed-sex (n=11-13 per group) were unilaterally injected with α-Syn PFFs into the dorsal striatum. Brain tissue was collected 1- and 3-months post-injection for immunohistochemical analysis of pSer129-α-Syn, neuronal integrity (TH), and immune markers (GFAP, Iba1). Repeated behavioural assays (e.g., open field) were conducted to correlate pathology with functional outcomes.
Results: Both hFcγRIIb Tg ($P<0.01$) and ITIM-mutant hFcγRIIb Tg ($P<0.05$) mice exhibit increased pSer129-α-Syn+ Lewy body-like pathology in the brain as compared to monomeric α-Syn-injected control mice. Importantly, mFcγRII KO mice present reduced pSer129-α-Syn+ burden ($P<0.05$) vs. receptor-expressing counterparts. High α-Syn pathology correlates with neurodegeneration. Mice expressing hFcγRIIb show ~30% nigral TH+ neuron loss ($P<0.001$) and reduced striatal fibre density ($P<0.05$), alongside impaired locomotion ($P<0.05$), measured 3 months after striatal injection of PFFs. In contrast, mFcγRII KO mice maintain TH+ neuronal integrity ($P>0.05$) and behavioural function.
Conclusions: FcγRIIb expression is critical for effective α-Syn propagation *in-vivo*, and intracellular receptor ITIM-dependent signalling is not required. These findings highlight FcγRIIb as a promising therapeutic target for PD research, supporting further exploration of FcγRIIb-targeted interventions for disease modification.

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SHIFT 01-032

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

THE IMPACT OF PARKINSON'S DISEASE-ASSOCIATED LIPID ALTERATIONS ON ALPHA-SYNUCLEIN RELEASE

Julie Jacquemyn[1], Brian Mariott[2], Ceili Green[3], Jeremy Wong[3], Nathanael Lee[2], Luis Atonal[3], Jinlan Chang[3], Jesse Jackson[2], Maria Ioannou[1]
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Aims: The intercellular transmission of misfolded α-synuclein has been proposed to play a role in the progression of Parkinson's disease. Alongside this, dysregulated lipid metabolism has recently emerged as a significant factor. However, the mechanisms behind α-synuclein spread, and the role of lipid alterations in this process, remain poorly understood. The goal of this project is to investigate the impact of Parkinson's disease-associated lipid alterations on α-synuclein release by extracellular vesicles.
Methods: Cortical neurons from postnatal rats and iPSC-derived dopaminergic neurons from PD patients with *GBA1* (N370S, W378G, L444P) and *LRRK2* (R1441H, G2019S) mutations, alongside isogenic controls, from male and female were studied. The membranes of these neurons were labelled by expressing mCherry-GPI or mVenus-CAAX. Cortical neurons were either treated with exogenous glucosylceramide tagged with the fluorophore nitrobenzofurazan or with conduritol-β-epoxide, a selective small molecule inhibitor of GCase, to mimic PD conditions and imaged live. Super-resolution live-cell imaging was performed alone or in combination with human α-synuclein preformed fibrils, which were generated and validated according to the MJFF protocol.
Results: We discovered that increased glucosylceramide induces the release of extracellular vesicles from primary cortical neurons and Parkinson's disease patient's dopaminergic neurons with *GBA1* and *LRRK2* mutations. These vesicles carry pathogenic α-synuclein fibrils, which are subsequently internalized by other neurons, leading to the spread of α-synuclein pathology.
Conclusions: Our findings highlight the role of extracellular vesicles as a key vehicle for α-synuclein transmission in response to lipid alterations found in Parkinson's disease.

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SHIFT 01-036

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
2 - 3 April 2025

HUMAN A53T-MUTATED SYNUCLEIN MOUSE MODEL WITH DISTURBED NIGRO-STRIATAL SYSTEM TO STUDY PARKINSON'S DISEASE

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Aims: Phosphorylation, misfolding and aggregation of a-synuclein (a -syn) are hallmarks of Parkinson's disease (PD) and other synucleinopathies. The A53T mutation in the SNCA gene encoding a-syn has been shown to promote oligomerization and aggregation of a-syn, ultimately contributing to neurodegeneration. To evaluate pathological aspects and the efficacy of new treatment strategies for PD, an induced mouse model expressing the A53T variant of a-syn was characterized.
Methods: The substantia nigra (SN) of 13-week-old C57BL/6J mice was unilaterally injected with an adeno-associated virus (AAV) carrying the human A53T mutated a-syn gene (AAV-hA53T). The contralateral SN was injected with AAV-empty control vector. After 8 weeks, mice's brains were collected and analyzed for a-syn, phosphorylated a -syn, tyrosine hydroxylase (TH), dopamine transporter (DAT), ionized calcium-binding adapter molecule 1 (Iba1), cluster of differentiation (CD) 3, and CD8 using the MSD immunosorbent assay, quantitative immunofluorescence and fluorescence *in situ* hybridization.
Results: Human a-syn RNA and protein and phosphorylation of a-syn at serine 129 levels were increased in the ipsilateral SN. The number of TH-positive neurons in the ipsilateral SN and fibers in the ipsilateral caudate putamen were significantly reduced. DAT signal in the AAV-hA53T ipsilateral SN was reduced. Further, an increase in Iba1 signal as well as CD3-positive T-cells, particularly cytotoxic CD8-positive T-cells could be observed.
Conclusions: In summary, the findings demonstrate that the AAV-hA53T vector successfully induces human a-syn expression resulting in significantly increased phosphorylated a-syn levels, neurodegenerative changes, including dopaminergic neuron loss, altered dopamine signaling, and an inflammatory response. Collectively, this model enables investigating pathways involved in disease progression, identifying biomarkers for early detection, and testing the efficacy of new drugs against PD as well as other synucleinopathies.

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SHIFT 01-037

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
2 - 3 April 2025

LOSS OF FRAGILE X MENTAL RETARDATION PROTEIN (FMRP) CONTRIBUTES TO STRIATAL DOPAMINE TRANSPORTER SURFACE ENRICHMENT AND DOPAMINE TURNOVER IN EARLY PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra. Dopamine (DA) levels are regulated by the dopamine transporter (DAT), and alterations in DAT activity provide insight into PD progression. We recently discovered an early and unexpected loss of fragile X mental retardation protein (FMRP) in both PD and incidental Lewy body pathology (iLBD), a condition considered a precursor to PD.This study aims to investigate the functional consequences of FMRP loss on DA homeostasis in both healthy and Parkinson's disease conditions.
Methods: Using a combination of biochemical, imaging, and molecular biology techniques, we studied FMRP-deficient mice to explore the role of FMRP in regulating DAT function in dopaminergic neurons.
Results: Mice lacking FMRP showed a significant increase in DAT surface expression and dopamine uptake in the striatum compared to wild-type controls. Reintroducing FMRP reduced DAT levels and normalized DA uptake. These results were confirmed in conditional FMRP knockout (KO) mice, specifically lacking FMRP in DA neurons. The increased DAT levels were also associated with enhanced motor task performance, highlighting FMRP's role in DAT trafficking and DA neurotransmission. Biochemical analyses revealed that protein kinase C (PKC) is a key regulator of DAT surface localization in FMRP KO mice, and activation of PKC restored normal DAT surface levels, suggesting that PKC signaling is crucial in FMRP-mediated DAT membrane regulation.
Conclusions: These findings uncover a novel mechanism by which FMRP influences DA signaling, with potential implications for understanding its role in neurodegenerative diseases like Parkinson's.

SHIFT 01-040

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

MTHFR DEFICIENCY AND SARS-COV-2 INFECTION SYNERGISTICALLY INCREASE THE RISK OF PARKINSON'S DISEASE.

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Aims: Methylene tetrahydrofolate reductase (MTHFR), a key enzyme in folate metabolism, affects various physiological processes like nucleotide synthesis, DNA repair, epigenetic regulation and neurotransmitter synthesis. Common functional genetic polymorphisms in MTHFR (20-40% worldwide prevalence) are associated with increased risk of vascular dementia (VD) and Parkinson's disease (PD), and Mthfr-deficient mice which model these polymorphisms exhibit cognitive deficits, cerebrovascular dysfunction, and heightened risk of PD-like pathology. Additionally, SARS-CoV-2 infection may accelerate onset or worsen pre-existing VD and PD. Therefore, we aim to investigate effect of SARS-CoV-2 mediated neuroinflammation, neurodegeneration and risk of PD in Mthfr-deficient mice
Methods: *Mthfr*$^{+/-}$ and wild-type mice (WT), aged 10 months, were intranasally infected with MA10 strain of SARS-CoV-2 (1×10^4 PFU) or with mock (PBS). 3-days post-infection, mice were euthanized and lung and brain tissues were examined through quantitative-PCR (qPCR) and immunohistochemistry. Plasma samples were processed for metabolomics analysis.
Results: *Mthfr*$^{+/-}$ and WT mice exhibited similar lung viral titers, with no detectable virus in brain following MA10 infection. However, qPCR and immunofluorescent staining revealed significantly reduced ZO-1, a blood-brain-barrier (BBB) tight junction protein, in brains of *Mthfr*$^{+/-}$ infected mice. MA10 infection also increased IL-1β mRNA and microglia count in *Mthfr*$^{+/-}$ mice. Metabolomics data showed significantly reduced plasma dopamine *in Mthfr*$^{+/-}$ infected mice. Additionally, MA10 infection significantly lowered tyrosine hydroxylase (TH) level and TH+ dopaminergic neuron count, and increased α-synuclein levels in substantia nigra of *Mthfr*$^{+/-}$ mice.
Conclusions: Acute experimental SARS-CoV-2 infection in context of reduced MTHFR function causes BBB disruption, neuroinflammation, and reduced plasma dopamine levels. It also lowers dopaminergic neuron count and TH levels, while increasing α-synuclein in substantia nigra. This is the first study to demonstrate that SARS-COV-2 infection may enhance risk of developing PD in individuals with MTHFR polymorphisms.

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SHIFT 01-041

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

MINING PARKINSON'S BLOOD CELL PROTEOMES REVEALS ENDOTYPE AND MECHANISTIC INFORMATION

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Aims: The clinical presentation of Parkinson's disease is heterogeneous with motor and non-motor symptoms, as well as general disease trajectories, differing broadly among patients. While the main cause for motor dysfunction can be tracked to the loss of *substantia nigra* dopaminergic neurons in the central nervous system, Parkinson's also affects peripheral organs in particular the blood and gut, where diverse signs of inflammation are found years before motor symptoms appear. This project analyses the proteome and several layers of post-translation modifications from Parkinsons patient peripheral mononuclear cells to gain insight on diseae biology.
Methods: We carried out data independent analysis LC-MS/Ms on PBMC cohorts from South-West Finland and from the Parkinson's Progression Marker Initiative (PPMI) containing samples from sporadic and genetic Parkinson's patients (LRRK2, GBA) and prodromal cases (1203 samples, 3 time points). LC-MS/MS was carried out using Evosep One 30 sample per day method on Oribitrap Lumos interfaced with FAIMS-pro with a single compensation voltage, in data independent acquisition mode with a daily run control.
Results: Protein abundance and post-translational modifications were analysed using Spectronaut® 18 yielding information on ~6700 protein groups after filtration and batch correction. Weighted Gene Correlation Network Analysis revealed endotypes where non-overlapping functions were enriched. Using AI -based software, post-translational modifications were measured, thus phosphorylation, glycosylation and citrullination changes provided new insight on pathway deregulation.
Conclusions: This is the first multi-PTM analysis of a Parkinson's cohort to be described. The results suggest paths for further study.

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SHIFT 01-046

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METAL IONS
2 - 3 April 2025

MOLECULAR MECHANISMS OF CU(II)-MODULATED A-SYNUCLEIN AGGREGATION

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Aims: Parkinson's disease pathology is closely linked to α-synuclein protein (αSyn) aggregation, resulting in potentially toxic oligomers and amyloid fibrils in the brain. Understanding these aggregation pathways is crucial for developing effective treatments. Redox-active Cu(II) ions are linked to the pathogenesis of Parkinson's disease and modulate αSyn aggregation. While Cu(II) ions are known to accelerate this aggregation, structural insights into their molecular interactions with αSyn are lacking.
Methods: In this study, we used *in vitro* aggregation kinetics assays to investigate the nucleation processes of αSyn fibril formation applying a global fit approach with different nucleation models. Further, we performed solution NMR HSQC titration experiments to identify the specific Cu(II) binding site. Additionally, diffusion NMR experiments were utilized to assess the impact of Cu(II) on the hydrodynamic radius of αSyn. Paramagnetic NMR studies, utilizing the paramagnetic properties of Cu(II) ions, were conducted to elucidate the structural characteristics near the copper binding site, providing insights into the local environment around the paramagnetic center.
Results: We found that Cu(II) ions significantly accelerate αSyn aggregation by specifically enhancing secondary nucleation, a process suggested to be the major source for generation of toxic αSyn oligomers. NMR HSQC experiments revealed multiple copper-binding sites in αSyn. Diffusion NMR experiments showed that the Cu(II)-bound state of the αSyn monomer has a smaller hydrodynamic radius compared to the unbound state, indicating a more compact Cu(II)-bound state. Additionally, ongoing paramagnetic NMR studies aim to clarify the structural characteristics of these copper-binding sites, and to identify structures of misfolded αSyn seeds.
Conclusions: These results provide details of the molecular mechanisms of αSyn aggregation and the modulation effects of copper ions, which could facilitate the design of novel treatment approaches.

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SHIFT 01-047

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METAL IONS
2 - 3 April 2025

EVALUATING THE IMPACT OF IRON OXIDATION STATE ON ALPHA-SYNUCLEIN AGGREGATION.

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Aims: Brain iron homeostasis is disrupted in various neurodegenerative disorders, including the synucleinopathies. One way in which iron may affect pathogenesis is through its impact on amyloid folding and aggregation. The influence of ferrous and ferric iron on alpha-synuclein is comparatively under-studied, and here we use electron microscopy, fluorescence and UV-vis spectroscopy, and mass photometry, to advance understanding of how iron affects alpha-synuclein.
Methods: Alpha-synuclein was incubated with/without ferrous or ferric iron and monitored using a set of complementary analytical methods. ThT fluorescence measurements were performed over one week to monitor beta-pleated sheet formation characteristic of fibril formation. TEM images were obtained at corresponding monitoring time point during the initial 72 hours, and mass photometry measurements were taken of these same samples to study the formation of early-stage oligomers for each treatment. UV-vis measurements were also recorded to monitor the iron oxidation state as a function of time in each treatment.
Results: TEM images evidenced different levels of aggregation for alpha-synuclein incubated with ferrous iron, versus ferric iron or buffer only. ThT fluorescence measurements revealed changes levels of beta-pleated sheet formation with ferrous iron, versus ferric iron or alpha-synuclein with buffer only. Mass photometry data suggest the addition of ferrous iron resulted in the production of intermediate early-stage oligomer species not present in alpha-synuclein incubated with ferric iron or buffer only.
Conclusions: The oxidation state of iron affected the aggregation behaviour of alpha synuclein in-vitro in a phosphate-free buffer and at physiological temperature. Alpha synuclein assembly in humans may therefore depend on how iron is (dys)metabolised in health and disease, as this will determine the oxidation state(s) of bioavailable iron in compartments where alpha synuclein assembly can occur.

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SHIFT 01-049

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2 - 3 April 2025

ALTERATIONS IN MITOCHONDRIAL DYNAMICS IN DEMENTIA WITH LEWY BODIES

Laurine Duquesne[1], Périne Millot[1], Claire Pujol[2], Claire Paquet[1,3], François Mouton-Liger[1]
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Aims: Dementia with Lewy bodies (DLB) is an α-synucleinopathy recognized as the second leading cause of dementia. Despite the large number of affected patients, the pathophysiological mechanisms of this disease remain poorly understood. Alterations in mitochondrial dynamics have been described in recent years in neurodegenerative diseases as an early pathological mechanism affecting neurons and glial cells, and can also be observed in peripheral immune cells from patients. In DLB, the potential role of mitochondrial dysfunction has been minimally or not at all explored. In this context, our objective was to investigate alterations in mitochondrial dynamics, specifically the fusion/fission balance in DLB patients.
Methods: In this retrospective, single-center study, we used peripheral blood mononuclear cells (PBMCs) from DLB patients and neurological controls followed at the Clinical Neurology Center (Fernand Widal Hospital, APHP). We also used post-mortem brain samples from DLB patients provided by the Neuro-CEB biobank. The concentration of proteins involved in mitochondrial dynamics was assessed by immunoblotting.
Results: Our results show that the protein FIS1, involved in mitochondrial fission, is significantly increased in post-mortem samples and PBMCs from DLB patients compared to control subjects. This increase is associated with specific dysregulations: (i) in post-mortem samples with an increase in BAP31 and (ii) in peripheral samples with an increase in the mitochondrial fission protein DRP1.
Conclusions: These results suggest mitochondrial dysfunction as a potential pathophysiological mechanism in DLB and may provide new tools to monitor the progression of these alterations in patients.

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SHIFT 01-050

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2 - 3 April 2025

24S/27-HYDROXYCHOLESTEROL BUT NOT CHOLESTEROL IMPAIR MITOCHONDRIAL FUNCTION AND THEREBY AFFECT NEURONAL CALCIUM SIGNALLING

Yuqing Feng[1], Bismoy Mazumder[1], Tasuku Konno[2], Ernestine Hui[1], Marius Brockhoff[1], Valentina Davi[2], Meng Lu[1], Edward Wards[1], Amberley Stephens[1], Wenyue Dai[1], Giuliana Fusco[3], Alfonso Simone[3], Edward Avezov[2], Clemens Kaminski[1], Gabriele Kaminski Schierle[1]
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Aims: There are mainly three types of cholesterol/metabolites in the brain: cholesterol, 24S-hydroxycholesterol (24S-HC), and 27-hydroxycholesterol (27-HC). Recent evidence shows significant enrichment of 24S-HC and 27-HC in the cerebrospinal fluid of Alzheimer's disease and Parkinson's disease (PD) patients, respectively, however how and which form of cholesterol contributes to disease pathology is still unknown. Thus, our aim is to study whether cholesterol and its metabolites alone or in the presence of disease related proteins can cause disease pathology.
Methods: COS-7 cells, SH-SY5Y cells and i3 cortical neurons derived from human induced pluripotent stem cells were treated with 24S-HC, 27-HC and cholesterol, respectively. Widefield microscopy and structured illumination microscopy were mainly used to assess the impact of cholesterol/metabolites at the cellular/organelle level.
Results: 24S-HC/27-HC significantly impairs mitochondrial fission/fusion in i3 cortical neurons and COS-7 cells. Furthermore, 24S-HC/27-HC decreases the spare respiratory capacity in COS-7 cells and causes a loss of synchronous calcium firing patterns in i3 cortical neurons with a dose-dependent response. The latter treatment also significantly decreases the relative calcium spike amplitude in i3 cortical neurons, which indicates a disturbance of calcium homeostasis. Additionally, 24S-HC and 27-HC, but not cholesterol bind to alpha-synuclein (aSyn) in vitro and increase aSyn levels in SH-SY5Y cells overexpressing aSyn. Notably, uptake of both aSyn and 24S-HC/27-HC leads to a loss of mitochondrial membrane potential in COS-7 cells.
Conclusions: In summary, our findings indicate a direct link between cholesterol metabolites 24S-HC/27-HC and mitochondrial dysfunction/dysregulated calcium homeostasis, while cholesterol itself does not elicit a similar effect. There are also partial correlations between 24S-HC/27-HC and aSyn, suggesting a potential link between cholesterol metabolism/aSyn and PD. Controlling levels of 24S-HC/27-HC may thus open new therapeutic avenues for neurodegenerative diseases, especially PD.

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SHIFT 01-051

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2 - 3 April 2025

A PHENOTYPIC SCREEN OF NOVEL COMPOUNDS FOR THE TREATMENT OF PARKINSON'S DISEASE

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Aims: Parkinson's is caused by the loss of dopaminergic neurons in the substantia nigra, characterised by motor symptoms such as tremor and rigidity. Current treatments for Parkinson's cannot treat the underlying causes of neurodegeneration, such as mitochondrial dysfunction. Cells from people with Parkinson's show reductions in ATP production, mitochondrial membrane potential (MMP), and mitochondrial bioenergetics. We have previously shown that the bile acid (BA) ursodeoxycholic acid can increase ATP production, MMP and Complex I activity. We hypothesise that other BAs may also have beneficial effects on patient-derived cells. We aim to identify a role for bile acids in the improvement of mitochondrial dysfunction and oxidative stress in Parkinson's disease patient-derived cells.
Methods: 83 compounds were screened at 1uM and 100nM in three patient lines for beneficial effects on ATP production and MMP. 20 compounds were selected based on increased ATP levels and assessed at 11 concentrations from 10uM to 100pM, in both the ATP and MMP assay. A final 6 compounds were selected for validation in a further 3 patient fibroblast cell lines, neurons, and astrocytes.
Results: Of the 83 compounds screened, 26 showed activity in the ATP screen, and 13 showed activity in the MMP screen. 6 compounds that were assessed in the dose-response screen were found to increase ATP production back to levels seen in control cells. These compounds had minimal effects on MMP.
Conclusions: Here we show the results of the final 6 compounds from the primary screen through to validation. These compounds increased total ATP production across 6 PD patient fibroblast lines with current testing in patient derived neurons and astrocytes, suggesting that bile acids could be used to treat Parkinson's.

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SHIFT 01-052

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2 - 3 April 2025

PARKINSON DISEASE-ASSOCIATED TOXIC EXPOSURES SELECTIVELY UPREGULATE VESICULAR GLUTAMATE TRANSPORTER VGLUT2 IN HUMAN CORTICAL NEURONS

Gary Ho[1], Karis Clark[1], Andrew White[1], Wojciech Paslawski[2], Kellianne Alexander[1], Shaoning Peng[1], Tracy Young-Pearse[1], Per Svenningsson[2], Dennis Selkoe[1]
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Aims: Parkinson disease (PD) is characterized by both motor and cognitive features. Motor symptoms primarily involve midbrain dopaminergic neurons, while cognitive dysfunction involves cortical neurons. Environmental factors account for the majority of PD risk. In rodent models, rare midbrain dopaminergic neurons which co-express the vesicular glutamate transporter 2 (vGlut2) are resistant to an array of toxins which induce dopaminergic neurodegeneration. However, it is unclear how, and with what degree of specificity, cortical glutamatergic neurons respond to PD-associated exposures regarding vGlut2. We investigated how vGlut2 levels change in stem cell derived human cortical glutamatergic neurons (iNs) following exposure to cellular stresses.
Methods: We tested a variety of PD-related and unrelated chemical exposures in cortical iNs, as well as pre-formed fibrils of alpha-synuclein (αS) compared to those of other proteins, followed by measurement of vGlut2 protein levels. We performed shRNA knockdown of vGlut2 measured cell viability.
Results: In cortical iNs, vGlut2 is upregulated in a highly specific manner to certain PD-related chemicals, such as rotenone, but not others, such as paraquat. Further, exposure to αS fibrils also increased vGlut2, while fibrils from non-PD related proteins such as transthyretin did not. This effect did not involve templated aggregation of endogenous αS, because it occurred in αS knockout iNs. We found that the knockdown of vGlut2 sensitized cortical neurons to rotenone, supporting a functional role in resilience. Thus, upregulation of vGlut2 occurs in a highly selective manner in response to specific PD-associated exposures in cortical iNs.
Conclusions: We demonstrated that upregulation of vGlut2 is a highly specific response to certain PD-related toxins that can be generalized to not only dopaminergic, but also cortical neurons, with important implications for PD dementia.

SHIFT 01-060

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2 - 3 April 2025

PATIENT-DERIVED MIDBRAIN ORGANOIDS OF GBA1-PARKINSON'S DISEASE RECAPITULATE LEWY PATHOLOGY AND GLUCOCEREBROSIDASE DYSFUNCTION

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Aims: To model Parkinson's disease (PD) neuropathology in midbrain organoids (MOs) derived from *GBA1*-related PD patients and to test the efficacy of ambroxol on glucocerebrosidase dysfunction and α-synuclein pathology.
Methods: MOs from induced pluripotent stem cells of two patients carrying the L444P *GBA1* variant and three healthy controls were generated with a novel dopaminergic-patterning protocol developed by our group and cultured for 150 days *in vitro* (DIV). MOs at 90 DIV were treated with ambroxol for 10 days. Samples collected in basal conditions and after treatment were analyzed by means of RNA sequencing, immunohistochemistry, Western blot, lipid analysis, calcium imaging, electron microscopy, and enzymatic activity assays. Dopaminergic neuron count was performed in TDE-clarified whole MOs by three-dimensional confocal microscopy analysis to assess neurodegeneration.
Results: MOs displayed features of human midbrain post-natal maturation (*e.g.*, key dopaminergic markers, neuromelanin pigmentation, neuronal lipid profile). Glucocerebrosidase enzymatic activity was reduced in *GBA1*-PD MOs, leading to increased levels of glucosylceramide. In *GBA1*-mutant MOs, misfolded glucocerebrosidase was retained in the endoplasmic reticulum and initiated the unfolded protein response. The reduced number of TH-positive cells versus the total number of NeuN-positive neurons in *GBA1*-PD MOs indicated dopaminergic neuron loss. *GBA1*-mutant MOs displayed detergent-resistant α-synuclein and aggregates of insoluble α-synuclein recapitulating the major defining biochemical, immunohistochemical, and ultrastructural features of Lewy pathology. Ambroxol treatment restored the localization of glucocerebrosidase to the lysosome and reduced the amount of α-synuclein and the load of Lewy-like pathology.
Conclusions: MOs display post-natal mature features, thus holding the potential for modelling age-related physiology and disease. MOs derived from *GBA1*-mutated patients recapitulate biochemical dysfunction and neuropathological hallmarks of PD neuropathology observed in *post-mortem* brains. Our

results support the role of ambroxol as a promising disease-modifying compound in PD.

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SHIFT 01-062

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
2 - 3 April 2025

EARLY SYNAPTIC DYSFUNCTION AND NEUROINFLAMMATION IN ALPHA-SYNUCLEIN MOUSE MODEL OF PARKINSON'S DISEASE

Fabrizio Gardoni[1], Michela Salvadè[1], Maria Mancini[2], Elisa Zianni[1], Maria Italia[1], Monica Diluca[1], Antonio Pisani[2]
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Aims: Multiple mechanisms contribute to Parkinson's Disease (PD) pathogenesis with a clear involvement of synaptic dysfunction, inflammatory events, oxidative stress and mitochondria dysfunctions in disease progression. Accumulating evidence demonstrated that misfolded proteins and inclusions contribute to the pathology of familial and sporadic PD. Alpha-synuclein (α-Syn) is the main component of these inclusions. Increasing evidence recently described the detrimental effects of αSyn fibrils on various neurotransmitter systems and brain regions. Interestingly, these studies demonstrated the toxic effect of αSyn preformed fibrils (αSyn-PFF) on glutamatergic neurotransmission in early stages of disease progression, long before the onset of significant dopaminergic nigrostriatal degeneration. Our group demonstrated that αSyn-PFF induces dendritic spines loss at cortico-striatal synapses, and this event was correlated with reduced post-synaptic availability of both AMPA and NMDA receptors. Conversely, despite evidence that αSyn-PFF can drive early defects at the excitatory glutamatergic corticostriatal synapse, the correlation of these events with behavioral alterations and the precise molecular events underlying these alterations remain unclear and represents the main aim of the present study.
Methods: Here we used α-syn-PFFs mice model allowing for a careful evaluation of the toxic effects induced by α-syn preformed fibrils from early stages of disease. We used combination of confocal imaging, electrophysiology, biochemistry, and behavioral assays.
Results: We performed a detailed analysis of the progression of the disease, focusing both on postsynaptic dysfunctions and the role of early neuroinflammatory events. In particular, we evaluated the efficacy of dimethyl fumarate (DMF), a potent Nrf2 activator, already marketed as an oral drug for relapsing forms of multiple sclerosis, to counteract early α-syn-mediated toxicity.
Conclusions: Data obtained demonstrated a very early molecular, morphological and functional alteration of the corticostriatal glutamatergic synapse in the α-syn-PFFs mice model.

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SHIFT 01-065

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2 - 3 April 2025

ATF4 PROMOTES DOPAMINERGIC NEURODEGENERATION BY ACTIVATING A TRANSCRIPTIONAL PROGRAM THAT INHIBITS MTOR ACTIVITY IN PARKINSON'S DISEASE MODELS

Matthew Demmings, Erica Kane, Elizabeth Tennyson, Kate Hurley, Joy Zhao, Nick Cruickshanks, Victoria Ciz, Jordan Krupa, Stephen Pasternak, Sean Cregan
University of Western Ontario, Robarts Research Institute, London, Canada

Aims: The Integrated Stress Response (ISR) is a protective cell signaling pathway, but during chronic stress, it becomes maladaptive and contributes to neurodegenerative diseases like Parkinson's Disease (PD). Previously, we have shown that ATF4, a key ISR regulator, has been shown to promote dopaminergic neuron loss in PD models. However, how chronic ATF4 activation leads to neurodegeneration remains unclear. This study aims to uncover the mechanisms by which ISR/ATF4 activation drives dopaminergic cell death.
Methods: We investigated ATF4's role in PD neurotoxin (MPP+, 6-OHDA) and α-synucleinopathy models using primary dopaminergic neurons from wildtype and ATF4-deficient mice, as well as *C. elegans* with *atfs-1* loss of function. Neurodegeneration and behavior were assessed in *dat-1* reporter animals and dopamine-mediated Basal Slowing Rate behavior. ATF4 function was studied via transcriptomics, immunofluorescence, in situ hybridization, and biochemical assays. Target genes were manipulated using viral vectors for overexpression and shRNA knockdown.
Results: *C. elegans* lacking the ATF4 ortholog *atfs-1* are resistant to dopaminergic neuron loss and dopamine-regulated behavioral impairments in both neurotoxin and α-synuclein PD models. Importantly, chronic ATF4 activation drives dopaminergic neuron degeneration through sustained inhibition of mTOR. ATF4 achieves this by inducing the transcription of SESN2, DDIT4, and Trib3, which collectively inhibit both mTORC1 and mTORC2 activity. Furthermore, we show that this inhibition of mTOR complexes promotes dopaminergic neuron death by facilitating the expression of PUMA, a pro-apoptotic member of the Bcl-2 family.
Conclusions: We have established that chronic ATF4 activation becomes maladaptive and promotes dopaminergic neurodegeneration by chronically inhibiting mTOR activity. Furthermore, we propose that this signaling pathway may have therapeutic relevance in a range of brain disorders exhibiting chronic ISR activation.

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SHIFT 01-066

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
2 - 3 April 2025

DIGITAL HEALTH TECHNOLOGY FEATURE SPACE OPTIMIZED TO DETECT DISEASE PROGRESSION IN EARLY PARKINSON'S DISEASE UNDER STABLE SYMPTOMATIC TREATMENT

Stefan Lambrecht[1], Bernhard Fehlmann[1], Yulia Gazizova[1], Leo Gschwind[1], Damian Kwasny[1], Florian Lipsmeier[2], Michael Lindemann[2], Marzia Scelsi[3], Thomas Kustermann[1], Ronald Postuma[4], Gennaro Pagano[1], Tania Nikolcheva[1], Werner Popp[1], Kirsten Taylor[1]
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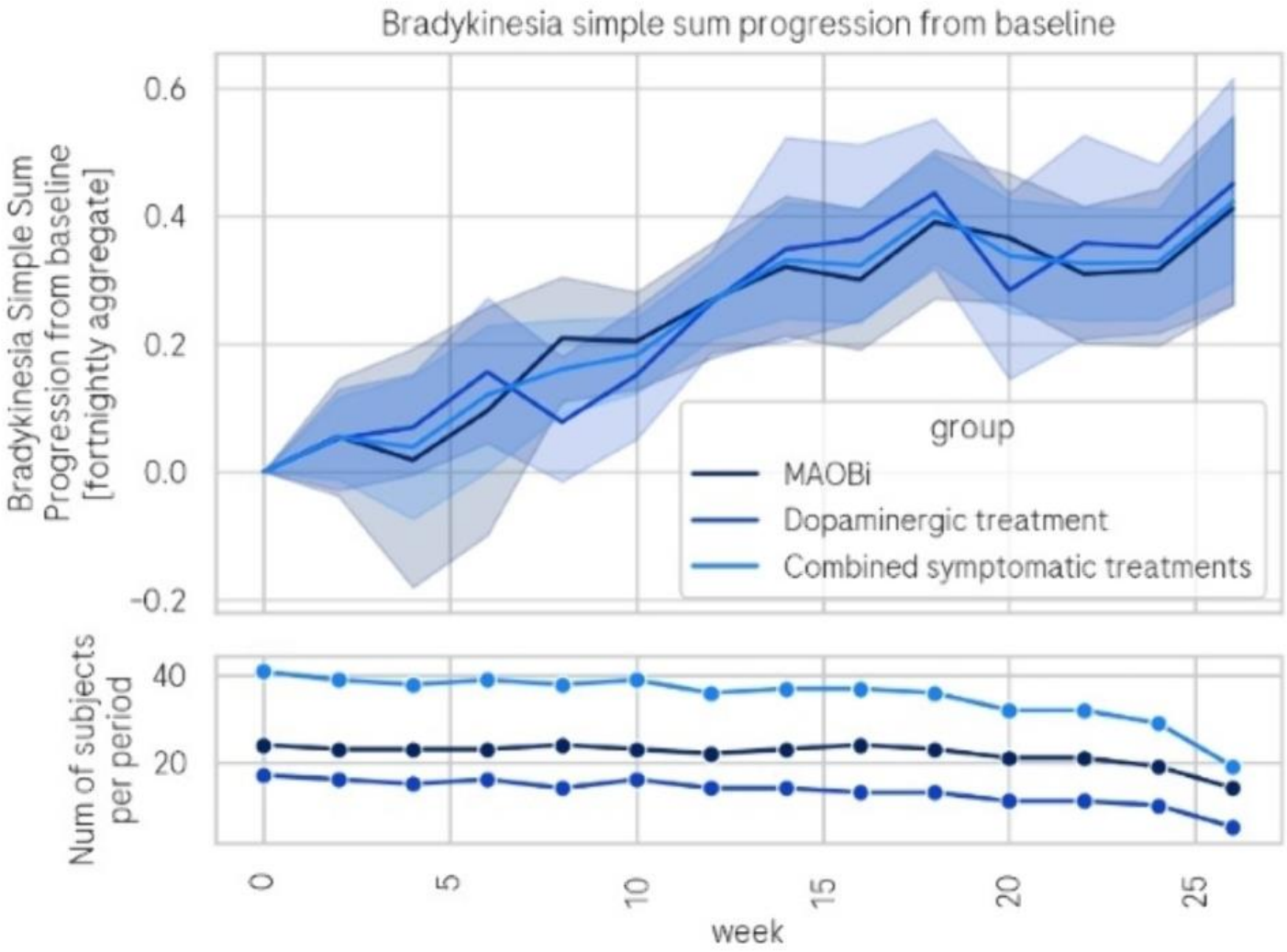
Aims: Assessing disease progression in individuals with early Parkinson's Disease (PD) can be challenging due to the fluctuating nature of the disease and symptomatic treatment masking progression signals. The aim is to develop DHT derived sensor features that are reliable and sensitive to progression in early PD populations under symptomatic treatment.
Methods: Novel DHT features were developed in collaboration with external experts, leveraging data from a subset of individuals with early-stage PD participating in the phase 2 PASADENA study (NCT03100149) or the observational "Parkinson's Disease Biomarker (PDB) Study". From the resulting feature space, a selection was made based on criteria including (1) test-retest reliability (2) sensitivity to progression and (3) selecting one feature per neurobiological concept. Ten features were selected [Table 1]. The five features pertaining to the bradykinesia domain were combined into a Bradykinesia simple sum (BSS) score. Features and scores were evaluated on 41 early-stage PD participants that were on symptomatic treatment (PASADENA placebo: n=24 on MAOBi; data censored at start of new symptomatic treatment; PDB: n=17; on dopaminergic treatment). Intra-class correlations (ICC) quantified baseline test-retest reliabilities. Exploratory, post-hoc linear mixed effects models (LMEs) tested for progression over 26 weeks at uncorrected alpha <=.2.
Results: The majority of the 10 selected features showed high test-retest reliability (median ICC = .87) , 9/10 of which showed sensitivity to progression (p-value < .07) [Table 1], as did the BSS (ICCs = .87; p-value < .001) [Table 1]. Sensitivity to progression of the BSS was present in both the MAOBi-cohort and the dopaminergic treatment cohort [Figure 1].

Table 1. Description and baseline characteristics of the selected features and bradykinesia simple score.

Domain	Symptom/ Functional Impairment	feature	Feature description and expected progression directionality	ICC	LME, 26 weeks, progression, p- value
Upper limb Bradykinesia	Slowness of movement	Hand turning speed median	Median of the average rotation speed over all rotations. Average rotation: mean rotation speed over a single rotation (e.g. max pronation to max supination); slower movements = smaller maximum speed	.94	.03
	Smaller/ restricted movements	Hand turning amplitude median	Median of angular displacements over all rotations (i.e. median turn range). Lower = smaller/reduced range of turns	.93	<.001
	Arrhythmic movements	Speeded tapping intertap interval cv	Coefficient of variation (standard deviation / mean) of time between taps, i.e. intertap interval corrected for speed; higher score = lower rhythmicity	.84	.04
Lower limb Bradykinesia	Slowness of gait	U-turn: turn speed median	Median turn speed among all turns. Lower = slower turns	.91	.002
	Arrhythmic movements	U-turn step time cv	Coefficient of variation of all step times; main conceptual difference to MAD: standardization by the mean. Lower = smoother / more regular movement.	.72	.06
Bradykinesia	Bradykinesia simple sum		Score combining the aforementioned 5 features, encompassing upper and lower limb bradykinesia. Higher = worse	.87	<.001
Speech	Vocal Volume	Free speech active speech level	Average power level of the digital active speech microphone signal, expressed in decibels relative to overload (dBov). Only test segments with detected speech activity are considered in the computation. Lower = speaking quieter.	.93	.002
	Vocal articulation	Free speech 2nd formant range	Difference between 95th and 5th percentile of the second formant trace estimated over voiced speech. Formant traces are computed over all test repeats within a test run to increase the reliability of the estimate. As vowel space continues to centralize, the second formant range is expected to shrink	.86	.07
	Vocal expressiveness	Free speech volume chunks mean std	Average volume standard deviation computed over individual voice speech segments, expressed in dB. The implementation ensures the feature is more robust to potential sudden changes in volume over the recording. Reduced expressiveness: results in reduced variability of volume and more monotone speech	.66	.003
	Vocal raspiness/hoarseness	Sustained phonation CPP mean	Average cepstral peak prominence calculated over voiced speech (segments of the microphone signal containing voiced sounds), in dB. Cepstral Peak Prominence (CPP) measures how strongly harmonic the speech is. Lower = speech gets more hoarse/breathy due to reduced vocal folds control.	.93	.034
	Vocal Volume decay	Sustained phonation volume decay (slope)	Drop of volume between start and end of longest phonation segment, normalized by the length of this segment, in decibels/second.	.83	.257

Figure 1: Progression plot on Bradykinesia simple sum



Conclusions: These preliminary results support the use of the selected DHT features for frequent and remote monitoring of early PD under symptomatic treatment.

SHIFT 01-068

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / DRUG DELIVERY SYSTEMS
2 - 3 April 2025

EXOSOME-MEDIATED DELIVERY OF PARKIN RESCUES MITOCHONDRIAL DYSFUNCTION IN PARKINSON'S DISEASE MODELS.

Chanhee Kim, Dong-Gyu Jo
Sungkyunkwan University, School Of Pharmacy, Suwon-si, Korea, Republic of

Aims: Parkinson's disease (PD) is characterized by impaired dopamine release and mitochondrial dysfunction, often associated with mutations in the Parkin (PRKN/PARK2) gene. Parkin, an E3 ubiquitin ligase, plays a crucial role in maintaining mitochondrial quality, making it a promising therapeutic target. In this study, we developed a novel strategy to deliver Parkin protein using engineered extracellular vesicles (EVs) equipped with photocleavable proteins, to enabling light-induced release of Parkin to restore mitochondrial function in PD models.
Methods: We engineered EVs to incorporate photocleavable proteins between Parkin and an exosomal membrane protein, allowing for the precise light-induced release of Parkin. Upon exposure to light of a specific wavelength, Parkin was effectively released into exosomes. The functionality of these Parkin-loaded EVs were assessed by evaluating their ability to enhance damaged mitochondria clearance and alleviate oxidative stress in PD models.
Results: Our results demonstrate that the light-induced release of Parkin from engineered EVs significantly improved mitochondrial quality and reduced oxidative stress. The Parkin EVs enhanced the removal of damaged mitochondria, and alleviated mitochondrial dysfunction in PD models.
Conclusions: This study presents a novel approach to addressing mitochondrial dysfunction in PD through EV-mediated Parkin delivery. The findings provide compelling evidence for the potential of EV-based therapeutic intervention for early-onset autosomal recessive PD linked to mitochondrial defects.

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SHIFT 01-074

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY
2 - 3 April 2025

FOOT TACTILE STIMULATION STRATEGIES FOR ALLEVIATING PAIN IN PARKINSON'S DISEASE: A FUNCTIONAL CONNECTIVITY STUDY

Karel Joineau[1], Christine Brefel-Courbon[2], Emeline Descamps[1], Mathilde Boussac[1], Estelle Harroch[2]
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Aims: The aim was to compare changes in pain intensity in PD patients who benefited either Foot Reflexology or Sham Massage, and to identify potential biomarkers of response based on functional connectivity.
Methods: Thirty PD patients with chronic pain participated in a double-blind, randomized controlled trial, receiving four sessions of either FR or SM, three weeks apart. The primary outcome was the change in pain intensity, measured by the Visual Analogue Scale (VAS), from the first session to three weeks after the fourth session. Secondary outcomes included comparing changes in other pain parameters, such as the nociceptive threshold. Cerebral functional connectivity was evaluated as an exploratory outcome.
Results: Pain intensity was reduced in both groups, with no significant differences in VAS scores between the FR and SM groups. However, distinct connectivity patterns in the medial pain system were observed in patients who responded well to both therapies, compared to non-responders.
Conclusions: FR was not more effective than SM in alleviating chronic pain in PD patients. The differences in connectivity patterns within the medial pain pathway may underlie the response to foot tactile stimulation (FR and SM).

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SHIFT 01-077

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2 - 3 April 2025

INCREASED BURDEN OF RARE VARIANTS ACROSS GENE EXPRESSION NETWORKS PREDISPOSES TO SPORADIC PARKINSON'S DISEASE

Eleanna Kara[1], Katelyn Vandersleen[1], Jiya Mody[1], Elena Eubanks[1], Neha Patel[1], Benjamin Sacks[1], Mahsa Darestani Farahani[1], Jinying Wang[1], Jordan Elliott[1], Nora Jaber[1], Fulya Akçimen[2], Sara Bandres-Ciga[2], Fadel Helweh[3], Jun Liu[1], Sanjana Archakam[1], Robert Kimelman[1], Bineet Sharma[1], Philip Socha[1], Ananya Guntur[1], Tim Bartels[4], Ulf Dettmer[5], M Maral Mouradian[1], Amir Bahrami[3], Wei Dai[1], Jean Baum[1], Zheng Shi[1], John Hardy[4]
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Aims: Through a recent high throughput screen, we identified two genes whose knock-down modifies alpha-synuclein propagation: TAX1BP1, encoding an autophagy receptor implicated in Parkin/PINK1-mediated mitophagy, and ADAMTS19, a metalloproteinase involved in the proteolytic cleavage of alpha-synuclein. We undertook follow up experiments and analyses to understand the mechanism with which those genes underlie the pathogenesis of Parkinson's disease (PD).
Methods: We used an M17D cell line expressing triple mutant (E35K+E46K+E61K) "3K" alpha-synuclein that spontaneously forms inclusions entrapping membranes, vesicles and lipids, which are key ultrastructural features of Lewy bodies. Gene knock-down of TAX1BP1 or ADAMTS19 followed by cell biology experiments were used to identify functions whose dysregulation impacts alpha-synuclein inclusions. Finally, genomic and transcriptomic analyses were used to establish the physiological relevance of our findings.
Results: Knock-down of TAX1BP1 or ADAMTS19 resulted in a significant increase in the number of alpha-synuclein inclusions and modulated the propensity of alpha-synuclein to phase separate into inclusions and to interact with lipids, which adds to a growing body of evidence that those pathways are dysregulated in PD. RNA sequencing revealed a number of genes that are differentially expressed after knocking down TAX1BP1 or ADAMTS19. Analysis of whole genome sequencing data from thousands of individuals showed that patients with PD carry an increased frequency of risk variants in those differentially expressed genes in comparison to healthy controls. Finally, Weighted Gene Co-expression Network Analysis (WGCNA) showed that the differentially expressed genes cluster within modules in the basal ganglia and the cortex, which are regions that develop high degrees of alpha-synuclein pathology.
Conclusions: This work indicates the promise of "functional genomics" screens to understand the genetic architecture and pathogenesis of neurodegenerative diseases.

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SHIFT 01-080

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2 - 3 April 2025

ASSOCIATION OF GLYMPHATIC SYSTEM MARKERS WITH SLEEP DISTURBANCES AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE.

Edoardo De Natale[1], Alana Terry[1], Heather Wilson[1], Holly Wright[1], Julie Wollaston Moss[1], Laurence Knowles[1,2], Flavia Niccolini[3,4], Sura Albayati[5], Daniel Sheehan[6], Marios Politis[1]
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Aims: The glymphatic system, which is regulated during sleep, has recently been linked to the pathophysiology of neurodegenerative disorders. This study explores the association between sleep quality, cognitive function, and glymphatic system molecular markers in individuals with Parkinson's disease (PwP).
Methods: 173 PwP (mean age 67.99±7.88) underwent a 15-night home sleep recording using actigraphy, and an assessment with a battery of cognitive tests including the Cambridge Neuropsychological Test Automated Battery (CANTAB). Participants had venous blood collection for measurement of AQP4 plasmatic levels. PwP were stratified according to established cut-offs of actigraphy sleep parameters: total sleep time, sleep latency, sleep efficiency (SE), and wakefulness after sleep onset (WASO).
Results: Preliminary analyses in the total cohort demonstrated that PwP with reduced SE ($p=0.026$) and WASO ($p=0.05$) had worse cognitive MoCA scores. Those patients (n=39) were subsequently stratified as "bad" sleepers. A subgroup of 70 PwP, showing no abnormalities on neither SE nor WASO, served as control "good" sleepers. Bad sleepers displayed longer disease duration, worse disease severity, and higher degree of non-motor symptoms burden (all $p<0.05$). In the cohort of bad sleepers, higher plasma AQP4 correlated with worse global cognition on MoCA ($R=-0.41$, $p=0.05$); worse performances on CANTAB Rapid Visual Processing test for attention ($R=0.52$ $p=0.027$); and decreased sleep efficiency ($R=-0.58$, $p=0.003$).
Conclusions: Poor sleep quality in Parkinson's patients is linked to worse cognitive performance. Higher levels of glymphatic markers AQP4 are associated with both sleep disturbances and cognitive decline, suggesting glymphatic dysfunction may play a role in these processes.

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SHIFT 01-081

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2 - 3 April 2025

RECENT TEMPORAL TRENDS IN PARKINSON'S DISEASE INCIDENCE, PREVALENCE, AND SEX DIFFERENCES IN FRANCE: A DECADE-LONG STUDY

Octave Guinebretiere[1], Fen Yang[2], Dang Wei[3], Fang Fang[2], Jean-Christophe Corvol[4], Thomas Nedelec[1]
[1]Paris Brain Institute, Icm, Paris, France, [2]Institute of Environmental Medicine, Stockholm, Sweden, [3]Karolinska Institutet, Institute Of Environmental Medicine, Stockholm, Sweden, [4]Sorbonne Université, Institut du Cerveau, Paris, France

Aims: This study assessed trends in the incidence, prevalence, and male-to-female ratio of Parkinson's disease (PD) in France. It also explored changes in the mean age of the PD population, age at death, and age at diagnosis in incident cases.
Methods: We analyzed data from the French National Health Data System (SNDS), covering 98% of the French population from 2011–2022. PD cases were identified using ICD-10 diagnostic codes and anti-parkinsonian drug prescriptions. Age- and sex-standardized incidence and prevalence rates were calculated using 2011 as the reference. Poisson regression was used to compute incidence rate ratios (IRRs) and their 95% confidence intervals (CIs). The male-to-female (M/F) ratio was derived from standardized rates for each year.
Results: A total of 442,666 PD cases were identified. Crude prevalence increased from 2.88 to 3.35 cases per 100,000 person-years, while prevalence adjusted for aging rose until 2018, then declined. The crude incidence rate remained stable. After standardizing for aging, a decreasing incidence trend emerged (IRR 0.984, 95% CI 0.983–0.985). The M/F ratio for incidence and prevalence increased from 1.21 and 1.03 to 1.43 and 1.12, respectively. Mean age at death rose by one year from 2011 to 2019, then stabilized. Mean age of PD cases and age at diagnosis also increased slightly.
Conclusions: After adjusting for population aging, PD prevalence appears to be stabilizing, challenging recent projections. The rising male predominance suggests potential sex-specific risk factors in PD development.

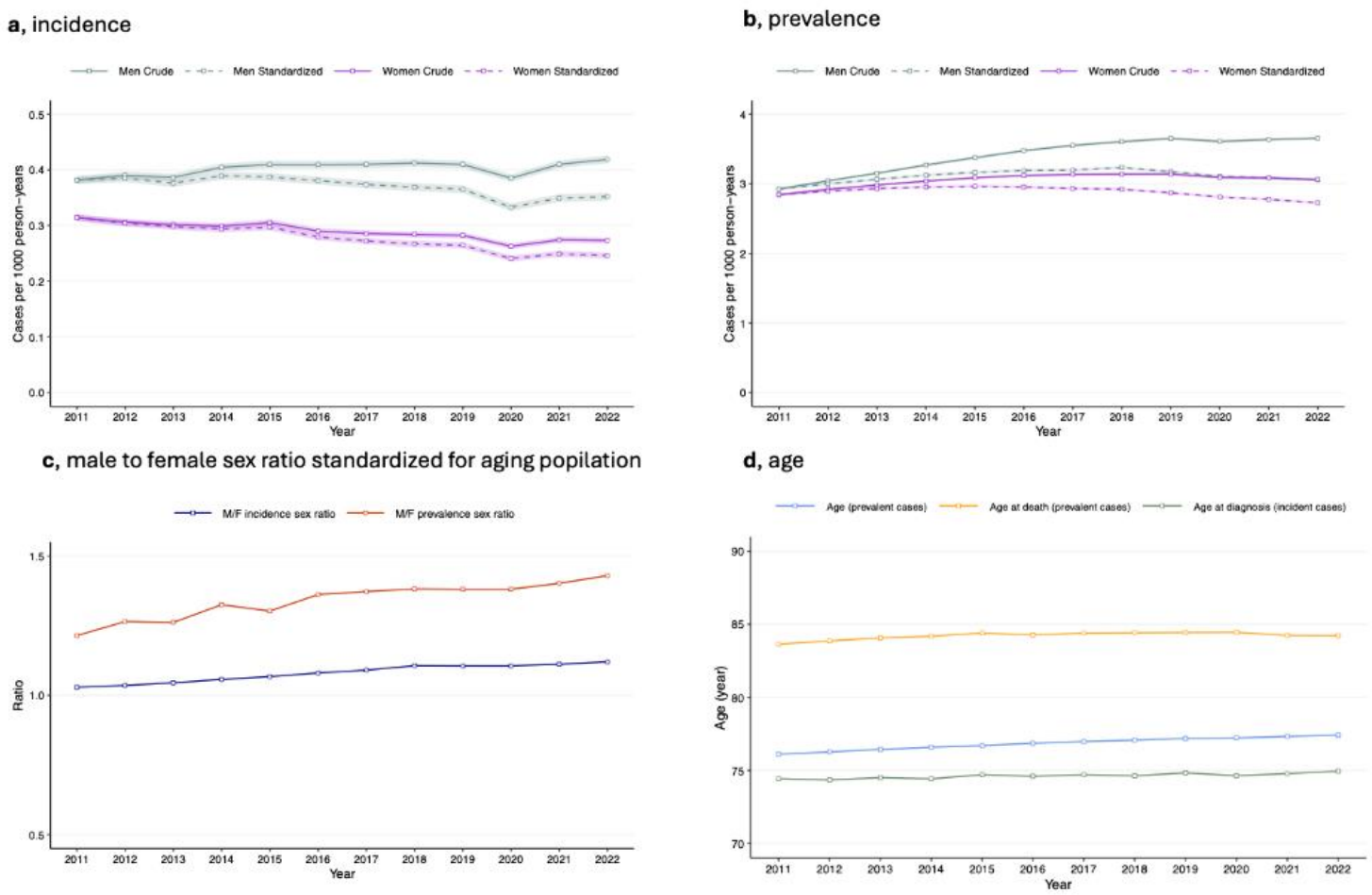

Figure 1. Recent temporal trends in the incidence (a), prevalence (b), and male-to-female ratio (c) of Parkinson's disease (PD) in France. Additionally, we present trends in the mean age of the overall PD population, mean age at death, and mean age at diagnosis in incident PD cases (d).

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SHIFT 01-087

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
2 - 3 April 2025

NOVEL DIGITAL MEASURES OF REACTION TIME AND DRAWING SPEED: A FEASIBILITY STUDY IN PATIENTS WITH NEURODEGENERATIVE DISORDERS AND IMMUNE MEDIATED INFLAMMATORY DISORDERS.

Francesca Cormack[1], Valentina Ticcinelli[2], Nicholas Taptiklis[1], Alexander Kaula[1], Walter Maetzler[3], Ralf Reilmann[4], Robert Latzman[5], Fai Ng[6], Victoria Mcrae[6], Kristen Davies[6], Janneke Van Der Woude[7], Julian Fierrez[8], Teemu Ahmaniemi[9], Meenakshi Catterjee[10]
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Aims: The IDEA-FAST consortium aims to further measurement of fatigue by capturing rich digital data from Parkinson's Disease, Huntington's Disease, and immune mediated inflammatory disorder (IMID) cohorts. Digital technologies can capture aspects of performance not available in conventionally administered assessments, which may increase sensitivity to disease or fatigue. Here, we explore cross-cohort differences in features from digital cognitive tasks, and their relationship to measures of disease severity and fatigue.
Methods: The sample comprised patients with neurodegenerative disease (n=33), IMID, (n=63), and healthy volunteers (n=38). Cognition Kit Digit Symbol Substitution test (DST) and the CANTAB Psychomotor Vigilance Test (PVT) were assessed on smartphones daily over ten days. For DST we calculated total correct responses over 90 seconds, and two measures unique to the digital DST: reaction time (time to initiate drawing) and movement time (time to complete drawing). We analysed cohort differences and relationship to baseline MoCA, Modified Fatigue Impact Scale measures of disease severity MDS-UPDRS.
Results: Significant group differences were observed in all cognitive measures after adjusting for age. DST reaction time task was slower for both PD and HD groups compared to controls and IMID. In contrast, patients with PD showed slower movement time than all other groups, including those with HD, who were not different from controls. In the PVT task, the opposite pattern was observed, with patients with HD showing slower RT relative the other groups, including those with PD, who were not different to controls.
Conclusions: In this small sample, measures of reaction time, movement time and vigilance, derived from brief digital assessments, may provide insights into the cognitive processes underpinning performance in different neurodegenerative diseases not evident in global accuracy measures.

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SHIFT 01-088

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
2 - 3 April 2025

ALGORITHMIC ASSESSMENT OF TREMOR RESPONSE DYNAMICS TO LEVODOPA IN PARKINSON'S DISEASE: A DATA-DRIVEN APPROACH TO DIAGNOSIS AND PROGRESSION MONITORING

Tiffany Jansen, Aiden Arnold, Trevor Haynes, Carrolee Barlow, Ro'Ee Gilron
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Aims: Generate algorithmic approaches to detect, quantify, and assess the dynamics of rest tremor response to levodopa in PD.
Methods: We evaluated 377 PD patients to assess the dynamics of tremor responsiveness to levodopa administered three different times of day: after waking, mid-day, and last dose of day. Using a validated tremor algorithm (MM4PD), we monitored tremor at one-minute resolution during activities of daily living (ADL). Tremor response was characterized by the time to reach a predetermined reduction in rest tremor, as well as the area under the curve (AUC) representing overall reduction in tremor. We further assessed tremor dynamics across levels of severity, from clinically meaningful to subclinical. For each levodopa medication dose, we computed the levodopa equivalent dose (LED) associated with specific dynamics of tremor reduction.
Results: Tremor response dynamics to levodopa were highly variable and somewhat dependent on tremor severity, with the morning dose generally showing the most consistent impact. Factors like phenotype, years since diagnosis, medication timing, and regimen complexity also influenced the response.
Conclusions: Unlike previous studies primarily focused on peak amplitude of tremor in response to a levodopa dose, this study examined the temporal dynamics of tremor reduction. Previous research highlighted tremor as the clinical sign with the highest odds ratio for predicting phenoconversion before diagnosis, and symptom response to levodopa is one of the cardinal clinical indicators for diagnosing PD. By integrating LED, tremor response dynamics, and years since diagnosis, our findings suggest this approach could ease the diagnostic burden on physicians and provide valuable insights into disease progression.

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SHIFT 01-093

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / FUNCTIONAL MRI
2 - 3 April 2025

HIGHER NETWORK ATTACK TOLERANCE LEVELS PRESERVE MOTOR FUNCTION IN PARKINSON'S DISEASE

Adrian Asendorf[1], Magdalena Banwinkler[1], Verena Dzialas[1], Kathrin Giehl[1,2], Hendrik Theis[1,3], Elena Guerra[1], Thilo Van Eimeren[1,3], Merle Hoenig[1,2]
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Aims: We tested whether individual functional network attack tolerance (NAT) serves as biological substrate of motor-reserve in Parkinson's disease (PD) by linking NAT to lifetime physical activity (PA) and general motor-performance.
Methods: Data from 25 patients with PD (Age= 62.25+-7.89; Sex(M/F)= 18/7) were included, comprising: 1) Lifetime PA, using the Historical Leisure Activity Questionnaire and accounting for activity intensity; 2) motor-performance as a composite z-score based on various motor tests, standardized to 39 healthy controls; 3) putaminal dopamine (DA)-integrity, derived from DaT-SPECT; 4) resting-state MRI. MRI data was used to construct a global network comprising 300 regions-of-interest, and four subnetworks (i.e. somatosensory (SMN), frontoparietal, attention, default-mode-network) at eight density thresholds (i.e. allowing top 10%-50% of connections of the network). Each of these networks was attacked by removing the network's nodes in descending order of their connectedness. After each node removal, the network's global efficiency was computed to define NAT. Global NAT and subnetwork NATs were submitted as dependent variables into cross-classified linear-mixed-models (LMM), including motor-performance, PA, putaminal DA-integrity, age, and sex as predictors, allowing for two random intercepts. Finally, we tested the interactive effect of PA and mean network NAT on motor-performance. Correction for multiple comparisons was performed (q-value).
Results: The LMMs yielded a significant positive effect of age (β=.04; p<.01; q=.04) and motor-performance (β=.08; p=.02; q=.04) on global NAT. For SMN-NAT, positive effects of motor-performance (β=.11; p<.01 ;q=.01) and DA-integrity (β=.58; p=.02; q=.08), and a negative effect of PA (β=-.002; p<.01; q=.02) were found. Furthermore, we observed a positive interaction of PA and SMN-NAT on motor-performance.
Conclusions: Tolerance of the SMN towards attacks, such as neurodegeneration, depends on DA-integrity and may be supported by lifetime PA in early PD.

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SHIFT 01-095

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2 - 3 April 2025

CENTAMINES: STANDARDIZATION OF DOPAMINERGIC IMAGING MARKERS FOR CLINICAL TRIALS

Roger Gunn[1], Zhen Fan[1], Graham Searle[1], Gaia Rizzo[1], Patrick Cella[2], Robert Comley[3], Gregory Klein[4], Luca Passamonti[5], Cristian Salinas[6], Adam Schwarz[2], Leonardo Iaccarino[7], Gilles Tamagnan[8], Jaime Eberling[9], Ken Marek[10], John Seibyl[8]
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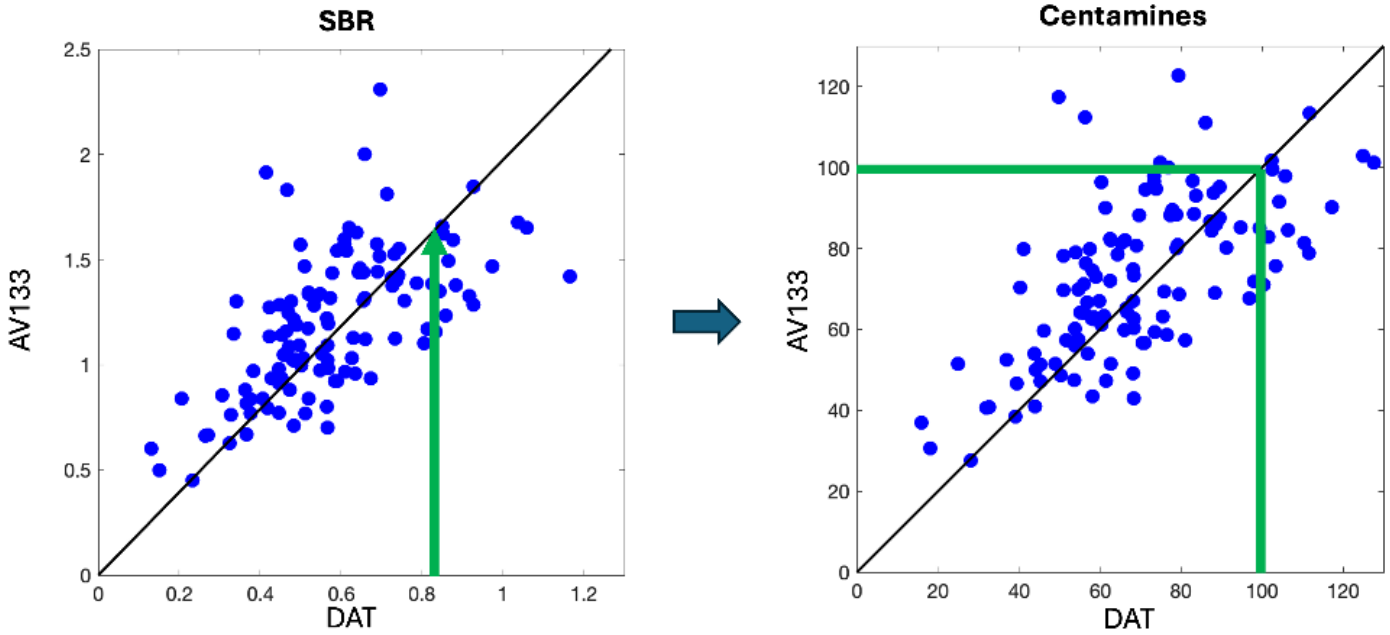
Aims: To define and operationalize a "Centamine" scale for interoperability of different molecular imaging agents targeting dopaminergic neuronal loss in Parkinson's disease (PD) and related disorders. The approach is analogous to the development of the Centiloid scale for Amyloid imaging markers which has had significant impact on the successful development of disease modifying drugs for Alzheimer's disease.
Methods: Markers of dopaminergic neuronal loss, like [^{123}I]Ioflupane (DAT) SPECT and [^{18}F]AV133 (VMAT2) PET, are central outcome measures in clinical trials of novel PD therapies and are used for subject eligibility and longitudinal assessment of disease modification. The ability to use multiple dopaminergic imaging markers as part of a single clinical trial would significantly expand access to imaging infrastructure, increase the power and speed of clinical trials whilst also simplifying their deployment and execution. The Centamines methodology is presented using head to head [^{18}F]AV-133 PET and DaT SPECT data from the PPMI sub-study (n=41 subjects had paired scans over a period of up to 4 years [n=2x123 scans]). In addition, healthy control DaT SPECT data from 184 subjects were used. SBR values were calculated for all scans using a quantitative image analysis pipeline.
Results: A strong linear relationship was obtained and the mapping between the two imaging markers was determined for the putamen as; AV133 SBR = 1.97 DAT SBR (95% CI = 1.88, 2.07) This enabled the mapping to a common scale, termed Centamines, using the mean healthy control DaT SBR value to anchor the scale at 100% (see Figure).



Conclusions: The Centamine scale will allow for the harmonisation of PD imaging markers measuring dopaminergic neuronal loss.

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SHIFT 01-096

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

REM WITHOUT ATONIA INDEX IS INVERSELY CORRELATED WITH CAUDATE ASYMMETRY IN DEMENTIA WITH LEWY BODIES

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Aims: Alpha-synucleinopathies, such as Dementia with Lewy Bodies (DLB), exhibit clinical heterogeneity, potentially due to distinct pathways of Lewy body accumulation. REM sleep behavior disorder (RBD) has been often associated with early brainstem involvement (i.e. "body-first" phenotype), while asymmetric nigrostriatal denervation has been suggested as a marker of “brain-first” phenotype. This study explored the relationship between polysomnographic features and nigrostriatal denervation, as assessed by DaT-SPECT, in patients with DLB.
Methods: We enrolled 13 DLB patients (69.71±8.39 years) diagnosed using McKeith 2017 criteria. All patients underwent clinical examination, polysomnography (PSG) to assess REM without atonia (RWA), and DaT-SPECT imaging. Quantitative DAT-SPECT analyses were performed using DaT-QUANT software, and Pearson's correlation was used to assess relationships between PSG findings and DAT-SPECT measures.
Results: Of the 13 patients, 11 showed evidence of RWA on PSG and 11 had abnormal DAT-SPECT findings. We found a significant positive correlation between sleep efficiency and striatal asymmetry (r=0.866, p=0.001), and a negative correlation between sleep latency and putamen asymmetry (r=-0.608, p=0.036). Additionally, caudate asymmetry was inversely correlated with the RWA index (r=-0.690, p=0.019) and positively correlated with motor symptoms (UPDRS, r=-0.697, p=0.025).
Conclusions: These findings suggest that patients with a higher RWA index (indicative of RBD) tend to have more symmetric nigrostriatal degeneration, aligning with the "body-first" phenotype. Conversely, those with lower RWA index and more pronounced motor symptoms show greater asymmetry in nigrostriatal denervation, consistent with a "brain-first" phenotype. Our results support the notion of two distinct pathological pathways in DLB, characterized by differing patterns of sleep disturbances and motor symptoms.

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SHIFT 01-097

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

HOUSTON, WE HAVE AI PROBLEM! QUALITY ISSUES WITH NEUROIMAGING-BASED ARTIFICIAL INTELLIGENCE IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

Verena Dzialas[1], Elena Doering[1], Helena Eich[1], Antonio Strafella[2], David Vaillancourt[3], Kristina Simonyan[4], Thilo Van Eimeren[1]
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Aims: Recent neuroimaging studies increasingly use AI to address challenges in Parkinson's disease (PD) diagnosis, prognosis, and intervention. With the growing accessibility of AI libraries, an in-depth understanding of the underlying algorithms is no longer essential for implementation. However, ensuring methodological standards is critical for the generalizability of results. Therefore, we systematically reviewed neuroimaging-based AI studies in PD and assessed their methodological validity.
Methods: A PubMed search yielded 810 studies, of which 244 were included that investigated the utility of neuroimaging-based AI for PD diagnosis, prognosis or intervention. We systematically categorized studies by outcomes and rated them with respect to five minimal quality criteria (MQC) pertaining to data splitting, data leakage, model complexity, performance reporting and indication of biological plausibility.
Results: We found that the majority of studies aimed to distinguish PD from healthy controls (54%) or atypical Parkinsonian syndromes (25%), while prognostic or interventional studies were sparse. Only 20% of evaluated studies passed all five MQC, with data leakage, non-minimal model complexity and reporting of biological plausibility as the primary factors for quality loss. Data leakage was associated with a significant inflation of accuracies. Very few studies employed external test sets (8%), where accuracy was significantly lower, and 19% of studies did not account for data imbalance. MQC adherence was low across all observed years and journal impact factors.
Conclusions: The significant number of studies failing to meet MQC highlights the need for strengthening interdisciplinary collaborations to enhance clinical utility and methodological quality. Beyond our MQC set, criteria such as code sharing, graphical analysis pipelines, addressing data imbalance, using external test sets, and end-to-end solutions are vital for improving the interpretability, generalizability, and clinical utility of future AI applications in neuroimaging for PD.

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SHIFT 01-101

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
2 - 3 April 2025

OPTIMIZING SPECIFICITY OF PET TRACERS FOR PROTEIN AGGREGATES: A MULTILEVEL APPROACH FROM IN VITRO SCREENING TO IN VIVO VALIDATION

Daniel Bleher[1], Ann-Kathrin Grotegerd[1], Ran Sing Saw[1], Ioannis Papadopoulos[1], Felix Schmidt[2], Andrei Leonov[2,3], Daniel Weckbecker[2], Madhushree Pethe[1], Sergey Ryazanov[2,3], Viktoria Ruf[4], Andreas Maurer[1], Christian Griesinger[3], Armin Giese[5], Kristina Herfert[1]
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Aims: Accurate *in vivo* quantification of aggregates of misfolded proteins is essential for early diagnosis, disease monitoring, and therapy evaluation in neurodegenerative diseases (NDDs). The development of PET tracers for misfolded proteins, such as alpha-synuclein, faces significant challenges due to co-pathologies of other misfolded proteins and potential off-target binding to enzymes like monoamine oxidases, receptors, and neuromelanin. This study presents a multi-tiered compound screening workflow, designed to improve the diagnostic precision of novel PET tracers and validate target engagement for clinical drug candidates, such as emrusolmin.
Methods: Initial compound screening for ligand specificity and selectivity was performed using radioligand binding assays on synthetic fibrils, followed by (micro)autoradiography and immunohistochemistry (IHC) on human brain tissue from synuclein- and tauopathy cases. Blocking studies using micro- and macro-autoradiography were conducted to assess specificity for on- and off-targets. In vivo studies on tracer pharmacokinetics were performed, as well as baseline scans and blocking studies in rodent models, including fibril-injection rat models and a A30P alpha-synucleinopathy mouse model. A CEREP panel was employed to rule out unexpected off-targets.
Results: Despite structural differences between synthetic and brain-derived fibrils, screening with reference compounds validated their usefulness in evaluating selectivity. A combination of high resolution (micro)autoradiography and IHC confirmed precise target engagement, with K_D and IC_{50} values determined on targets. *In vivo* studies demonstrated binding specificity and the ability to distinguish between alpha-synuclein aggregates and off-targets, highlighting the potential clinical applications.
Conclusions: This preclinical tracer development workflow allowed us to confirm the target engagement of the drug candidate in clinical trials, highlighting its potential for diagnosing synucleinopathies and evaluating alpha-synuclein-targeted therapies using PET. This approach will ultimately advance the precision and effectiveness of NDD diagnostics and treatments.

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SHIFT 01-102

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
2 - 3 April 2025

COMBINING D-BETA-HYDROXYBUTYRATE (DBHB) AND NICOTINAMIDE RIBOSIDE (NR) WITH EXERCISE IMPROVES BRAIN ENERGETICS IN PARKINSON'S (PD) DISEASE: RESULTS OF A PILOT STUDY

Stephen Cunnane[1], Mélanie Fortier[1], Valérie St. Pierre[1], Karine Groulx[1], Christian-Alexandre Castellano[1], Etienne Croteau[1], Marie-Christine Morin[1], Christian Bocti[1], Bernard Cuenoud[2]
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Aims: Compared to age-matched healthy controls, global brain glucose extraction is at least as impaired in PD as in Alzheimer disease (AD). Whether brain ketone extraction is affected in PD is unknown. Exercise improves some functional outcomes in PD and increases brain ketone uptake in AD. Ketones and NR may also be neuroprotective. This Phase 1 trial (NCT04322461) aimed to assess whether combining DBHB+NR with exercise (DBHB+NR+Ex) would have an additive benefit for brain energy metabolism in PD over DBHB+NR alone.
Methods: N=10 PD were recruited according to MDS criteria. They continued their prescribed medication and all received DBHB+NR+Ex: two doses of DBHB+NR/day (at breakfast and supper) providing a total of 24 g/day DBHB + 1 g/day NR, plus supervised, moderate, aerobic exercise 3 d/wk for 2 months. Ketone (^{11}C-acetoacetate) and FDG-PET and cognitive and physical evaluations were done after a single dose of DBHB+NR before starting the intervention and again after the 2-month intervention.
Results: At 2 months, DBHB+NR+Ex raised plasma ketones 1.6-fold more than the single dose of DBHB+NR and by 65-fold vs. baseline. DBHB+NR+Ex raised global brain ketone uptake by 1.5-fold more than the single dose of DBHB+NR and by an estimated 22-fold vs. baseline (μmol/100g/min), with a trend towards higher FDG uptake in the Substantia Nigra ($p=0.09$). DBHB+NR+Ex increased attention and psychomotor speed by 17% on the Cantab test (sec; $p<0.05$). Measures of physical performance, blood pressure and plasma metabolites did not change post-intervention.
Conclusions: This pilot study provides three novel features of brain energy metabolism in PD: (i) a possible improvement in energy metabolism by the Substantia Nigra, (ii) increased ketone uptake on DBHB+NR alone, (iii) 50% higher plasma ketones and brain ketone uptake with DBHB+NR+Ex vs. DBHB+NR alone.

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SHIFT 01-103

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
2 - 3 April 2025

ENHANCING PET TRACER DEVELOPMENT FOR NEURODEGENERATIVE DISEASES USING A COMPREHENSIVE WORKFLOW FOR AMYLOID FIBRIL PRODUCTION, QUALITY CONTROL, AND LIGAND SCREENING

Ann-Kathrin Grotegerd[1], Daniel Bleher[1], Benedikt Reith[1], Felix Schmidt[2], Myeongkyu Kim[3], Anneli Vollert[4], Andrei Leonov[2,3], Sergey Ryazanov[2,3], Christian Griesinger[3], Andreas Maurer[1], Armin Giese[5], Kristina Herfert[1]
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Aims: Accurate *in vivo* detection and characterization of protein aggregates are critical for understanding the pathology of neurodegenerative diseases (NDDs). For efficient PET tracer development, chemical compound libraries are screened towards binding specificity and selectivity using recombinant or brain-derived human fibrils in *in vitro* binding assays. Here, we present a workflow for amyloid fibril production and quality control for screening of large compound libraries.
Methods: Fibril monomers of α-synuclein (αSYN), amyloid-β ($A\beta_{1-40}$ and $A\beta_{1-42}$) and tau (2N4R-Tau_{441}) were transferred to the corresponding aggregation buffer and fibrils were produced in a controlled aggregation phase in the presence and absence of lipids. Quality control was performed using Thioflavin T (ThT) fluorescence to confirm the presence of fibril-specific secondary structure and negative staining transmission electron microscopy (TEM) to assess fibril length and morphology. Fibrils were then screened by radioligand saturation binding assays using tritiated reference compounds such as [^{3}H]MODAG-005, [^{3}H]PiB, and [^{3}H]MK-6240 as positive controls. Novel F-18 tracer candidates were subsequently characterized via radioligand competition assays.
Results: Amyloid fibril aggregation kinetics could be successfully monitored with ThT and showed an increase in fibril-specific secondary structure over time. TEM confirmed typical fibril morphology and length. Radioligand saturation assays revealed evidence for ligand-specific binding sites with B_{max} and K_d values in agreement with the literature. In addition, novel F-18 tracer candidates screened by radioligand competition binding assays were identified and selected for further development.
Conclusions: The use of binding assays, alongside ThT fluorescence assays and TEM, confirmed the successful production of structurally consistent fibrils. The established workflow not only supports the reproducible production of NDD-relevant protein fibrils, but also increases the reliability of subsequent binding assays, thus enabling the successful characterization of novel tracer candidates.

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SHIFT 01-113

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

DETERMINING THE DIAGNOSTIC ACCURACY OF PLASMA PTAU181, PTAU217, AB42/40, GFAP, AND NFL FOR DETECTING AMYLOIDOSIS IN A-SYNUCLEINOPATHIES

Alena Smit[1], Laia Montoliu-Gaya[2], Edward Wilson[1], Nicholas Ashton[2,3,4,5], Burak Arslan[2], Melanie Plastini[1], Christina Young[1], Joseph Winer[1], Marian Shahid-Besanti[1], Hillary Vossler[1], Veronica Ramirez[1], Geoffrey Kerchner[6], Katrin Andreasson[1], Victor Henderson[1], Thomas Montine[7], Lu Tian[8,9], Elizabeth Mormino[1], Henrik Zetterberg[2,10,11,12], Kathleen Poston[1,13], Carla Abdelnour[1]
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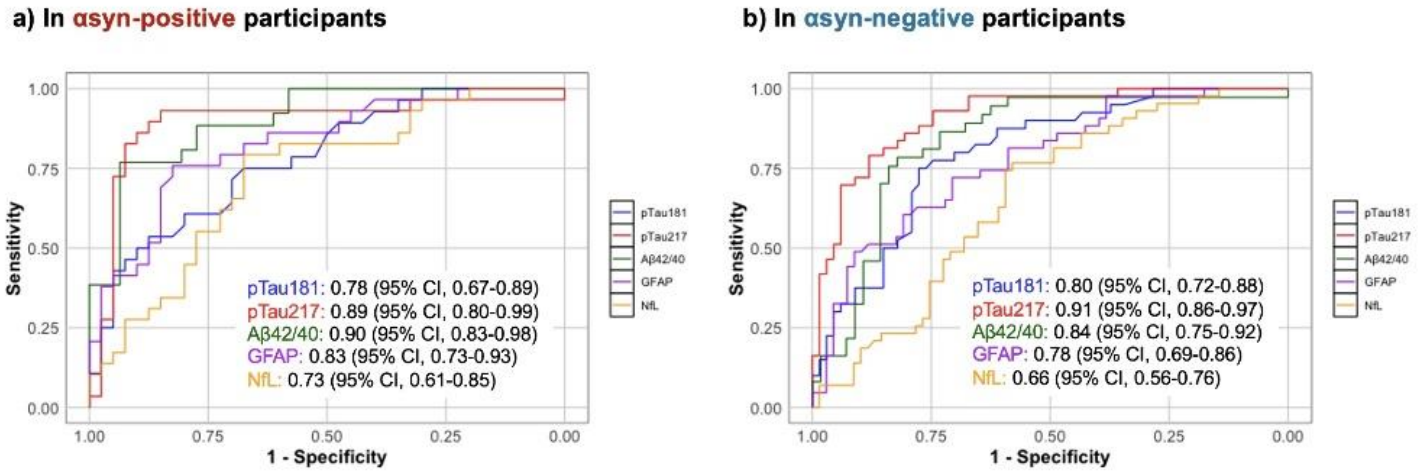
Aims: Co-occurring amyloidosis (Aβ), tauopathy, and alpha-synucleinopathy (αsyn) are frequently found in patients with neurodegenerative diseases, and can now be identified in vivo. Novel plasma biomarkers are highly accurate in detecting Aβ; however, their use in αsyn-positive individuals remains unexplored. Investigating these biomarkers in αsyn-positive individuals is crucial for their potential use in clinical trials as screening or stratification tools. This study evaluated the diagnostic accuracy of plasma pTau181, pTau217, Aβ42/40, GFAP, and NfL for detecting Aβ in αsyn-positive and αsyn-negative individuals.
Methods: We included 180 participants: 69 Aβ-/αsyn-, 44 Aβ+/αsyn-, 39 Aβ-/αsyn+, and 28 Aβ+/αsyn+. Plasma pTau181 and Aβ42/40 were measured with the Lumipulse G platform, pTau217 with the ALZpath pTau217 assay, and GFAP and NfL with the Neurology 2-plex E kit (Quanterix). αsyn status was determined with the CSF SAAmplify-αsyn Test, and Aβ status with the CSF Aβ42/40 ratio measured with the Lumipulse G platform. The diagnostic accuracy of plasma biomarkers for detecting Aβ was evaluated with ROC curve analyses and compared with the DeLong test.
Results: Plasma biomarker levels were abnormal in Aβ-positive groups, regardless of αsyn status. NfL levels were higher in Aβ+/αsyn+ than in Aβ+/αsyn- cases. Plasma pTau217 and Aβ42/40 showed the highest diagnostic accuracy individually (AUC up to 0.91) for detecting Aβ in αsyn-positive and αsyn-negative participants (Figure). pTau271 and Aβ42/40 had similar diagnostic accuracy both individually and combined.

Figure: Diagnostic accuracy of plasma biomarkers in differentiating Aβ-positive from Aβ-negative participants



Conclusions: Plasma pTau217 and Aβ42/40 accurately detected Aβ in αsyn-positive individuals. Coexistence of Aβ and αsyn was associated with increased neurodegeneration. These preliminary findings indicate that plasma pTau217 and Aβ42/40 could be used in clinical trials for Aβ screening and stratification to evaluate treatment response differences in α-synucleinopathies like dementia with Lewy bodies and Parkinson's disease.

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SHIFT 01-114

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

PLATELETS OF PATIENTS WITH DEMENTIA WITH LEWY BODIES ARE ENRICHED IN IMMUNE MODULATORS AND NEUROTROPHIC GROWTH FACTORS

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Aims: Dementia with Lewy Bodies (DLB) is the second cause of degenerative dementia after Alzheimer's disease (AD). Due to their frequent overlap, specific biomarkers are mandatory to achieve reliable clinical diagnosis. Previously we found that the DLB platelet transcriptome overexpresses neuroinflammation related genes, and here, we profiled protein levels of nineteen of these genes in platelets and platelet-poor plasma in DLB comparing with AD and controls.
Methods: Nineteen analytes including six neurotrophic and angiogenic growth and repair factors and thirteen pro- and anti-inflammatory immune modulators were analyzed by a custom Luminex Multiplex Protein Assay in lysed platelets (PLTs) and platelet-poor plasma (PPP). Samples were obtained from thirteen DLB patients, AD patients and control individuals (n=13, each).
Results: In PLTs, of the six growth and repair factors, five (PDGF-BB, PlGF-1, NCAM-1, SDF-1-alpha and BDNF) were significantly increased in DLB and AD vs controls. In PPP, NCAM-1 and SDF-1-alpha were increased only in DLB vs controls. Ten out of thirteen immune-modulator proteins (IFN-gamma, IL-1-beta, IL-6, IL-17A, TNF-alpha, MIF, IL-8, IP-10, IL-5, IL-10), were increased in DLB-PLTs vs CTRLs, and four (MIF, IL-5, IL-8, IP-10,) also compared to AD. Additionally, IL-6, IP-10 and IL-10 levels were also elevated in DLB-PPP vs both CTRLs and AD. All five, MIF, IL-6, IL-8, IP-10 and IL-10 have been related to neuroinflammation. Considering that blood-brain-barrier disruption has been described in neurodegenerative disorders, and PLTs have been proposed as mediators between blood and brain, changes in their content and consequent protein release might contribute to disease.
Conclusions: DLB-PLTs are enriched in proteins related to neuroinflammation, some of which are released to plasma. The suitability of MIF, IL-8, IL-6, IP-10 and IL-10 as DLB biomarkers must be further investigated.

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SHIFT 01-115

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

PREVALENCE OF LEWY BODY DISEASE AND PHENOTYPIC ASSOCIATIONS IN ITALIAN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

Simone Baiardi[1,2], Serena Caldera[2], Franco Magliocchetti[2], Sabina Capellari[1,2], Stefano Cappa[3,4], Naike Caraglia[5], Maria Cotelli[6], Camillo Marra[5,7], Francesca Miraglia[8,9], Daniela Perani[10], Alberto Redolfi[6], Patrizia Spadin[11], Fabrizio Tagliavini[12], Nicola Vanacore[13], Fabrizio Vecchio[8,9], Paolo Rossini[9], Piero Parchi[1,2]
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Aims: To determine the prevalence of Lewy body disease (LBD), and its influence on the clinical and laboratory phenotype in a heterogeneous multicentric cohort of patients diagnosed with mild cognitive impairment (MCI).
Methods: In this cross-sectional study, we assessed LBD by cerebrospinal (CSF) α-synuclein seed amplification assay (α-syn SAA) in 351 MCI subjects from the Italian multicenter INTERCEPTOR cohort. At baseline, each participant underwent detailed neurological assessment, neuropsychological testing, brain glucose metabolism ([18F]FDG-PET) evaluation, MRI volumetry of the hippocampus, CSF Alzheimer's disease (AD) biomarker (p-tau, t-tau, Aβ1-42, and Aβ1-40) determination, and *APOE* genotyping.
Results: The mean age was 71.8±6.9 years, 50.1% were women, and 57.5% of participants had a CSF biomarker profile within the AD continuum (A+ or A+T+). The α-syn SAA was positive for LBD in 36 (10.3%) participants. LBD-positive individuals were older (75.5 vs. 72.0 years, p=0.016) and more frequently males (66.7% vs. 47.8%, p=0.032) than the LBD-negative ones. They had fewer memory complaints (72.2% vs. 86.8%, p=0.020) but a higher prevalence of attention deficits (44.4% vs 28.4%, p=0.048). Additionally, in the LBD-positive group, we found a trend toward a higher frequency of core clinical features of dementia with Lewy bodies (parkinsonism 5.7% vs 1.0%; fluctuations 5.9% vs 1.0%; visual hallucinations 5.6% vs 0%) and delirium episodes (5.6% vs. 1.0%). In contrast, there were no significant differences in neuropsychological profiles, the prevalence of [18F]FDG-PET hypometabolism, hippocampal atrophy, *APOE*ε4 frequency, and CSF AD biomarker positivity between groups.
Conclusions: About 10% of MCI patients were LBD-positive. LBD was associated with age and a higher prevalence of attention deficits, motor signs, and psychiatric symptoms. The relatively low LBD prevalence in the cohort might have negatively influenced the identification of further differences

between LBD-positive and LBD-negative participants.

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SHIFT 01-116

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

A QUANTITATIVE LEWY FOLD-SPECIFIC ALPHA-SYNUCLEIN AGGREGATION ASSAY AS A POTENTIAL PROGRESSION MARKER FOR PARKINSON'S DISEASE

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Aims: Misfolded α-synuclein (αSyn) is the hallmark of α-synucleinopathies like Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA). We developed a seed-amplification-assay (SAA) with enhanced specificity for Lewy-fold α-synucleinopathies and introduced a quantifiable measure correlating with clinical severity.
Methods: Cerebrospinal fluid of 170 patients with neurodegenerative diseases and controls was analyzed. The cohort included α-synucleinopathies (MSA, PD, DLB), mixed 3-repeat/4-repeat tauopathies (Alzheimer's Disease, AD), 4-repeat tauopathies (Progressive Supranuclear Palsy, PSP), frontotemporal dementia (FTD), and controls. To validate strain specificity, brain homogenates from 30 neuropathologically diagnosed cases of Lewy body disease, MSA, PSP, and controls were employed.
Results: Blinded measurements demonstrated 97.8% sensitivity and 100% specificity for Lewy-fold α-synucleinopathies, correctly identifying PD and DLB while excluding MSA. Concordant with existing literature and available neuropathological data, co-pathology was observed in some AD, FTD, and PSP cases. A novel Lewy-Fold-Pathology (LFP) score, based on positive signals in a dilution series of CSF samples, provided a quantitative measure of αSyn seeds. The LFP-score significantly correlated with clinical severity scores such as Hoehn and Yahr stage, UPDRS-III, and MoCA. Longitudinal tracking in a subset of PD cases showed progressive increases corresponding with clinical deterioration. This highlights our assay's capability to monitor disease progression at an individual level.
Conclusions: Our Lewy-fold-specific SAA enhances ante mortem diagnosis and differentiates Lewy-fold α-synucleinopathies from MSA. It holds promise as a progression marker and pharmacodynamic biomarker in clinical trials for αSyn-targeting therapies.

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SHIFT 01-117

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SPECT
2 - 3 April 2025

DOPAMINERGIC CONNECTIVITY ACROSS ALPHA-SYNUCLEIN SPECTRUM

Alice Galli[1], Andrea Pilotto[1], Cinzia Zatti[1], Fabio Placidi[2], Francesca Izzi[2], Enrico Premi[3], Silvia Caminiti[4], Luca Presotto[5], Andrea Rizzardi[1], Marcello Catania[1], Alessandro Lupini[6], Leandro Purin[6], Maria Pia Pasolini[6], Agostino Chiaravalotti[2], Mariana Fernandes[2], Carmen Calvello[2], Silvia Lucchini[7], Francesco Bertagna[8], Barbara Paghera[8], Daniela Perani[9], Daniela Berg[10], Alessandro Padovani[1], Claudio Liguori[2]
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Aims: The impairment of dopaminergic network is a core feature of alpha-synucleinopathies. Less is known about involvement and reconfiguration of nigrostriatal and mesolimbic dopaminergic circuitries in the alpha-synuclein spectrum. We aim to investigate in vivo the dynamic changes of local and long-distance dopaminergic connectivity in patients with isolated REM sleep behavior disorder (iRBD), Parkinson's Disease (PD), and Dementia with Lewy Bodies (DLB).
Methods: Brain 123I-FP-CIT SPECT was acquired for patients with iRBD, PD, and DLB. Age and sex-matched controls were selected for each group of patients. Dopaminergic connectivity alterations were analyzed using correlation analysis. Briefly, a correlation matrix was computed for each group of patients and controls. Fisher's transformation was applied to each coefficient and a z-test was performed to assess significant changes between patients and controls.
Results: iRBD subjects showed significant dopaminergic connectivity alterations both in nigrostriatal (13%) and mesolimbic (13%) networks, primarily involving subcortical nodes. Of note, statistically significant altered connectivity in mesolimbic network was mostly due to an involvement of hyper-connectivity, while alterations in nigrostriatal network were due to a prominent hypo-connectivity. In DLB patients there were significant connectivity alterations mostly in mesolimbic (27%) rather than nigrostriatal (10%) network. Indeed, we found a higher proportion of hypo-connectivity primarily affecting cortico-limbic nodes. In PD patients there was a higher percentage of connectivity alterations involving nigrostriatal (20%) rather than mesolimbic (10%) networks, due to an involvement of hypo-connectivity in basal ganglia and pre-frontal nodes.
Conclusions: This study indicates that dopaminergic connectivity alterations are core features of alpha-synucleinopathies since prodromal stages, involving both nigrostriatal and mesolimbic projections. The shift from an increased to a decreased connectivity might be hallmark of transition from prodromal to more severe stages of the disease.

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SHIFT 01-118

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SPECT
2 - 3 April 2025

MOTOR DYSFUNCTION IN PRODROMAL AND CLINICAL PARKINSON'S DISEASE: THE ROLE OF DOPAMINE DEPLETION IN STRIATAL SUBREGIONS

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Aims: The aim of this study was to investigate whether region-specific dopamine depletion of striatal subregions contributes to motor symptoms in patients with prodromal and clinical Parkinson's disease (PD).
Methods: Neuroimaging and behavioral data of 279 prodromal and 285 clinical patients with PD were downloaded from the Parkinson's Progression Marker Initiative (www.ppmi-info.org). Based on normalized dopamine transporter SPECT images, standardized uptake value ratios (SUVRs; reference: occipital lobe) for the sensorimotor, executive, and limbic region of the striatum were extracted using the Oxford-GSK-Imanova Striatal Connectivity Atlas. Motor symptoms were quantified using the MDS-UPDRS-III. First, regional SUVRs were compared between groups and correlated with MDS-UPDRS-III scores. Next, the prodromal and clinical group were matched according to their striatal sensorimotor SUVRs and subsequently, striatal executive and limbic SUVRs of these matched groups were compared to assess the potential compensatory function of executive and limbic dopaminergic innervation. Finally, moderation analyses were performed to assess whether executive or limbic SUVRs moderate the association between dopamine depletion in the sensorimotor striatum and MDS-UPDRS-III scores in the clinical PD group.
Results: SUVRs of all three striatal subregions were significantly decreased in clinical compared to prodromal PD. In clinical PD, lower sensorimotor SUVRs were associated with lower motor function, but not SUVRs in executive or limbic subregions. In the matched groups, neither the executive nor the limbic SUVRs differed significantly. Moreover, no significant moderation effect was observed in the clinical cohort.
Conclusions: Dopamine loss in the sensorimotor striatum is strongly associated with motor symptoms in clinical PD. However, at least in this cohort, this relationship does not seem to be negatively moderated by dopaminergic depletion in the executive or limbic striatal subregion.

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SHIFT 01-120

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

SUPINE SLEEP POSITION AND BASAL FOREBRAIN ATROPHY IN PARKINSON DISEASE

Sonia Farokhnia, Philipp Valko, Heide Baumann-Vogel, Sandra Loosli, Esther Werth, Christian Baumann, Simon Schreiner
University Hospital Zurich, Department Of Neurology, Zurich, Switzerland

Aims: Most people sleep mainly on their side, but people with neurodegenerative disease, such as Parkinson's (PD) or Alzheimer's, mainly sleep in a supine position. Supine sleep influences obstructive sleep apnea and sleep-dependent brain clearance, two factors that could contribute to neurodegeneration. However, the importance of excessive supine sleep in people with established neurodegenerative disease remains unclear. Here, we investigated if supine sleep relates to neurodegeneration, i.e. brain atrophy, in people with PD.
Methods: We retrospectively included 123 people with PD who had undergone detailed clinical assessments, video-polysomnography with recording of body positions during sleep using a positional sensor, and structural MRI at 3 Tesla, which we used for volumetric analysis with the CAT toolbox.
Results: Patients spent a median time of 187.4 min in a supine sleep position, corresponding to 61% of total sleep time. More supine sleep was associated with regional brain atrophy, mainly in the basal forebrain but also involving frontal cortical areas. The association of supine sleep with brain atrophy persisted after controlling for potential confounders, such as sleep apnea. Nocturnal hypoxemia burden (% of sleep time <90% oxygen saturation) was an independent, yet partially synergistic (with supine sleep), predictor of basal forebrain atrophy. Supine sleep was not associated with motor symptoms or nocturnal position changes.
Conclusions: Excessive supine sleep is a potential marker of neurodegeneration involving the basal forebrain. More studies are warranted to investigate if body positions during sleep influence neurodegenerative disease, for example through nocturnal hypoxemia or sleep-dependent brain clearance.

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SHIFT 01-124

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY, ANTI-OXIDANT
2 - 3 April 2025

IDENTIFICATION OF PATIENT DERIVED ANTIBODIES WITH THERAPEUTIC POTENTIAL TO COUNTER PD ASSOCIATED INFLAMMATION

Jorge Dias
Alchemab Therapeutics, Cambridge, United Kingdom

Aims: α-Synucleinopathies have highly heterogeneous pathology and like other neurodegenerative diseases currently lack effective treatments. Alchemab Therapeutics' approach identifies naturally-occurring protective antibodies convergent in resilient patients. The platform has successfully identified novel targets and potential therapeutic antibodies derived from resilient patients across Alzheimer's disease, Frontotemporal Dementia and Huntington's disease. Here the approach was used to discover a patient derived, novel therapeutic antibody for Parkinson's disease (PD) and associated α-Synucleinopathies.
Methods: Patient samples from a PD cohort were characterised using Alchemab's innovative discovery platform which integrates advanced omics, bioinformatics, and machine learning to identify resilience-associated targets and their antibodies. A particularly promising antibody-target pair was subsequently characterised for its ability to modulate inflammation, in an *in vitro* PD triculture system.
Results: ATL6026 was discovered as an antibody enriched in resilient individuals, and exact target deconvoluted. As the target plays a role in the prostaglandin pathway, an in vitro triculture assay was established, which used preformed fibrils of α-synuclein to induce PD associated inflammation. ATL6026 was able to reduce the levels of inflammatory cytokine IL-6 in this assay and was shown to be via a direct reduction in the target.
Conclusions: Prostaglandins are key modulators of multiple pathogenic mechanisms that play a role in PD. Antibody ATL6026 is derived from patients at risk of developing PD but resisting disease progression. ATL6026 has demonstrated ability to attenuate inflammation *in vitro*. Further work is ongoing to characterise ATL6026's ability to reduce neuroinflammation and PD pathology *in vitro* and *in vivo*. Collectively, this suggests that modulating prostaglandin levels with ATL6026 may represent a novel therapeutic MoA in PD. The novel resilience associated targets being discovered with Alchemab's platform represent a promising new way to tackle these devastating diseases.

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SHIFT 01-127

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
2 - 3 April 2025

DISCOVERY AND DEVELOPMENT OF NOVEL PROTEASOME ACTIVATORS TO TREAT PARKINSON'S AND OTHER NEURODEGENERATIVE DISEASES

Diogo Feleciano
Booster Therapeutics GmbH, Berlin, Germany

Aims: Discovery and development of a first-in-class 20S proteasome activator to treat Parkinson's Disease and other neurodegenerative diseases.
Methods: High Throughput Screening to identify 20S proteasome activators; in vitro cell viability assays; medicinal chemistry approaches to optimize small molecules; structure-based drug design with X-Ray; primary culture of dopaminergic neuronal models, injured with alpha-synuclein PFFs leading to accumulation of alpha-synuclein aggregates, loss of proteasome activity, and neurodegeneration; DMPK, compound exposure studies; in vivo safety studies; in vivo model of Parkinson injured with alpha-synuclein PFFs in the substantia nigra leading to alpha-synuclein aggregation in dopaminergic neurons, and neurodegeneration.
Results: Developed DGRADX, a platform to identify, profile and optimize 20S proteasome small molecule activators. DGRADX comprises in vitro assays, X-Ray, ML/AI, medicinal chemistry approaches, and neuroprotection assays. Booster identified compounds that are neuroprotective against alpha-synuclein accumulation and restore proteasome activity. Lead compound has shown to be effective in ex and in vivo PD models. In an animal PD model, the lead compound was neuroprotective, reduced a-synuclein aggregates, restored proteasome activity, reduced cellular stress, and improved motor function.
Conclusions: We are developing a therapy that can modify the progression of the disease in individuals with PD by restoring proteasomes, which are impaired in the brains of people with PD. Our preclinical data supports that restoring proteasomes is neuroprotective, protects from alpha-synuclein accumulation, and helps alleviate stress in multiple pathways.

SHIFT 01-130

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / CELL TRANSPLANTATION
2 - 3 April 2025

ASTROCYTE CO-TRANSPLANTATION WITH HPSC-DERIVED DONOR CELLS INHIBITS A-SYNUCLEIN SPREAD IN A HUMANIZED PARKINSON'S DISEASE MODEL

Mi-Yoon Chang, Sanghun Lee
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Aims: Clinical trials exploring cell therapy for Parkinson's disease (PD) using human pluripotent stem cell (hPSC)-derived neural stem/precursor cells (Og-NSCs) have shown promise by successfully engrafting midbrain dopamine (mDA) neurons in preclinical models induced with parkinsonian toxins. However, these models fail to accurately mimic the brain conditions of PD patients, potentially leading to variations in clinical outcomes. We introduced neural stem/precursor cells (NSCs) derived from hPSC-generated human midbrain-like organoids (organoid-derived NSCs; Og-NSCs) as an optimal cell source for PD therapy.
Methods: Og-NSCs contain astrocyte precursors that differentiate into neurotrophic astrocytes alongside mDA neurons. Here, we evaluated mDA neuron engraftment by transplanting Og-NSCs into PD model rats exhibiting human a-synuclein (α-syn) pathology. Twelve weeks post-transplantation, a significant proportion of the grafted mDA neurons displayed Lewy body (or neurite)-like α-syn inclusions, indicating robust host-to-graft transmission of α-syn pathology. Compared to the 6-OHDA model, mDA neuron engraftment in the α-syn-PD rat striatum was markedly reduced.
Results: Incorporating astrocyte precursors in Og-NSCs had minimal impact on impeding α-syn transmission, accompanied by delayed astrocyte appearance from grafted Og-NSCs during the early post-transplantation phase, marked by vigorous infiltration of pro-inflammatory immune cells into the grafts. Conversely, augmenting donor cells with hPSC-derived astrocytes, thus ensuring the presence of grafted astrocytes early post-transplantation, almost completely halted α-syn transmission, resulting in significantly fewer visible Lewy body-like inclusions in the grafts and substantially improved mDA neuron engraftment.
Conclusions: These findings underscore the importance of including astrocytes in donor cell populations to enhance graft cell survival and function in the PD patient brain.

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SHIFT 01-131

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2 - 3 April 2025

BONE MORPHOGENETIC PROTEINS 5/7 (BMP5/7) DEMONSTRATE THERAPEUTIC EFFECTS IN DIFFERENT ALPHA-SYNUCLEIN-BASED PARKINSON'S DISEASE MOUSE MODELS AND IPSC-DERIVED DOPAMINERGIC NEURONS

Claude Brodski[1], Aleksandar Rajkovic[2], Dmitrii Komkov[2], Vukasin Jovanovic[3], Zagorka Vitic[4], Anastasiia Kotliarova[5], Joy Kahn[1]
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Aims: Aims: Neurotrophic factors are prime candidates for the development of disease-modifying therapies due to their ability to restore and maintain the functional integrity of impaired, but not yet lost, neurons. Clinical trials investigating neurotrophic factors like GDNF for Parkinson's disease (PD) indicated that these substances are generally safe, however they did not shown effectiveness, potentially due to their inability to protect dopaminergic (DA) neurons against alpha-synuclein toxicity. Here, we evaluated the efficacy of bone morphogenetic proteins 5/7 (BMP5/7) in protecting DA neurons from alpha-synuclein-induced toxicity.
Methods: Methods: The therapeutic effects of BMP5/7 were investigated in two mouse models of PD: one employing viral vectors to overexpress A53T mutant human alpha-synuclein and the other utilizing alpha-synuclein preformed fibrils (PFFs). For the iPSC-based PD models, we used DA neurons derived from A53T mutation carriers. To block BMP signaling, SMAD1, an essential component of the intracellular BMP signaling pathway, was genetically inactivated by conditional mutagenesis and LDN212854 was applied for pharmacological inhibition.
Results: Results: In both mouse PD models, virally-delivered BMP5/7 prevented the loss of DA neurons and their projections, as well as associated motor impairments. Notably, BMP5/7 also demonstrated therapeutic effects even when administered after the onset of motor symptoms. In iPSC-derived DA neurons from PD patients, BMP5/7 significantly ameliorated neuropathological changes. Conversely, genetic and pharmacological inhibition of BMP signaling in mice led to increased alpha-synuclein and p129-alpha-synuclein levels in TH+ neurons, accompanied by DA neuron loss and motor impairments. Currently, we are further validating the efficacy of BMPs in a head-to-head comparison with GDNF.
Conclusions: Conclusions: Our results highlight BMP5/7 as promising disease-modifying drug candidates for PD, warranting further investigation and validation.

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SHIFT 01-132

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2 - 3 April 2025

DISEASE-MODIFYING STRATEGY TO HALT THE PROGRESSION OF PARKINSON'S DISEASE: A GENE THERAPY APPROACH

Ayman Faroqi, Kenneth Davis, Destiny Regalia, Danilyn Amerna, Monica Castanedes-Casey, Whitney Davis, Hiroaki Sekiya, Dennis Dickson, Pam Mclean
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Aims: Evidence supports a gene dosage contribution of *SNCA* to Parkinson's disease (PD) pathogenesis making downregulation of alpha-synuclein (aSyn) an attractive disease-modifying strategy. The aim of this study is to develop a novel gene therapy strategy to reduce aSyn expression in the CNS, potentially decreasing aggregation and propagation and halting disease progression in patients.
Methods: A single adeno-associated virus (AAV) CRISPR interference (CRISPRi) construct expressing kinetically inactive *Staphylococcus aureus* Cas9 fused to the transcriptional repressor KRAB and a single-guide RNA (sgRNA) directed towards a sequence near the transcriptional start site (TSS) of *SNCA* was generated and validated in HEK293T cells. BAC transgenic mice expressing human *SNCA* on a mouse *Snca*-null background were transduced bilaterally via intracerebroventricular injections at postnatal day 0 with AAV.CAP-B10 packaged virus expressing the human-specific sgRNA or nontargeting control sgRNA. Six months post-injection, mice were euthanized; one hemisphere was processed for biochemistry while the other fixed for immunohistochemistry.
Results: After 6 months, brain-wide transduction of AAV CRISPRi was confirmed and a significant decrease in *SNCA* mRNA (61.9±2.9%) and aSyn protein (62.3±4.8%) was detected. In addition to reduced total aSyn, a significant decrease in phosphorylation of serine 129 (pSyn) (92.5±5.4%) was observed. Immunohistochemistry confirmed reduction in pSyn immunoreactivity and proximity ligation assay revealed decreased oligomeric aSyn species following *SNCA* knockdown.
Conclusions: Whole-brain transduction of AAV CRISPRi targeting the human *SNCA* TSS results in downregulation of aSyn *in vivo* after 6 months and demonstrated a significant reduction in both mRNA and protein levels. Additionally, we observe a reduction in pSyn expression biochemically and by immunohistochemistry and a decrease in oligomeric aSyn species by specialized staining. Current studies are testing efficacy in adult mouse brain using brain-permeable AAV serotypes.

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SHIFT 01-135

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2 - 3 April 2025

SEMAPHORIN 4D BLOCKING ANTIBODY PEPINEMAB REVERSES ALPHA-SYNUCLEIN-INDUCED DAMAGE TO BLOOD BRAIN BARRIER IN A HUMAN BRAIN-ON-A-CHIP MODEL

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Aims: Accumulation of toxic protein aggregates, such as alpha-synuclein (αSyn), amyloid beta (Aβ), and mutant huntingtin, are believed to trigger a series of pathogenic events, including gliosis, neuroinflammation, compromised blood brain barrier (BBB), and neuronal loss. These events are key drivers of neurodegeneration and cognitive dysfunction. We have previously reported that semaphorin 4D (SEMA4D) is upregulated in diseased or damaged neurons during progression of Alzheimer's and Huntington's Disease (AD, HD), triggering astrocyte reactivity and gain of inflammatory processes (DOI: 10.1186/s12974-022-02509-8). Further, we discovered that SEMA4D disrupts endothelial tight junctions forming the BBB (DOI: 10.1016/j.nbd.2014.10.008). Pepinemab, blocking antibody to SEMA4D, appears to protect and restore healthy astrocyte functions and to slow or prevent disease progression in clinical studies of AD and HD. Herein, we sought to investigate the ability of pepinemab treatment to repair αSyn-induced BBB dysfunction and prevent associated inflammatory mechanisms in a human brain-chip model.
Methods: We employed a human brain-chip model comprised of neurons, astrocytes, microglia, pericytes, and microvascular brain endothelial cells, cultured under physiological fluid flow. Upon establishment of intact BBB, α-Syn fibrils were added to the parenchymal channel for 3 days, and effects of pepinemab antibody treatment on BBB permeability and markers of tight junctions and neuroinflammation were evaluated.
Results: Addition of α-Syn fibrils increased apparent permeability (P_{app}) of the BBB, and subsequent treatment with pepinemab antibody reversed this and other effects of integrating α-Syn fibrils into the brain chip model. Data characterizing neuroinflammation will also be presented.
Conclusions: SEMA4D is a key effector molecule with multi-faceted mechanisms of action. These results, together with prior clinical experience and favorable tolerability of pepinemab in clinical studies, support the broad application and development of pepinemab in neurodegenerative disease.

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SHIFT 01-140

On-Demand Oral Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2 - 3 April 2025

A NOVEL, BRAIN PENETRANT TRPML1 AGONIST AMELIORATES PATHOLOGY, INFLAMMATION AND NEURODEGENERATION IN AN IN VIVO MOUSE MODEL OF PARKINSON'S DISEASE.

Valerie Cullen, Soheil Aghamohammadzadeh, Xiangyang Yu, Junsheng Yang, Yongchang Qiu
Lysoway Therapeutics, Inc, Cambridge, United States of America

Aims: To assess a novel TRPML1 agonist in a mouse model of pathological alpha-synuclein transmission and neuroinflammation.
Methods: We have identified a potent and brain-penetrant TRPML1 agonist which induces lysosomal calcium release and subsequent pleiotropic downstream effects on the autophagy-lysosomal pathway (ALP). The agonist was administered orally for 35 days to aged mice concurrently receiving intra-nigral injection of alpha-synuclein protofibrils. Additional groups also received conduritol B epoxide (CBE) to inhibit lysosomal GCase activity, as a second hit to the ALP.
Results: The TRPML1 agonist treatment was well tolerated with no adverse clinical signs or body weight changes. In the alpha-synuclein injected mice, a significant loss (approximately 25%) in the number of dopaminergic (TH^+) neurons was observed, accompanied by a concomitant increase in total alpha-synuclein load, as well as accumulation of alpha-synuclein phosphorylated on serine129 (40-50% increase in both). These changes were exacerbated by the additional GCase inhibition (35% TH^+ cell loss, 60-80% increase in pathological synuclein). Co-treatment with Lysoway's TRPML1 agonist reduced or abolished the accumulation of pathological alpha-synuclein and, in the CBE arms, significantly rescued the survival of TH^+ neurons. These neuroprotective effects were accompanied by a significant mitigation of microglial activation and astrocyte proliferation, as quantified by Iba1 and GFAP histochemical staining, respectively. Finally, CBE treatment caused accumulation of toxic glucosyl-sphingosine (GluSph) in plasma, due to build-up of GCase substrate. Co-treatment with our TRPML1 agonist resulted in an approximate 40% decrease in plasma GluSph, reflecting an overall improvement in lysosomal GCase activity.
Conclusions: Lysoway's TRPML1 agonist potently protected dopamingeric neurons from alpha-synuclein transmission, inflammation and neurodegeneration, in an *in vivo* model of PD. Future studies will establish PK/PD relationships, assess biomarker changes and measure functional improvements.

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SHIFT 01-144

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS
2 - 3 April 2025

MOLECULAR CHARACTERIZATION OF MARMOSETS AS A MODEL OF ALZHEIMER'S DISEASE

Gregory Carter[1], Sonal Kumar[1], Annat Haber[1], Stephanie Hachem[2], Thais Rafael Guimaraes[2], Catrina Spruce[1], Duc M. Duong[3], Nicholas T. Seyfried[3], Takeshi Murai[2], Jung Eun Park[4], Lauren Schaeffer[4], Amantha Thathiah[4], Gregg Homanics[5], Afonso Silva[4], Stacey Sukoff Rizzo[4]
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Aims: The gradual progression of Alzheimer's disease (AD) and the inaccessibility of middle-aged brain tissue has limited therapeutic strategies and early interventions. In vivo models enable study of molecular, imaging, and behavioral changes associated with cognitive aging. We have performed genetic, genomics, and proteomic analyses of marmosets as a model of aging and dementia.
Methods: We performed whole-genome sequencing on over 100 marmosets, including a propagating line of genetically engineered *PSEN1* mutants, and computationally assessed standing genetic variation. RNA-seq and tandem mass tag proteomics were used on brain tissue from mutant and age-matched wildtype animals to identify AD-relevant signatures. Plasma biomarkers and proteomics were measured and association tests were performed for sex, age, and genotype.
Results: We identified abundant standing genetic variation at multiple AD risk loci, with damaging variants predicted in *ABCA7*, *BIN1*, and other candidate genes. Transcriptome and proteome effects in brains of young *PSEN1* carriers mimicked some the changes in aged human late-onset AD cases. Blood biomarkers of neurodegeneration were strongly correlated but only weakly associated with age, suggesting potential genetic influences.
Conclusions: Standing genetic variation in AD genes and disease-like alterations in brain gene and protein abundances support the utility of the common marmoset as a model of Alzheimer's disease. These studies provide a roadmap for deep molecular analysis of aging marmosets in precilnical dementia studies.

SHIFT 01-145

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS
2 - 3 April 2025

IN VITRO HUMAN BRAIN MODEL MIMICKING PHYSIOPATHOLOGIC CROSSTALK OF MAJOR BRAIN-RESIDENT CELLS IN NORMAL AND ALZHEIMER'S DISEASE CONTEXTS

Soohyun Kim, Sanghun Lee
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Aims: The interactions among neurons, glia, and vascular cells are crucial for brain function and disease. We aimed to create an in vitro human brain model incorporating all major brain-resident neurons and glia in a 3D vascularized matrix, simulating their crosstalk in normal and Alzheimer's disease (AD) conditions.
Methods: Human pluripotent stem cells (hPSCs) were used to derive neurons (N), astrocytes (A), microglia (M), oligodendrocytes (O), and vascular cells (V) in scalable quantities. These cells were co-cultured in a 3D vascularized matrix (termed 'V-NAMO'). Optimal conditions for culture medium, scaffold matrix, and cell ratio were established to support the co-culture. To model sporadic AD based on the 'amyloid scaffold hypothesis', amyloid beta (Aβ) treatment conditions were optimized. The V-NAMO model was analyzed using immunocytochemical, functional, electrophysiological, and single-cell transcriptome techniques.
Results: A series of gene expression, phenotypic, and morphometric analyses showed that V-NAMO cultures significantly differed from those cultured individually and closely resembled the adult human brain in vivo, validating the model's relevance. The optimized Aβ treatment in V-NAMO replicated AD-specific Aβ and Tau pathologies, neuroinflammation, neuron/synaptic degeneration, and cerebral amyloid angiopathy (CAA). Electrophysiological analysis revealed that neuronal hyperexcitability in early V-NAMO culture transitioned to decreased excitability over time, indicating the model's potential to study AD progression. Notably, microglia exhibited a protective role early in AD, while vascular cells promoted disease progression. Finally, the relevance of the Aβ-treated V-NAMO as an in vitro human sporadic AD model was further confirmed by observing AD-specific single-cell transcriptomic changes.
Conclusions: The V-NAMO culture model provides a valuable platform for studying normal human brain physiology and AD pathologies, offering insights into disease mechanisms and potential therapeutic targets.

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SHIFT 01-147

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

DISTINCT VULNERABILITY OF MEMORY AND EMOTIONAL CIRCUITS TO AMYLOID-B AND TAU PATHOLOGIES IN ALZHEIMER'S DISEASE

Maria Dolores Capilla López[1,2], Ángel Deprada[1,2], Paula Sotillo[1,2], Yuniesky Andrade Talavera[3], Irene Martínez Gallego[3], José Rodríguez Alvarez[1,2], Antonio Rodríguez Moreno[3], Arnaldo Parra Damas[1,2], Carlos A. Saura[1,2]
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Aims: Alzheimer's disease (AD) is characterized by memory loss and neuropsychiatric symptoms, but the mechanisms by which amyloid-β (Aβ) and tau drive synaptic dysfunction underlying memory and emotional disturbances in dementia remain unclear.
Methods: We employed behavioral, electrophysiological, tissue clearing, pathological and cell-specific transcriptomic techniques to study sex and aging effects of Aβ and tau pathologies on memory and emotional circuits in neuronal-specific mutant amyloid precursor protein (APP), Tau and double APP/Tau transgenic mice.
Results: APP/Tau mice of both sexes show Aβ pathology and increased phosphorylated tau in early AD vulnerable brain regions. However, whereas Tau and APP/Tau mice develop spatial memory deficits associated with hippocampal tau pathology, APP and APP/Tau mice show innate anxiety and fear behaviors linked to intracellular Aβ in the amygdala. Pathological tau potentiates Aβ-mediated long-term potentiation (LTP) impairments in the hippocampus but counteracts the negative effects of Aβ on LTP in the amygdala. APP/Tau mice show synaptic tau accumulation, reduced synaptic proteins and impaired excitatory neurons activation in the hippocampus. Transcriptomic profiling showed region-specific and common transcriptional changes in the hippocampus and BLA in APP/Tau mice, including deregulation of 63 AD-associated synaptic and inflammatory genes.
Conclusions: Aβ and tau synergize to replicate key pathological, behavioral, synaptic, and transcriptional changes in AD. The distinct effects on memory neural circuits underscore the need to target both pathological hallmarks in AD therapy. Supported by grants from Ministerio de Ciencia e Innovación of Spain (PID2022-137668OB-I00, BES-2017-082072), Generalitat de Catalunya (2021-SGR00142) and BrightFocus Foundation (A2022047S).

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SHIFT 01-148

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

HUMANISATION OF MAPT IN AN AGED APP KNOCK-IN MOUSE MODEL DRIVES TAU PRE-TANGLE PATHOLOGY

Sneha Desai[1,2], Elena Camporesi[2], Gunnar Brinkmalm[2], Kritika Goyal[3], Argyro Alatza[4], Jack Wood[1,2], Abdulaziz Aljawder[1], Sumi Bez[5], Jeffrey Savas[3], Damian Cummings[1], Jörg Hanrieder[2,4], Frances Edwards[1]
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Aims: Current Alzheimer's disease mouse models rely on mutations in *Mapt* to develop neurofibrillary tangles. However, a model that allows for the study of pathological tau development driven by rising amyloid-β (Aβ), without *Mapt* mutations, is crucial for advancing effective treatments. Here, we investigated the effects of heterozygous humanised *Mapt* in aged *App*$^{NL-F}$ knock-in mice
Methods: We profiled tau proteoforms using immunoprecipitation followed by liquid chromatography-mass spectrometry (IP-MS) and western blotting. Tau and Aβ aggregates were further investigated using hyperspectral florescent imaging, combining conformation-sensitive amyloid staining with immunohistochemistry. *In vitro* field potential electrophysiology recordings from CA3-CA1 hippocampal synapses were also performed to study the effect of humanised *Mapt* on basal synaptic transmission and plasticity in wildtype and *App*$^{NL-F}$.
Results: Tau phosphorylation levels increased at multiple sites on the proline-rich domain and the C-terminus region in 24-month-old *App*$^{NL-F}$ x *Mapt*^{het} mice compared to 18-month-old *App*$^{NL-F}$ x *Mapt*^{het} and age-matched *App*$^{NL-F}$ mice. Cored plaques particularly promote tau hyperphosphorylation, facilitating pre-tangle tau aggregation in the somatodendritic compartment, detected by amyloid staining and antibodies targeting tau phosphorylation epitopes, pT217 and pS396. Initial electrophysiology results suggest that *App*$^{NL-F}$ x *Mapt*^{het} mice exhibit larger excitatory postsynaptic potentials compared to controls. However, the increase in the long-term potentiation magnitude is independent of the humanisation of *Mapt.*
Conclusions: Aged *App*$^{NL-F}$ x *Mapt*^{het} mice have increased tau phosphorylation relative to plaque maturity and within the neuronal soma, influenced by age, the humanisation of *Mapt* and Aβ deposition. This novel model, where rising Aβ drives tau pre-tangle pathology, offers a new platform for drug development and testing with greater translational relevance to human Alzheimer's disease. The implications of this will be further investigated using proteomics.

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SHIFT 01-149

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

MODELING SPATIAL TRANSCRIPTOMICS AND PROTEOMICS WITH FUNCTIONAL CONNECTOMICS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE (AD)

Elizabeth Hipskind[1], Lindsay Fadel[1], Steen Pedersen[2], Caitlyn Ortiz[2], Jonathan Romero[2], Eric Shin[2], Md. Abul Hassan Samee[2], Robia Pautler[1,2]
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Aims: Functional connectivity (FC) is a measure of communication between brain regions and can be measured non-invasively using magnetic resonance imaging (MRI). We aim to understand the relationship between learning and memory, FC changes in the brain, and underlying transcriptomic and proteomic changes in AD.
Methods: We used the APP/PS1 mouse model of AD at 3-months (before plaque deposition), 6-months (beginning of plaque deposition), and 10-months (plaque accumulation). First, Morris Water Maze was used to assess spatial learning and memory. Next, FC was measured between 30 brain regions using resting-state functional MRI. Finally, we performed high resolution spatial transcriptomics/proteomics. We used machine learning (ML) modeling to identify functional connections that predict learning and memory performance at 6-months and 10-months. The spatial omics data are being modeled to explain the mechanisms.
Results: As reported, 6-month-old APP/PS1 mice begin to exhibit memory deficits, while both learning and memory deficits are seen at 10-months. We observed a pattern of increasing FC (hyperconnectivity) across all 3 time points. At 6-months, ML identified the temporal cortex-hippocampus connection as the largest predictor of spatial learning, while dentate gyrus-subiculum predicted memory performance. At 10-months, the model identified insula-ectorhinal cortex and cortical subplate-entorhinal as the largest predictors of spatial learning and memory, respectively. We are modeling spatial proteomics and transcriptomics in corresponding brain regions to understand the mechanism of the FC changes.
Conclusions: Increased FC precedes cognitive deficits, demonstrating potential as a non-invasive tool for early disease detection in APP/PS1 mice. ML identified FC changes that explain spatial learning and memory performance. Interestingly, the largest contributors vary with age, suggesting different compensatory strategies across disease progression. Spatial omic profiles will help enhance our understanding of AD's neurobiological underpinnings to identify therapeutic targets.

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SHIFT 01-152

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
2 - 3 April 2025

APOLIPOPROTEIN E4 CONTRIBUTES TO ALZHEIMER'S DISEASE NEUROPATHOLOGY IN DOWN SYNDROME

Breanna Dooling, Rose Summers, Daphne Quang, Molishree Joshi, Hector Esquer, Huntington Potter, Noah R. Johnson
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Aims: Adults with Down syndrome (DS) develop Alzheimer's disease (AD) brain pathology by their 40s due to triplication of the amyloid precursor protein (APP) gene on chromosome 21, and most develop clinical symptoms by age 50-60. Inheritance of the apolipoprotein E (apoE) ε4 allele (*APOE4*) is the strongest risk factor for AD besides age, whereas the ε3 allele (*APOE3*) does not change AD risk. The *APOE4* genotype is associated with earlier and more rapid cognitive decline in both typical AD and DS-associated AD (DS-AD); however, understanding of the associated mechanisms is lacking.
Methods: We developed cerebral organoids (COs) from trisomy 21 (T21) and disomy 21 (D21) *APOE3/3* human induced pluripotent stem cell (hiPSC) lines. We then used CRISPR-Cas9 editing to modify our hiPSCs from an *APOE3/3* genotype to *APOE4/4* in DS hiPSCs and in matched control hiPSCs disomic for chromosome 21. We differentiated these hiPSCs into COs as well as into monolayer cultures of astrocytes and microglia.
Results: There was a significant decrease in size from D21 COs to T21 COs. T21 COs also accumulated more apoE and Aβ than D21 COs and at earlier timepoints. T21 and *APOE4/4* each resulted in increased microglial size and decreased microglial roundness. T21 astrocytes accumulated more apoE than D21 astrocytes. T21 *APOE4/4* astrocytes exhibited increased cell death compared to T21 *APOE3/3* astrocytes at an early timepoint.
Conclusions: *APOE4/4* further accelerates and enhances AD neuropathologies in people with DS. Understanding the molecular and cell type-specific changes caused by *APOE4* as compared to *APOE3* in DS-AD will aid in the development of more targeted and proactive therapies to alleviate dementia risk in individuals with DS.

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SHIFT 01-162

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2 - 3 April 2025

EFFECT OF KLOTHO GENETIC VARIANTS ON BRAIN TRANSCRIPTOMES IN AGING MICE

Gregory Carter[1], Anna Tyler[2], Christoph Preuss[1], Dylan Garceau[1], Kevin Kotredes[1], Michael Sasner[1]
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Aims: The VS haplotype of the longevity factor klotho (KL) has been associated with decreased risk of Alzheimer's Disease (AD) and reduced AD brain pathology in APOE4 carriers. To further explore the role of human variants of KL on AD pathology, we introduced the two human KL alleles, the common FC haplotype and the protective VS haplotype, into C57BL/6J mice.
Methods: We generated homozygous and heterozygous animals for each haplotype, FC and VS, balanced with the wildtype mouse haplotype (FS). We measured whole brain gene expression at four months and 12 months and identified differentially expressed genes across mice carrying the different KL haplotypes.
Results: At four months of age, there were no differentially expressed genes. However, at 12 months of age, there were 609 differentially expressed genes across the different haplotypes. These genes were enriched for synaptic function and protein translation at the synapse. Genes that were down-regulated by the protective VS allele were enriched for synapse-related terms, and those that were up-regulated by the protective VS allele were enriched in ribosome- and translation-related terms. In general, genes that were upregulated by the protective VS allele were down-regulated by the common FC allele relative to the wild type mouse allele. We mapped these outcomes to human Alzheimer's disease study cohorts and found additional metabolism-related differences that mimic signatures in postmortem AD brains.
Conclusions: These data demonstrate how the introduction of KL human variants to mice provides a age-dependent, translatable mechanistic model that will improve our understanding of the role of KL in aging and Alzheimer's Disease.

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SHIFT 01-167

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / SECRETASES
2 - 3 April 2025

SPECTRUM OF Γ-SECRETASE DYSFUNCTION AS A UNIFYING PREDICTOR OF ADAD AGE AT ONSET ACROSS PSEN1, PSEN2 AND APP CAUSAL GENES

Sara Gutierrez Fernandez[1], Cristina Gan Oria[1], Wim Annaert[1], John Ringman[2], Nick Fox[3], Natalie S. Ryan[3], Lucía Chávez-Gutiérrez[1]
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Aims: The overarching goal of this study is to elucidate the molecular mechanisms underlying the variability in age at onset (AAO) across different genetic forms of Autosomal Dominant Alzheimer's Disease (ADAD).
Methods: Our study examined 28 *PSEN2* and 18 *APP* (transmembrane domain) mutations, alongside previously and newly characterized *PSEN1* variants. We expressed mutants in *psen1/psen2* double-knockout mouse embryonic fibroblasts or HEK293 cells, and assessed γ-secretase function by measuring the full Aβ peptide spectrum. Relationships between Aβ profile shifts and AAO were established using linear regression models. AAO data were compiled from literature. The resulting correlations predicted biochemical AAOs, while cross-gene analyses identified common patterns and gene-specific effects.
Results: The biochemical assessment of alterations in γ-secretase processivity induced by PSEN1 variants has emerged as a robust tool for evaluating ADAD pathogenicity, AAO, and disease progression. Our analysis of PSEN1, PSEN2, and APP mutations extends this approach to encompass all three ADAD causal genes. We found consistent mutation-induced impairments in γ-secretase processivity across all three causal genes. Mutation-induced Aβ profile alterations, arising from impaired γ-secretase processivity, exhibited a linear correlation with AAO for each causal gene. These correlations are described by parallel but shifted lines (similar slopes but different Y-intercepts). Our data enabled prediction of AAO from biochemical data. The comparison of these biochemical predictions and clinical AAOs identified families/carriers with clinical AAOs diverging from the predicted (biochemical) AAO values.
Conclusions: This biochemical analysis of ADAD causality and established quantitative relationships deepen our understanding of ADAD pathogenesis, offering potential for predictive AAO modeling with implications for clinical practice and genetic research. Our findings also support the development of therapeutic strategies modulating γ-secretase across different genetic ADAD forms and potentially more broadly in AD.

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SHIFT 01-169

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2 - 3 April 2025

HARNESSING AMYLOID BETA LEVELS AND ISOFORMS FOR ALZHEIMER'S DISEASE DIAGNOSIS AND TREATMENT

Chuanhai Cao[1], Xiaoyang Lin[2], Ning Shen[3], Haiqiang Yang[4]
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Aims: To determine the association of Aβ and its isoforms with AD, and develop methods to test isoforms and accurately quantify them.
Methods: 1. Monomeric Aβ preparation: HFIP was used to force the peptide into monomer and then qliquoted into 100 ug/vial and the dried into powder. 2. Aggregation assay: The prepared film was diluted with DMF, DMSO, NaOH, and $NH_4 \cdot H_2O$ to 40 μM, then submitted to 37^oC for aggregation for the time designated in each assay. 3. ThT and CV assays are used for the testing Aβ aggregation. 4. Brain tissue lysis were prepared by using RIPA buffer. 5. Silver staining, Sandwitch ELISA and western blotting are used for isoform detections. 6. Transmission electron microscopy (TEM) was used for isoform visualization.
Results: We found out that the follwoing factors are essential for diagnosis and prognosis of AD: 1. the microenvironment, such (as pH value), and inflammation can induce or promote Aβ aggregation; 2. Antibodies used for detection or therapy are isoform dependent and can lead to different conclusions; 3. Some peptides can promote Aβ aggregation and they can be used as pathological markers; 4. Protein levels from the brain can mask Aβ levels; 5. Monomeric Aβ at the biological level is beneficial, but oligomer Aβ is toxic to neurons; 6. Anti-Aβ isoform specific antibodies can cross-recognize other isoforms.
Conclusions: Our results strongly support that Aβ is still a valid marker for AD if a reliable and consistent method is employed. Increasing protein synthesis can prevent Aβ-related AD; protein metabolome is a good approach for AD biomarker identification and therapeutic development. Blocking the formation of oligomeric Aβ should be a major effort in developing a cure for or slowing the progression of AD.

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SHIFT 01-170

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2 - 3 April 2025

EVALUATING THE LINK BETWEEN HEARING LOSS AND ALZHEIMER'S DISEASE NEUROPATHOLOGY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Avinash Chandra[1], Benjamin Levett[2], Sheena Waters[1], Petra Proitsi[1], Yue Liu[1], Chris Hardy[2], Jason Warren[2], Charles Marshall[1]
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Aims: Different theories have been posited for the relationship between hearing loss and an increased risk of dementia. However, the neurobiological mechanisms that account for this link are not well understood. In the current study we performed a systematic literature review and meta-analysis to evaluate the nature and strength of the evidence for associations between neuropathology characteristic of Alzheimer's disease, amyloid-β (Aβ) and tau, with hearing loss.
Methods: We conducted searches in electronic biomedical databases for articles published in peer-reviewed literature that evalulated direct associations between hearing loss and AD neuropathology using molecular biomarkers or histopathology. In addition to conducting a synthesis of the literature, for a selection of studies we performed meta-analyses that examined pooled and subgroup (based on hearing or neuropathological measure) effects and meta-regression. Aβ and tau studies were evaluated seperately.
Results: We screened 6224 articles and included 22 studies after independent review and quality assessment. In cross-sectional in vivo studies, associations between hearing loss and Aβ burden were evidenced (r=0.09; 95% CI, 0.02-0.16). Stronger associations were shown for tau pathology (r=0.16; 95% CI, 0.08-0.23). Associations with amyloid only remained significant for central hearing or PET studies after stratification. Moderators included hearing measure, study setting, and correlation. Systematic review indicated mixed results.
Conclusions: Taken together, results from this study indicates that a weak association between hearing loss and AD pathology exists. However, subgroup findings, together with those from tau studies, suggest that central auditory processes may be uniquely vulnerable to more direct neuropathological influences in the brain that are linked to Alzheimer's disease. Further investigation using longitudinal and causal methdoology is warranted.

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SHIFT 01-171

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2 - 3 April 2025

EXPLORING THE MECHANISMS OF AMYLOID BETA ISOFORM INTERPLAY IN AN ALZHEIMER'S DISEASE IPSC MODEL.

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Aims: Deposits of amyloid beta (Aβ) are one of the key hallmarks of Alzheimer's disease (AD), where aggregation into oligomers and fibrils activates toxicity pathways which lead to neuronal death. The two most abundant isoforms, Aβ40 and Aβ42, are present in different amounts in the brain, with Aβ40:Aβ42 ratio decreasing in AD. This indicates that high Aβ40:Aβ42 ratio has a protective function and could mitigate Aβ42 induced toxicity, as shown in animal models. However, we do not understand this mechanism. We aim to determine how the changing ratios of Aβ40 and Aβ42 drive dysfunction in AD model and how increasing the levels of the potentially protective Aβ40 restore the detrimental effects seen in AD.
Methods: Aβ40 and Aβ42 co-aggregation rates have been established using *in vitro* ThT assays. Then, using iPSC-derived cortical neuron models, we will measure how endogenous levels of Aβ isoforms change in our model and how these are correlated with neuronal health. Finally, we will also incubate the cortical neurons with recombinant Aβ of different isoform ratios to examine the neuronal dysfunction that occurs.
Results: We have determined that the rate of aggregation is over two-fold faster with increased Aβ42:40 ratio using *in vitro* aggregation assays. Using the iPSC-derived cortical neuron model, we will examine how changing Aβ isoform ratios affects neuronal health by measuring cytokine release, neuronal outgrowth and synaptic changes. Finally, we will examine the structure of the Aβ aggregates using super-resolution microscopy and correlate how their changing structural features shift their function from healthy to disease states.
Conclusions: This can determine how the interplay between Aβ40 and Aβ42 impacts neuronal health in an AD model to give insight into the role of this proteins' toxic aggregation mechanisms.

SHIFT 01-172

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2 - 3 April 2025

ORPHAN DRUGS IN ALZHEIMER'S DISEASE: CROSSROAD OF AMYLOID PATHOLOGY AND LYSOSOMAL STORAGE DISEASES

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Aims: Increased Aβ deposition plays a central role in the pathogenesis of AD, and deficient autophagy has been observed in AD. Strategies to control Aβ clearance and aggregation that target autophagy-related proteins have considerable potential for treating AD. Lysosomal storage diseases are inborn errors of metabolism characterized by the accumulation of excessive substrates in various organs' cells due to the defective functioning of lysosomes. Cerliponase alfa is an enzyme that delivers tripeptidyl peptidase1 directly to the brain of children with late infantile neuronal ceroid lipofuscinosis (LINCL) type 2. Gaucher disease is also a rare, inherited, and the most common LSD. Homozygous mutations in the *GBA1* gene encoding glucocerebrosidase (GC) reduce the degradation capacity of lysosomes and cause accumulation of misfolded proteins. In this presentation, the effects of two orphan drugs used clinically in LINCL type 2 and Gaucher disease will be discussed on neuronal autophagy in *in vitro* Alzheimer's Disease (AD) studies. To test this hypothesis the effects of cerliponase alfa and taliglucerase alfa on Aβ accumulation in mouse hippocampal neurons (HT-22 neuronal cells) exposed to $fA\beta_{1\text{-}42}$ (a toxic fragment of full-length Aβ) and markers of autophagy-lysosome pathway related to AD were investigated.
Methods: TEM imaging, Western blot, immunocytochemistry, ELISA, and q-PCR have been used.
Results: Our *in vitro* findings indicate that both cerliponase alfa and taliglucerase alfa decrease Aβ load and modulate the autophagy pathways in mouse hippocampal neuronal cell lines (HT-22). They significantly reverse the $fA\beta_{1\text{-}42}$-associated decrease in *BECN-1* and *ATG5* gene expression and $fA\beta_{1\text{-}42}$-associated increase in pmTOR/mTOR expression in HT-22 cells. Cerliponase alfa also significantly increases SIRT1 activity in HT-22 cells.
Conclusions: Therefore, we suggest that these orphan drugs could be considered promising novel therapeutics for neurodegenerative diseases in which autophagy pathways are impaired.

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SHIFT 01-185

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2 - 3 April 2025

RBFOX1 ASSOCIATION WITH FAMILIAL EARLY ONSET ALZHEIMER'S DEMENTIA

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Aims: Identify protective genetic variants against Alzheimer's Disease (AD) using families with exceptional healthy aging by: (1) searching for AD risk variants within familial Early Onset Alzheimer's Disease, and (2) searching for protective genetic modifiers in older unaffected carriers of risk variants.
Methods: Our study was restricted to LLFS participants (n=3,476) with cognitive and functional data available for consensus dementia diagnosis. Using the age at onset as a quantitative outcome, we conducted a genome-wide multipoint linkage analysis of families with EOAD within the LLFS cohort (6 families, 13 EOAD and 14 late onset cases). Analyses were adjusted for sex, field center, principal components, kinship matrix, and Alzheimer's dementia status. Loci yielding significant scores (LOD ≥3.3) were tested using single-SNP association analysis in two additional independent cohorts: 1) 84 EOAD families from Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA); 2) 1,220 families from The National Institute on Aging Alzheimer's Disease Family Based Study (NIA-LOAD FBS). For further characterization of the results, genotype-phenotype relationships were examined in the LLFS cohort using a global cognitive endophenotype and plasma $A\beta_{42/40}$ biomarkers.
Results: The strongest linkage signal was observed at the *RBFOX1* locus on chromosome 16 (LOD=4.41 for early and late families combined; LOD=1.65 for EOAD families). Within the LLFS cohort, *RBFOX1* variants were significantly associated with cognition (n=2,389, rs74004347, $p=8x10^{-6}$), and plasma amyloid levels (n=1,714, rs142440215, $p=9x10^{-5}$). The association between *RBFOX1* and earlier age at onset was also observed in EOAD Caribbean-Hispanic families (n=505, rs140898228, $p=6x10^{-4}$), and in late onset families (n=3,413, rs62013964, $p=6x10^{-5}$).
Conclusions: Our findings suggest that *RBFOX1*, a neuron-specific splicing factor, may be involved in EOAD pathogenesis, nominating it as potential therapeutic target for delaying or preventing onset of dementia.

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SHIFT 01-186

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2 - 3 April 2025

ENDOTHELIN-CONVERTING ENZYME-2 (ECE-2) DEFICIENCY AND BETA-AMYLOID HOMEOSTASIS: IMPLICATIONS FOR ALZHEIMER'S DISEASE RISK AND PROGRESSION

Dana Clausen[1,2], Javier Pacheco-Quinto[2], Hui Peng[2], Kevin Beck[1], Elizabeth Eckman[2]
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Aims: Endothelin-converting enzyme-2 (ECE-2) is an Aβ-degrading enzyme expressed in subpopulations of cortical and hippocampal GABAergic interneurons known to be vulnerable in AD. In mice, ECE-2 overexpression reduces amyloid pathology, while ECE-2 knockout causes increased Aβ accumulation. The recent identification of a rare, monoallelic loss-of-function mutation in ECE2 in a family with late-onset AD implicates impaired ECE-2 activity as a risk factor for AD. We hypothesize that in sporadic AD, age-related reductions in ECE-2 expression may contribute to pathogenesis. In this study, we further characterized the role of ECE-2 in Aβ homeostasis and determined whether changes in ECE-2 mRNA and protein expression occur during aging and during the progression of amyloid pathology in mice.
Methods: Brains from ECE-2 knockout mice, TgCRND8 APP-transgenic mice, and wild-type controls were processed to prepare synaptosomes, extracellular-enriched fractions, and total and synaptosomal RNA. Aβ was measured by ELISA. ECE-2 protein and mRNA were analyzed by western blot and qRT-PCR.
Results: ECE-2 protein is present in synapses and regulates both intrasynaptic and secreted Aβ in a gene-dosage dependent manner. The effect of ECE-2 deficiency was most pronounced in the hippocampal extracellular fraction (60% increase in Aβ). ECE-2 transcript and protein levels decreased with age in wild-type mice, with a ~50% reduction in synaptic cortical and hippocampal protein between 2 and 20 months. In 20-month-old APP-transgenic mice, Ece2 mRNA levels were lower than in 2-month-old wild-types, but synaptic ECE-2 protein levels were significantly elevated (2-5x).
Conclusions: ECE-2 deficiency, caused by age-related downregulation or genetic alteration, may influence AD risk via impaired synaptic Aβ homeostasis. Increased synaptic ECE-2 protein concentration in aged transgenic mice may reflect a compensatory response or defective neuronal proteostasis associated with late-stage amyloid pathology.

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SHIFT 01-187

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2 - 3 April 2025

DYRK1A PLASMA LEVELS IN DOWN SYNDROME PATIENTS WITH(OUT) (QUESTIONABLE) ALZHEIMER'S DISEASE.

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Aims: Individuals with Down Syndrome (DS) have a significantly higher risk of developing Alzheimer's disease dementia (AD), with considerable variability in the onset of symptoms. In DS individuals, the overexpression of DYRK1A due to trisomy 21 may contribute to neurodevelopmental challenges and is also implicated in the increased risk of developing Alzheimer's disease later in life. Studies suggest that aberrant DYRK1A activity may influence amyloid precursor protein processing and tau phosphorylation, two key factors involved in the pathology of Alzheimer's disease. The aims of this study are the following; To investigate the biological function and potential of Dyrk1A, we wanted to examine whether DYRK1A plasma concentrations could be a biomarker for diagnosing Alzheimer's Disease in Down Syndrome [1]. To investigate potential correlations between Amyloid b, phosphorylated forms of tau, total tau and DYRK1A plasma concentrations.
Methods: A study population of in total 143 individuals with DS with or without (questionable) AD was established from specialized care facilities in Flanders, Belgium, between February 2019 and December 2021. We used the Homebrew Simoa technology to detect DYRK1A levels in the plasma collected at inclusion. Additionally, we used the Simoa for the detection of Amyloid b, phosphorylated forms of tau and total tau **in the aforementioned study population.**
Results: We will present correlations between the DYRK1A concentration and the presence of a clinical diagnosis of (questionable) AD in DS, and whether the DYRK1A has an additional predictive value towards the conversions of non-AD tot AD.
Conclusions: If we find significant correlations in the plasma levels of DYRK1A in patients with(out) (questionable) AD and their clinical dementia status, DYRK1A could potentially be investigated as a biomarker for the diagnosis of AD in DS.

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SHIFT 01-190

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2 - 3 April 2025

PHARMACOLOGICAL INHIBITION OF NA/H EXCHANGER ISOFORM 1 ATTENUATES ALZHEIMER'S DISEASE PATHOGENESIS IN APP/PS1 MICE

Jenelle Collier[1], Shamseldin Metwally[1], Mary Mcfarland[1], Sanjana Krishna[2], Pallavi Kurella[1], Victoria Fiesler[1], Mark Stauffer[3], Gulnaz Begum[1], Julia Kofler[4], Dandan Sun[1]
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Aims: Reactive astrogliosis has been indicated as one of the earliest pathological biomarkers observed in Alzheimer's Disease (AD) pathology, appearing before amyloid-beta (Aβ) plaques, Tau neurofibrillary tangles, and cognitive deficits. We previously reported that upregulation of Na+/H+ exchanger isoform 1 (NHE1) protein in reactive astrocytes contributes to neuroinflammation and cognitive function deficits in murine models of ischemic stroke and vascular stenosis
Methods: In this study, we utilized AD human post-mortem and APP/PS1dE9 (APP) mouse brain tissues to determine whether upregulation of NHE1 in astrocytes contributes to AD pathogenesis using immunostaining and behavioral assays.
Results: In both AD human and middle-aged APP mouse brain tissues, we detected significantly elevated NHE1 protein expression in glial fibrillary acidic protein expressing (GFAP+) reactive astrocytes in cortical and hippocampal regions, compared to control groups. Furthermore, increased astrocytic NHE1 protein and GFAP protein were detected in proximity to amyloid-beta (Aβ) plaques in APP mouse brains. We then tested the efficacy of pharmacological inhibition of NHE1 with its inhibitor HOE642 in attenuating AD pathology in APP mice. Vehicle-treated APP/PS1dE9 mice (APP.Veh) exhibited hyperactive locomotor behavior at 4-months and 7-months of age, compared to the wild-type littermate mice (WT.Veh). In contrast, APP mice treated with NHE1 protein inhibitor HOE642 (APP.HOE) displayed significantly less hyperactive locomotor behavior ($p<0.01$) and failed to show significant anxiety-like behavior at 7-months of age. Additionally, the same cohort of APP.HOE mice showed a decrease in the density of Amyloid fibrils detected with anti-Aβ fibril antibody OC.
Conclusions: In summary, we detected NHE1 protein upregulation in reactive astrocytes in AD brains. Pharmacological inhibition of NHE1 protein attenuated pathological Aβ fibril oligomer density and hyperactive locomotor behaviors in APP mice, emerging as a potential early therapeutic target for AD.

SHIFT 01-200

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2 - 3 April 2025

SOLUBLE EPOXIDE HYDROLASE UPREGULATION IN ALZHEIMER'S DISEASE PROMOTES BLOOD-BRAIN BARRIER DYSFUNCTION

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Aims: The study aims to explore how soluble epoxide hydrolase overexpression in Alzheimer's disease (1) is triggered by the presence of amyloid beta (Aß) and its subsequent effects on neurodegenerative processes, (2) affects VE-cadherine dynamics, and (3) contributes to pericyte loss.
Methods: This study utilizes an array of genetically modified mouse models for histological analyses, alongside cell culture techniques, to investigate the intricate mechanisms underlying sEH overexpression on AD pathogenesis.
Results: In this study, we identify the pivotal role of soluble epoxide hydrolase (sEH) in blood-brain barrier disruption in AD. Not only is sEH upregulation associated with amyloid plaques and cerebral amyloid angiopathy (CAA), but it is also accompanied by compromised vascular integrity, as indicated by reduced expression and pathological morphological changes of adherens junctions, and decreased pericyte coverage. Remarkably, genetic ablation of astrocyte-specific sEH in our AD model led to a notable reduction in amyloid-β load, including CAA, and restored vascular integrity. Furthermore, we have found that, in otherwise healthy mice, when sEH is artificially upregulated, there is a localized disruption to VE-Cadherin and associated pericyte loss.
Conclusions: This finding underscores the importance of sEH in VE-Cadherin dynamics, and therefore, the importance of regulating sEH activity in order to maintain vascular homeostasis. This suggests that targeting sEH could be a potential early-intervention therapy for AD.

SHIFT 01-201

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2 - 3 April 2025

METHYLENETETRAHYDROFOLATE REDUCTASE GENE POLYMORPHISM EFFECT ON BBB PERMEABILITY AND PERFUSION IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: This study examined the impact of the methylenetetrahydrofolate reductase (MTHFR) c.677C>T polymorphism on blood-brain barrier (BBB) permeability and perfusion in elderly individuals with amyloid-positive normal cognition (NC) or mild cognitive impairment (MCI). The T allele of this polymorphism is linked to reduced enzymatic activity and hyperhomocysteinemia (H-Hcy), potentially contributing to Alzheimer's disease (AD) through neurotoxic effects. However, the relationship between MTHFR status and BBB permeability in AD remains unclear.
Methods: We enrolled 33 elderly participants with amyloid-positive normal cognition (NC, n = 9) or mild cognitive impairment (MCI, n = 24) between June 2018 and May 2020 at Konkuk University Medical Center. Diagnoses were based on the NIA-AA criteria for preclinical and prodromal Alzheimer's disease. MTHFR c.677C>T polymorphism analysis was performed on 32 participants using polymerase chain reaction and HinFI restriction enzyme digestion, identifying 23 CT/TT carriers and 9 CC homozygotes. BBB permeability (Ktrans) and perfusion (Vp) were measured using dynamic contrast-enhanced MRI. Statistical analyses adjusted for age, sex, and APOE status.
Results: Non-T allele carriers (CC) exhibited higher Ktrans than T allele carriers (CT/TT). Significant increases in Ktrans were observed in the left frontal ($p = 0.005$) and right frontal lobes ($p = 0.039$), left medial ($p = 0.017$) and lateral orbitofrontal regions ($p = 0.033$), and left hippocampus ($p = 0.050$). In white matter, higher Ktrans values were found in the left frontal ($p = 0.042$), occipital ($p = 0.014$), parietal ($p = 0.012$), and temporal lobes ($p = 0.005$). Vp was higher in the right frontal lobe in CC than CT/TT ($p = 0.049$).
Conclusions: Contrary to our initial hypothesis, we found that non-T allele carriers exhibited higher Ktrans than T allele carriers. These results suggest that the T allele of the MTHFR c.677C>T polymorphism may compensate for BBB integrity, possibly mitigating the impact of reduced enzymatic activity and hyperhomocysteinemia.

SHIFT 01-205

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

MODULATION OF EXTRACELLULAR MATRIX AND GLIAL MORPHOMETRY IN TAU PATHOLOGY

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Aims: The role of extracellular matrix (ECM)-glial interactions in the early development of neurofibrillary tangle (NFT) pathology in Alzheimer's disease (AD) is still poorly understood. Recent studies suggest that alterations in ECM, perineuronal and perisynaptic nets (PNN/PSN), surrounding specific neuronal populations such as GABAergic interneurons, are linked to AD pathogenesis, where tau pathology induces the loss of GABAergic interneurons, leading to disrupted synaptic plasticity and behavioral impairments. This study aims to investigate how ECM modulation influences tau propagation in AD.
Methods: We administered a 10-week diet containing 2.5% (w/w) 4-methylumbelliferone (4MU), a hyaluronic acid synthesis inhibitor, to tau-propagation rat models. Following treatment, the animals were perfused, and brain tissue was analyzed via immunohistochemistry. We assessed ECM integrity using markers such as Wisteria floribunda agglutinin (WFA), hyaluronic acid-binding protein (HABP), chondroitin sulfate proteoglycans (CSPGs), and Tenascin-R. Glial morphometry, including shape descriptors, skeleton, and Sholl analysis, was performed using glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor molecule 1 (Iba-1) markers for astrocytes and microglia respectively. NFT load was evaluated with AT8 (p-tau ser202/thr205) and Thioflavin-S staining.
Results: Our results demonstrated significant astrocytic atrophy, with reduced branching and volume, impairing their neuronal support functions. ECM reduction correlated with increased microglial phagocytic activity and reactivity, indicating heightened surveillance with significant reduction in tangle load. These findings suggest that ECM modulation profoundly affects glial morphology and function during tau propagation.
Conclusions: These findings indicate that 4-MU may hold promise as a therapeutic agent by modulating ECM composition and glial responses, potentially mitigating tau-related neurodegeneration in AD. This work was supported by funding from the The EU Joint Programme – Neurodegenerative Disease Research (JPND), WesternND and Multi-MEMO, as well as Agentúra na podporu výskumu a vývoja (APVV-23-0436).

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SHIFT 01-206

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

ANATOMICAL CHARACTERIZATION OF PT217-TAU IN AGED RHESUS MACAQUE ASSOCIATION CORTICES: REVEALING SEEDING AND NEURODEGENERATION WITHIN HIGHER-ORDER CORTICAL CIRCUITS

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Aims: Developments in Alzheimer's disease (AD) have revealed a novel fluid-based pT217-tau biomarker, in CSF and plasma, that predicts AD prior to cognitive deficits. Understanding the role of pT217-tau is important in assessing efficacy of novel treatments aimed at early-stage disease. However, it is unknown why pT217-tau is effective in predicting brain pathology, as little is known about early, soluble pT217-tau brain expression. The etiology of pT217-tau in aging brains can be probed in the rhesus macaque model of sporadic AD, where perfusion-fixation allows capture of phosphorylated proteins in their native state.
Methods: We utilized multi-label immunofluorescence and immunoelectron-microscopy to examine the subcellular localization of early-stage pT217-tau in entorhinal cortex and dorsolateral prefrontal cortex of aged macaques with naturally occurring tau pathology and assayed pT217-tau levels in plasma.
Results: pT217-tau labeling is primarily observed in postsynaptic compartments, accumulating within: 1) dendritic spines on the calcium-storing smooth endoplasmic reticulum spine apparatus near asymmetric glutamatergic-like synapses, and 2) in dendritic shafts, where it aggregated on microtubules, often "trapping" endosomes associated with Aβ42. The dendrites expressing pT217-tau were associated with autophagic vacuoles and dysmorphic mitochondria, indicative of early neurite degeneration. We observed trans-synaptic pT217-tau trafficking between neurons within omega-shaped bodies and endosomes, specifically near excitatory, but not inhibitory synapses. We also examined pT217-tau in blood plasma in macaques across age-span and observed a statistically significant age-related increase in pT217-tau.
Conclusions: These data provide the first direct evidence of pT217-tau trafficking between neurons near synapses to "seed" tau pathology in higher brain circuits, interfacing with the extracellular space to become accessible to CSF and blood. The expression of pT217-tau in dendrites with early signs of degeneration may help to explain why this tau species can herald future disease.

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SHIFT 01-207

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

ALPHA SYNUCLEIN CO-PATHOLOGY ACCELERATES AMYLOID ASSOCIATED TAU ACCUMULATION IN ALZHEIMER'S DISEASE

Nicolai Franzmeier[1], Sebastian Roemer-Cassiano[1], Alexander Bernhardt[2], Amir Dehsarvi[1], Anna Dewenter[1], Anna Steward[1], Lukas Frontzkowski[1], Zeyu Zhu[1], Johannes Gnörich[3], Julia Pescoller[1], Fabian Wagner[1], Fabian Hirsch[2], Hannah De Bruin[4], Rik Ossenkoppele[5], Carla Palleis[6], Michael Schöll[7], Johannes Levin[6], Matthias Brendel[8], Günter Höglinger[6]
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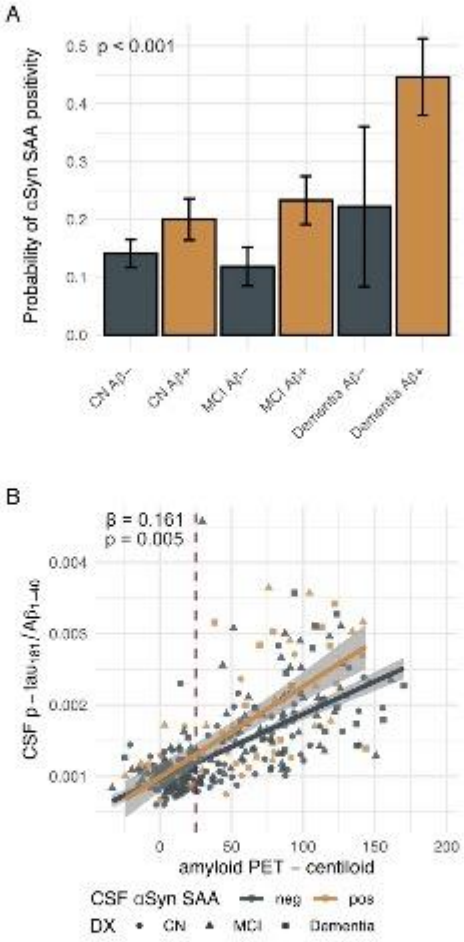
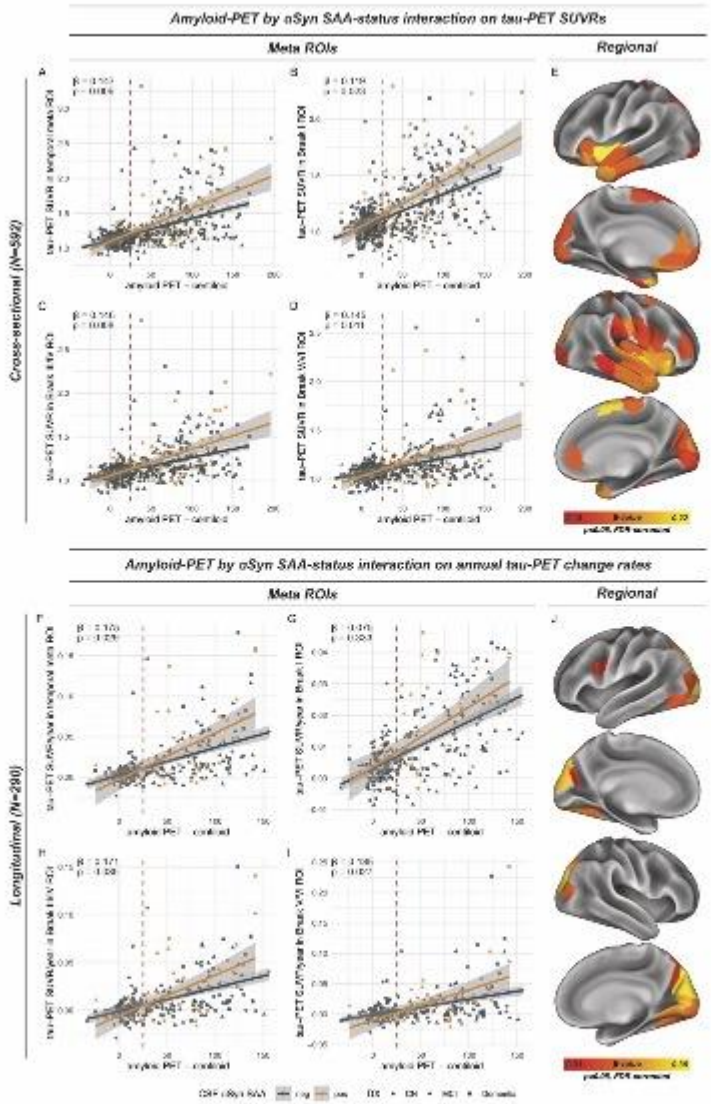
Aims: Alpha-Synuclein (α-Syn) is a hallmark pathology in Parkinson's disease but also the most common co-pathology in Alzheimer's disease (AD). Preclinical studies suggest that α-Syn can amplify amyloid-beta (Aβ)-associated tau aggregation, implying that α-Syn co-pathology may contribute to the Aβ-induced tau aggregation observed in AD. To investigate this, we combined a novel CSF-based seed-amplification assay (SAA) to determine α-Syn positivity with PET neuroimaging in a large cohort ranging from cognitively normal individuals to those with dementia, examining whether α-Syn co-pathology accelerates Aβ-driven tau accumulation and cognitive decline.
Methods: In 284 Aβ-positive and 308 Aβ-negative subjects, we employed amyloid-PET, Flortaucipir tau-PET, and a CSF-based α-Syn SAA assay to detect in vivo α-Syn aggregation. CSF p-tau181 measures were available for 410 subjects to assess early tau abnormalities. A subset of 155 Aβ-positive and 135 Aβ-negative subjects underwent longitudinal tau-PET over approximately 2.5 years. Using linear regression models, we analyzed whether α-Syn positivity was linked to stronger Aβ-related increases in baseline fluid and PET tau biomarkers, faster Aβ-driven tau-PET increase, and more rapid cognitive decline.
Results: α-Syn positivity was more common in Aβ+ subjects (CN/MCI/Dementia: CN/MCI/Dementia: 20/23/45%, Fig.1A) compared to Aβ- subjects (14/12/22%; $p<0.001$) and increased with clinical severity. α-Syn positivity was associated with stronger Aβ-related p-tau181 increases ($p=0.005$, Fig.1B), tau-PET uptake ($p<0.006$, Fig.2A-E), and faster Aβ-driven tau-PET increases ($p=0.024$, Fig.2F-J) over time in tau-vulnerable brain regions. Additionally, α-Syn positivity was linked to faster Aβ-related ($p<0.001$), but not tau-related, cognitive decline ($p=0.972$).

Figure 1:



Barplot, illustrating the probability of αSyn SAA positivity stratified by amyloid status and clinical syndrome severity (A). Scatterplot illustrating the interaction effect between amyloid-PET and αSyn SAA status on cross-sectional levels of CSF p-Tau$_{181}$/Aβ$_{1-40}$ as an indicator of earliest tau pathophysiology. Diagnostic groups are indicated by shape, the cut-point of amyloid-PET positivity is indicated by the dashed red line at 25 centiloids. The beta value indicates the strength of the amyloid-PET x CSF αSyn SAA interaction effect.

Figure 2:



Scatterplots illustrating the interaction effect between global amyloid-PET (i.e. centiloid) and αSyn SAA status on tau-PET SUVRs for meta ROIs (A-D) and regional analyses (E), as well as for annual tau-PET SUVR change rates (F-J). Diagnostic groups are indicated by shape, the cut-point of amyloid-PET positivity is indicated by the dashed red line at 25 centiloids. Beta value indicates the strength of the amyloid-PET x CSF αSyn SAA interaction effect.

Conclusions: These findings suggest that α-Syn co-pathology, detectable via CSF-based SAA, is more prevalent in advanced AD and is associated with accelerated tau pathology which drives faster cognitive decline. This highlights that a-Syn co-pathology may accelerate amyloid-driven AD pathophysiology.

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SHIFT 01-208

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2 - 3 April 2025

DISENTANGLING TAU PATHOLOGY: HOW FIBRIL STRUCTURE AND POST-TRANSLATIONAL MODIFICATIONS DRIVE SEEDING CAPACITY

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Aims: The accumulation of hyperphosphorylated, aggregated tau in neurons is one of the hallmarks of Alzheimer's disease (AD). Recent work in structural biology has solved the structure of tau fibrils in several tauopathies and found that the structure of tau fibrils varies between diseases, but fibril structure is conserved among patients within the same disease, suggesting that tau fibril structure relates to its pathogenicity. Tau fibrils derived from AD brain (AD PHF) seed AD-like pathology in wild-type (WT) mice, yet efforts to recapitulate this seeding with recombinant fibrils have failed. We hypothesized that recombinant fibrils that recapitulate the core region structure of AD tau and PTM pattern will show similar seeding capacity to AD tau.
Methods: We screened recently developed recombinant tau fibrils to investigate how tau fibril structure and PTMs are related to tau seeding capacity in primary cortical neurons. We then assessed selected fibrils through hippocampal injection into WT and *MAPT* KI mice.
Results: The screening method showed that fibrils more closely resembling the core structure of an AD PHF had a higher seeding capacity than other fibrils. We also found that full-length recombinant tau fibrils containing PTMs had a higher seeding capacity than full-length fibrils without PTMs. However, the replication of the core structure in truncated fibrils nor the presence of PTMs alone are insufficient to fully replicate the seeding capacity of AD PHFs. Our finding of altered seeding capacity due to fibril structure was replicated in *MAPT* KI mice.
Conclusions: The structure and PTM patterns of tau fibrils appear to be closely tied to fibril pathogenicity. We believe that the generation of fibrils that more closely resemble AD PHFs can lead to improved model systems of tau pathology in AD.

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SHIFT 01-210

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
2 - 3 April 2025

POSITIVE ALLOSTERIC MODULATORS OF SERCA PUMP AS POTENTIAL THERAPEUTICS FOR ALZHEIMER'S DISEASE

Russell Dahl[1], Ilya Bezprozvanny[2]
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Aims: Alzheimer's disease (AD) is an irreversible neurodegenerative disease that affects millions of people worldwide. AD does not have a cure and most drug development efforts in the AD field have been focused on targeting theamyloid pathway based on the "amyloid cascade hypothesis". However, in addition to the amyloid pathway,substantial evidence also points to dysregulated neuronal calcium (Ca2+) signaling as one of the key pathogenicevents in AD, and it has been proposed that pharmacological agents that stabilize neuronal Ca2+ signaling mayact as disease-modifying agents in AD. In our studies we set out to evaluate the hypothesis that positive allostericregulators (PAMs) of the Sarco/endoplasmic reticulum Ca2+ ATPase (SERCA) pump might act as such Ca2+ stabilizing agents.
Methods: To test this hypothesis we evaluated a number of SERCA PAMs in in vitro and in vivo experiments with 5xFAD, APP/PS1 and APPKI transgenic models of AD.
Results: We demonstrated that SERCA PAMs are able to rescue loss of synaptic spines, prevent hippocampal LTP defects, rescue autophagy defects and improve behavioral readouts in cognitve assays and normalize expression of endoplasmic reticulum (ER) stress genes in transgenic models of AD.
Conclusions: The results of our studies supported a hypothesis that the SERCA pump is a potential novel therapeutic drugtarget for AD and that SERCA PAMs that we invented are promising lead molecules for developing diseasemodifying agents in AD and possibly other neurodegenerative disorders.

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SHIFT 01-211

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
2 - 3 April 2025

INTEGRATIVE MULTI-OMICS PATHWAY ANALYSIS ACROSS HUMAN BRAINS AND 3D CELLULAR MODELS REVEALS THE P38 MAPK-MK2 AXIS AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

Sang Su Kwak[1], Pourya Naderi Yeganeh[2], Rudolph Tanzi[1], Winston Hide[2], Doo Yeon Kim[1]
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Aims: Alzheimer's disease (AD) involves complex pathological cascades across different brain cell types, creating challenges for current therapeutic strategies that primarily target amyloid-β (Aβ) accumulation. While 2D/3D human cellular models offer valuable insights into these intricate disease mechanisms, there is currently no comprehensive, unbiased tool/platform to systematically evaluate the similarities between AD cellular models and brain tissues, nor their potential therapeutic relevance.
Methods: We unbiasedly assessed mechanistic similarities between AD brains and 2D/3D human cellular models to identify the dysregulated pathways based on transcriptomic datasets. We also cross-compared dysregulated pathways from phosphoproteomics analysis. As a proof of concept, we pharmacologically targeted the top pathways to evaluate their effects on AD pathology in our 3D cellular models.
Results: We identified 83 dysregulated transcriptomic pathways shared between AD brains and the cellular model, including the upregulation of p38 mitogen-activated protein kinase (MAPK) pathways. Elevated levels of active p38 MAPK were observed in the 3D AD cellular model, human brains, and 5XFAD mice, mainly localized to presynaptic dystrophic neurites. Unbiased phosphoproteomics analysis further confirmed a significant increase in p38 MAPK substrate phosphorylation driven by Aβ42 accumulation. Notably, targeting p38 MAPK with a clinical p38α/β MAPK inhibitor, which has not been previously tested for AD, significantly reduced Aβ-induced tau pathology, Aβ accumulation, neuronal loss, and microglial activation in 3D AD cellular models and human microglia. Additionally, we found that MAPK-activated protein kinase 2 (MK2) plays a crucial role in mediating Aβ-induced tau pathology, underscoring the importance of the p38 MAPK-MK2 signaling axis.
Conclusions: This study underscores the value of integrated pathway activity analysis for AD drug discovery. Our results also highlight the critical role of protein kinase networks, particularly the p38 MAPK-MK2 axis, in driving AD pathology.

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SHIFT 01-214

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ILYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
2 - 3 April 2025

THE PROTEOSTASIS NETWORK RESPONSE TO CHRONIC ENVIRONMENTAL STRESS: LINKING SURVIVAL TO PROTEIN AGGREGATION IN A HUMAN NEUROBLASTOMA CELLULAR MODEL

Niccolò Candelise[1], Emiliano Montalesi[2], Daniela Caissutti[2], Antonella Ferrante[1], Rita Pepponi[1], Roberta Misasi[2]
[1]Italian National Institute of Health, National Center For Drug Research Ad Evaluation, Rome, Italy, [2]Sapienza University of Rome, Experimental Medicine, Rome, Italy

Aims: Proteins tend to misfold upon stressful events that alter their homeostasis, leading to protein aggregation. Tight regulation of protein synthesis, folding and degradation, defined as proteostasis network (PN), is required to ensure the functionality of the cell. Most neurodegenerative disorders are associated with the alteration of this network. We describe the alteration in key components of the PN during chronic stress. We further link these alterations with the increase in the amyloid burden and with the aggregation of the protein TDP-43, a major player in the onset of Amyotrophic Lateral Sclerosis.
Methods: Human Neuroblastoma SH-SY5Y cells were employed for this study. Cells were treated with a panel of stressors including serum deprivation (SD); oxidative stress with Sodium Arsenite (Ars) or Paraquat (PQ); osmotic stress with Sorbitol (Sorb). Cells were treated for 24h and 72h and analyses of key players of the PN were investigated by Western Blot, spectrophotometric assays and flow cytometry. immunofluorescence staining was conducted to detect pathology-related phosphorylated TDP-43 and stress granules formation. We developed an assay to detect the amyloid burden in cells by exploiting the binding of Thioflavin-S to cross-beta structures, the building block of amyloids.
Results: chronic treatments elicited a strong response in terms of expression of PN proteins. Amyloid burden increased only after 72h, regardless of the type of stressors. Cell viability was not significantly altered along treatments. TDP-43 shows cytoplasmic localization, phosphorylation and aggregation after 72h of treatment independent of stress granules formation.
Conclusions: Our result suggests that TDP-43 is a central player in the response to chronic insults. In the absence of any genetic engineering, PN alterations correlate with increased amyloid burden, reflecting the global welfare of the cellular system.

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SHIFT 01-215

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

COVID-19 EXACERBATES NEUROINFLAMMATION IN EXPERIMENTAL VASCULAR DEMENTIA

Grant Talkington, Gregory Bix, Saifudeen Ismael
Tulane University School of Medicine, New Orleans, United States of America

Aims: The neurological complications of COVID-19, particularly in individuals with pre-existing vascular risk factors, remain poorly understood. This study investigated the potential synergistic effects of experimental vascular dementia and SARS-CoV-2 infection on neuroinflammation and blood-brain barrier (BBB) integrity in mice.
Methods: 12 Female C57Bl/J6 wild-type mice [GB1] were subjected to bilateral carotid artery stenosis (BCAS) to model vascular dementia, followed by intranasal infection (1x10^4 PFU) with mouse-adapted SARS-CoV-2 (MA10 strain) two weeks later. Four experimental groups were established of 12 animals each for a total of 48: mock (PBS control), BCAS alone[GB2] , MA10 infection alone, and combined BCAS+MA10. Neuroinflammation and BBB integrity were assessed three days after infection/mock through RT-qPCR, immunohistochemistry, and immunofluorescence analyses.
Results: The combined BCAS+MA10 group exhibited significantly increased expression by RT-qPCR of inflammatory markers CCL-2 and IL-6 in brain tissue compared to mock controls ($p<0.05$). Immunohistochemical analysis revealed increased microglial activation (Iba-1 staining) in the cortex and striatum of BCAS+MA10 mice. Astrocyte activation, measured by GFAP fluorescence, was significantly enhanced in the striatum of BCAS+MA10 mice, with increases in percentage area, average size, and total area of GFAP-positive cells compared to all other conditions ($p<0.05$). BBB integrity was compromised in all experimental conditions, with the combined BCAS+MA10 group showing the most pronounced reductions occludin.
Conclusions: This study demonstrates that pre-existing experimental vascular dementia exacerbates the acute neuroinflammatory response to SARS-CoV-2 infection, characterized by enhanced microglial and astrocyte activation and compromised BBB integrity. These findings suggest a potential mechanism for the increased severity of neurological complications in COVID-19 patients with vascular risk factors and highlight the need for targeted interventions in this vulnerable population.

SHIFT 01-216

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

IMPAIRED GLIAL INSULIN SIGNALING IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE: AN ANIMAL MODEL STUDY

Wenqiang Chen[1,2]
[1]Steno Diabetes Center Copenhagen, Herlev, Denmark, [2]Harvard Medical School, Joslin Diabetes Center, Boston, United States of America

Aims: To define the role of brain insulin resistance in the pathogenesis of Alzheimer's Disease (AD)
Methods: we created separate conditional knockout mouse lines, including iGIRKO (inducible astrocyte-specific insulin receptor knockout) and MG-IRKO (inducible microglia-specific insulin receptor knockout) and crossed these lines with 5xFAD mouse model of AD, to create iGIRKO/5xFAD and MG-IRKO/5xFAD, respectively.
Results: Both resultant mice exhibited glial activation and increased levels of Aβ plaque. Specifically, loss of insulin signaling in microglia results in elevated neuroinflammation and metabolic reprograming with an increase in glycolysis, which result in impaired uptake of Aβ.
Conclusions: insulin signaling in astrocyte and microglia plays a key role in cellular metabolism, neuroinflammation and cellular uptake of Aβ, such that reduced insulin signaling in these cells alters behaviors and accelerates AD pathogenesis.

SHIFT 01-217

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

TOLL-LIKE RECEPTOR 4 IN PARKINSON'S DISEASE

Carmela Conte[1], Angela Ingrassia[2], John Brevè[2], John Bol[2], Evelien Timmermans-Huisman[2], Anne-Marie Van Dam[2], Tommaso Beccari[1], Wilma Van De Berg[2]
[1]University of Perugia, Pharmaceutical Sciences, Perugia, Italy, [2]Vrije Universiteit Amsterdam1081 HZ Amsterdam, Department Of Anatomy And Neurosciences, Amsterdam, Netherlands

Aims: Toll-like receptors (TLRs) are a group of innate immune receptors widely distributed in the CNS that play a critical role in neuroinflammation and in several neurodegenerative diseases including Parkinson's disease. Here, we aimed at investigate the expression levels of TLR4 and αSyn in substantia nigra (SN) and medial temporal gyrus (GTM) of post-mortem brain tissues from patients with PD. Moreover, we analysed the posphoSer129-αSyn (pS129-αSyn) levels considered the most common used marker of αSyn pathology as well as the Iba1 a marker microglia activation.
Methods: Post-mortem human brain tissue was obtained from the Netherlands Brain Bank and the Department of Anatomy and Neurosciences of VU University Medical Center (VUmc, Amsterdam, The Netherlands). A total of 60 samples (15 cases and 15 control donors per GTM and SN) were analysed by qPCR. A total of 25 samples (6 PD/PDD donors and 6 controls for GTM; 6 PD/PDD donors and 7 controlled cases for SN) were analysed by immunofluorescence and confocal microscopy for TLR4, pS129-αSyn, and Iba1. The pS129-αSyn immunoreactivity was to confirm cytopathology.
Results: In the present study, we observed that the levels of TLR4 were increased in the substantia nigra (SN) and in the middle temporal gyrus (GTM) of patients with PD, while αSyn was downregulated, probably because of the significant depletion of dopaminergic neurons. In PD patients, we also found co-localization between TLR4 and pS129-αSyn and between TLR4 and glial Iba-1 in SN Lewy bodies and pyramidal neurons within GTM compared with the same regions of the control donors.
Conclusions: Our findings provide evidence that TLR4 is up-regulated in PD patients. Moreover, the co-localizations between TLR4 and pS129-αSyn and Iba1 suggest a physical interaction that could evoke the activation of inflammatory response.

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SHIFT 01-218

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

LOSS OF GLYOXALASE-1 ENHANCES NEUROINFLAMMATION AND NEURODEGENERATION INDEPENDENT FROM ABETA PATHOLOGY IN APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

Aminat Imam-Fulani[1], Swetha Rao[2], Sam Phillip[1], Krishina Chennavajula[1], Joyce Meints[1], Swati More[2], Michael Lee[1]
[1]University of Minnesota, Neuroscience, Minneapolis, United States of America, [2]University of Minnesota, Center For Drug Design, Minneapolis, United States of America

Aims: Alzheimer's disease (AD) is characterized by Aβ deposits, oxidative stress, and inflammation. In AD, increase in oxidized sugars (methylglyoxal, MG) link oxidative stress with inflammation as MG leads to advanced glycation endproducts (AGE) that promote inflammation. AD associated increase in MG/AGE is thought to result from decrease in the glyoxalase (Glo1), an enzyme that is responsible for GSH-dependent metabolism of MG. Thus, we tested if genetic loss of Glo1 exacerbate AD-related pathology in the $APP_{swe}/PS1_{DE9}$ (APP/PS1) model of cerebral amyloid pathology.
Methods: To determine the role of Glo1 in AD, we generated APP/PS1 mice lacking one ($Glo1^{Het}$) or both ($Glo1^{KO}$) copies of the Glo1 gene and analyzed them at 12 months of age. We used biochemical analysis for oxidative stress and Glo1 function and quantitative neuropathological analysis.
Results: Biochemical and Western blot analysis revealed a significant increase in the levels of MG and advanced glycation end-products (AGE) in APP/PS mice lacking Glo1. Surprisingly, the constitutive loss of Glo-1 did not exacerbate Ab pathology in APP/PS1 mice, while partial loss of Glo1 activity in $AP/Glo1^{Het}$ led to a significant increase in overall Ab pathology. The results indicate a developmental compensatory response to the complete loss of Glo1 expression. The increased MG and AGE levels are are associated with increased inflammation. Analysis of activated microglia using CD68 staining show that despite the reduced Ab pathology in the $APP/PS1/Glo1^{KO}$ mice, the level of CD68 staining was much higher than in the $APP/PS1/Glo1^{WT}$ mice. Analysis of TH+ afferents and TH+ neurons in the Locus Coeruleus, showed a greater loss of TH+ afferents and neurons in Glo1 deficient APP/PS1 mice.
Conclusions: We show that Glo1 is important for modulating neuroinflammation resulting from MG/AGE formation and subsequent neurodegeneration in AD. Further, neuroinflammation, rather than Aβ pathology, correlates with neurodegeneration in APP/PS1 model.

SHIFT 01-228

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ISYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
2 - 3 April 2025

PRESYNAPTIC APP METABOLITES: A DOUBLE-EDGED SWORD OF COMPENSATORY RESPONSES AND EXCITOTOXICITY

Akshay Kapadia, Ezgi Daşkın, Anne-Sophie Hafner
Radboud University, Section Neurobiology, Donders Institute For Brain, Cognition And Behaviour, Nijmegen, Gelderland, Netherlands

Aims: This study investigates the molecular mechanisms behind Alzheimer's disease (AD) onset, focusing on presynaptic processing of amyloid precursor protein (APP) and its implications for synaptic pathology. Early synaptic deficits in AD may stem from issues with APP and its proteolytic products, particularly APP-Carboxyl Terminal Fragments (APP-CTF) like C99, and amyloid-β (Aβ) peptides. We hypothesize that deficits in APP processing is a key factor in initiating synaptic dysfunction.
Methods: Using transgenic vGLUT1-GFP mice, we isolated and sorted synapses for biochemical analysis. Wild-type primary cortical neurons were treated with γ-secretase inhibitors to increase APP-CTF accumulation or enhance amyloidogenic APP processing. We assessed mitochondrial function, local protein synthesis, and monitored neuronal calcium dynamics and synaptic vesicle activity.
Results: Our findings show that full-length APP, APP-CTFs, and their processing enzymes localize primarily to excitatory presynaptic compartments. Inhibition of γ-secretase caused significant accumulation of APP-CTFs, leading to disrupted calcium dynamics and impaired synaptic vesicle release. This accumulation also resulted in mitochondrial dysfunction and dysregulated local protein synthesis, independent of Aβ. While increasing Aβ concentrations could initially rescue cell-autonomous defects in synaptic excitatory/inhibitory function (hyperexcitability), this compensatory response ultimately fails, leading to synaptic loss and neurodegeneration.
Conclusions: In conclusion, presynaptic APP-CTF accumulation, particularly C99, is critical in early synaptic dysfunction associated with AD, disrupting calcium dynamics, mitochondrial function, and local protein synthesis. While Aβ peptides may provide temporary compensatory responses, prolonged exposure leads to synaptic failure. Our study highlights the need to target APP-CTF accumulation and modulate Aβ interactions as potential strategies to delay or prevent AD onset. Understanding these mechanisms is vital for developing effective therapeutic approaches to address early synaptic impairments in AD.

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SHIFT 01-229

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING
2 - 3 April 2025

DISTINCT METABOLIC PROGRAMS DRIVE CELL TYPE- AND MORPHOLOGY-SPECIFIC LIPID DROPLET ACCUMULATION IN ALZHEIMER'S DISEASE

Shoxruxxon Alimukhamedov[1], James Haberberger[1], Michael Haney[2], Tony Wyss-Coray[1,3], Alina Isakova[1]
[1]Stanford University, The Phil & Penny Knight Initiative For Brain Resilience, Stanford, United States of America, [2]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America, [3]Stanford University, Neurology And Neurological Sciences, Stanford, United States of America

Aims: The role of lipid metabolism in Alzheimer's Disease (AD) pathology remains underexplored, particularly in how lipid droplets (LDs) accumulate in distinct brain cell types and regions. This study aims to characterize LD accumulation in relation to AD pathology, focusing on its spatial distribution and correlation with disease severity, gene expression, and cell type specificity.
Methods: We applied spatial transcriptomics and lipidomics to analyze LDs, proteins, and RNA transcripts in brain tissue from control, APOE3/3, and APOE4/4 AD patients. Differential gene expression (DEG) analysis was performed on anatomical sub-regions, and machine learning models predicted pathology based on LD distribution.
Results: LDs were found near amyloid-beta plaques, with the highest accumulation in microglia and astrocytes. APOE4/4 carriers showed a significantly higher LD burden than APOE3/3 and controls. Niche-dependent LD zonality was observed, with certain cell types in specific regions displaying greater LD accumulation. Importantly, LDs in astrocytes and microglia were linked to distinct lipid metabolism pathways, characterized by up- and downregulated genes related to lipid transport and storage. LD size and frequency correlated with gene expression profiles, inflammation, and plaque proximity.
Conclusions: LD accumulation is closely associated with AD pathology, particularly in APOE4/4 carriers. While LDs were present in multiple cell types, the gene programs governing lipid metabolism differed between astrocytes and microglia, suggesting cell-type-specific regulation of lipid handling in the brain. These findings identify potential therapeutic targets for modulating lipid metabolism in neurodegenerative diseases and warrant further investigation into the underlying mechanisms.

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SHIFT 01-230

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING
2 - 3 April 2025

POTENTIAL DIRECT ROLE OF SYNUCLEIN IN DOPAMINE TRANSPORT AND ITS IMPLICATIONS FOR PARKINSON'S DISEASE PATHOGENESIS

Meewhi Kim, Ilya Bezprozvanny
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Aims: Parkinson Disease (PD) is a progressive neurodegenerative disorder that is caused by dysfunction and death of dopaminergic neurons. Mutations in the gene encoding α-synuclein (ASYN) have been linked with familial PD (FPD). Despite important role of ASYN in PD pathology, its normal biological function has not been clarified, although direct action of ASYN in synaptic transmission and dopamine (DA +) release have been proposed. In the present report we propose a novel hypothesis that ASYN functions as DA +/H+ exchanger that can facilitate transport of dopamine across synaptic vesicle (SV) membrane
Methods: 1. Modeling of ASYN and pHILP structures and membrane distance measurements 2. Membrane-association energy calculations.
Results: By bioinformtics anlaysis we discovered close similarity in domain structure of ASYN and pHILP, a designed peptide developed to mediate loading of lipid nanoparticles with cargo molecules. We reasoned that carboxyterminal acidic loop D2b domain in both proteins binds cargo molecules. By mimicking DA + association with E/D residues in D2b domain of ASYN using Tyrosine replacement approach (TR) we have been able to estimate that ASYN is able to transfer 8-12 molecules of dopamine across SV membrane on each DA +/H+ exchange cycle. Our results suggest that familial PD mutations (A30P, E46K, H50Q, G51D, A53T and A53D) will interfere with different steps of the exchange cycle. We also predicted that similar impairment in ASYN DA +/H+ exchange function also occurs as a result on neuronal aging due to changes in SV lipid composition and size and dissipation of SV pH gradient.
Conclusions: Proposed novel functional role of ASYN provides novel insights into its biological role and its role in PD pathogenesis. lar mechanism for FPD and sporadic age related PD.

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SHIFT 01-233

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
2 - 3 April 2025

MEDIATIVE PATHWAYS FOR ALZHEIMER'S DISEASE AND RELATED DEMENTIA IN DIVERSE HISPANIC/LATINO COMMUNITIES

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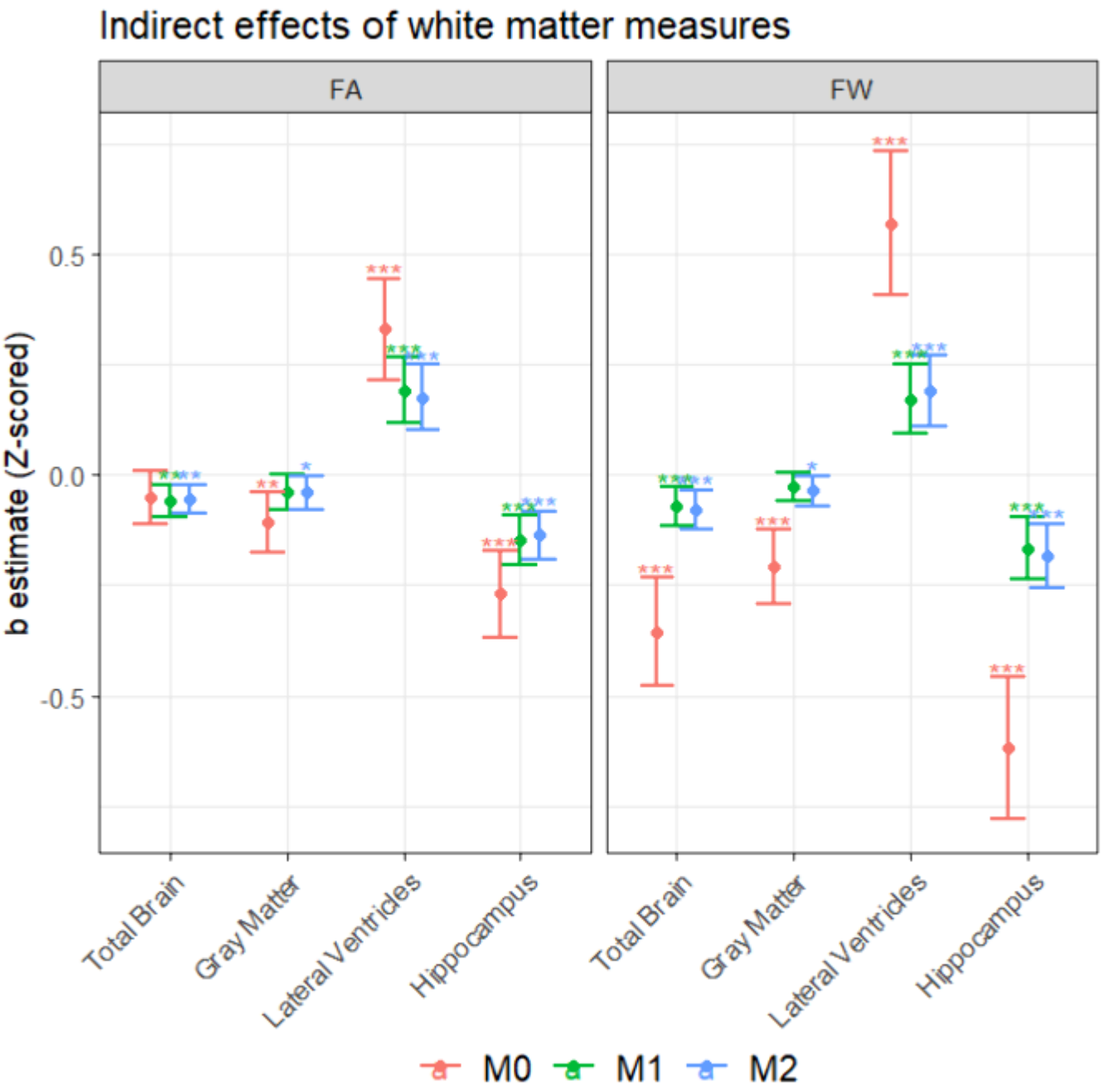
Aims: Hispanic/Latino populations in the US are rapidly growing and have an increased risk for Alzheimer's Disease and Related Dementias (ADRD) compared to non-Hispanic Whites. This could be partly explained by the higher prevalence of certain cardiovascular disease risk factors, such as diabetes. Evidence links diabetes to ADRD risk, yet less is known about mechanistic pathways through which diabetes increases ADRD risk, especially in non-selective community dwelling aging adults. Hispanic/Latino communities are understudied, and existing work suggest distinct pathophysiology for ADRD in these populations; more mixed pathology that involves both vascular and AD types. Therefore, it is important to explore mechanisms that could lead to neurodegeneration among Hispanic/Latino individuals, particularly in the context of diabetes.
Methods: We used n=2,627 from the HCHS/SOL, SOL-INCA and SOL-INCA MRI. Outcomes included total brain, gray matter, hippocampus, and lateral ventricle volumes. The primary exposure was diabetes status (based on American Diabetes Association guidelines). Mediators included plasma neurofilament light chain (NFL), Aβ42/40, ptau181, white matter hyperintensities, free water, and fractional anisotropy. Complex survey adjusted generalized structural equation models were used to estimate direct, indirect, and total effects. We adjusted for sociocultural and vascular factors in models.
Results: The reference group was no diabetes NFL, but not ptau181 or Aβ42/40, mediated the associations between diabetes and outcomes (except hippocampus; ~15% proportion mediated). Fractional anisotropy and free water mediated associations between diabetes and outcomes (~50% proportion mediated). No significant mediations were found with prediabetes.

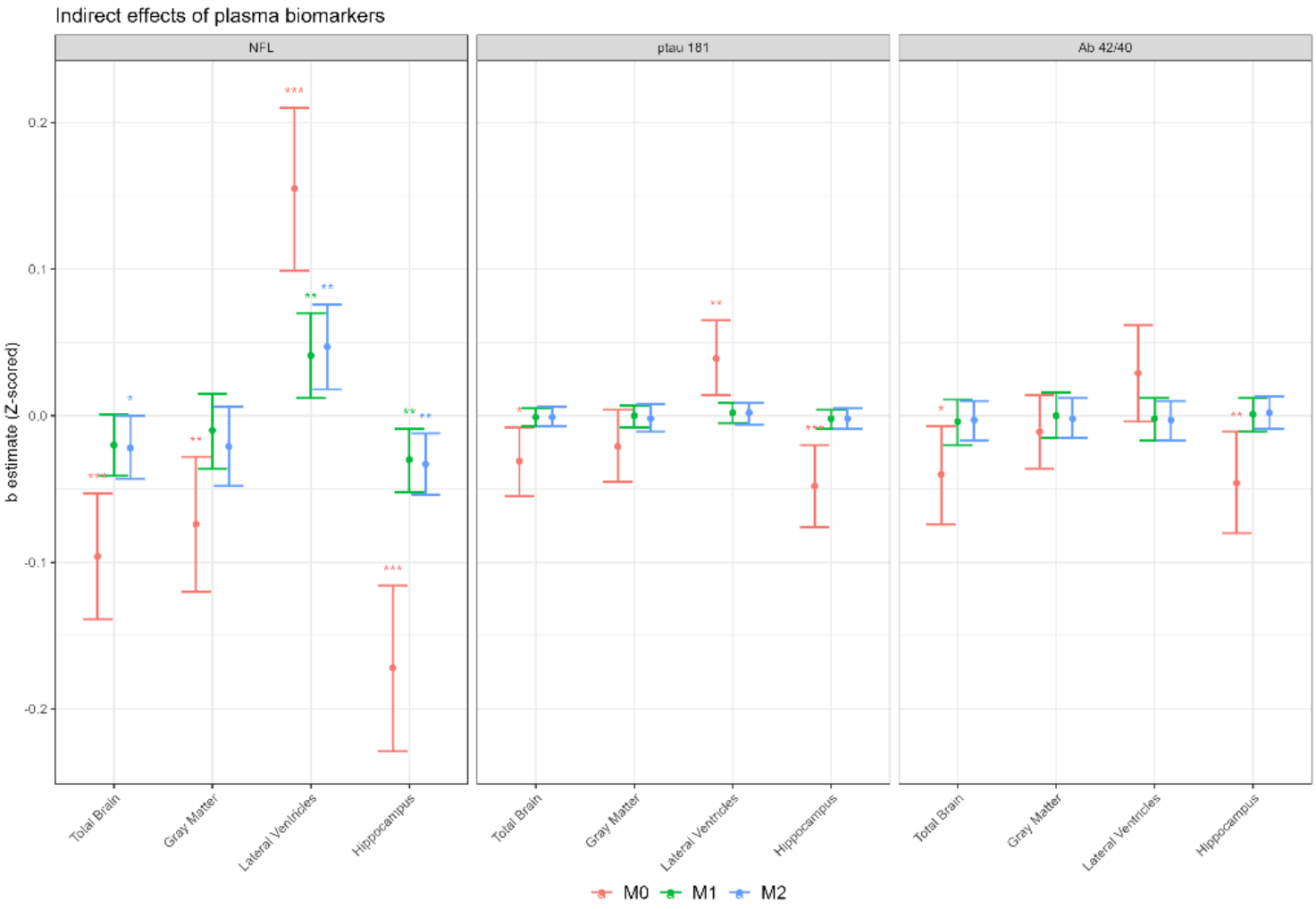
	Female	Male	Total
N	1764	863	2,627
Diabetes	26.43%	23.92%	25.32%



FA= fractional anisotropy; FW = free water

M0 = unadjusted, M1= sociocultural adjustments, M2 = M1 + vascular adjustments

* = p<0.05; ** = p<0.01; *** = p<0.001



NFL=neurofilament light chain; ptau = phosphyrilated tau; Ab = amyloid beta

M0 = unadjusted, M1= sociocultural adjustments, M2 = M1 + vascular adjustments

* = p<0.05; ** = p<0.01; *** = p<0.001

Conclusions: Based on the ATN framework, diabetes may lead to brain atrophy through non-AD specific pathways. Our findings suggest vascular mechanisms have larger contributions to brain atrophy than ATN markers in the context of diabetes.

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SHIFT 01-236

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
2 - 3 April 2025

ALTERATIONS IN GUT MICROBIOTA DIVERSITY IN EARLY-STAGE ALZHEIMER'S DISEASE AND ITS CONNECTION TO BRAIN AMYLOID LOAD

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Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by memory loss and significant behavioural changes. Recent research highlights the critical role of gut dysbiosis in AD pathogenesis, with observed alterations in the gut microbiome among individuals with AD or mild cognitive impairment (MCI). However, the specific variations in microbiota during the preclinical stages of AD, marked by cerebral amyloidosis without cognitive impairment, remain poorly understood. This study aimed to address this knowledge gap.
Methods: Study participants, including 17 cognitively unimpaired Amyloid beta (CU Aβ) +ve and 54 CU Aβ ve- individuals, were selected from highly characterised cohorts and underwent Pittsburgh compound B-positron emission tomography to determine their amyloid status. Faecal samples from all participants were collected and analysed using shotgun metagenomic sequencing to examine the taxonomic composition of the gut microbiota.
Results: The analysis revealed significant differences in microbial taxa abundances between CU Aβ+ and CU Aβ- groups. At the phylum level, Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, and Verrucomicrobia were predominant in both groups. At the class level, high abundance was noted for *Bacteroidia, Clostridia, Gammaproteobacteria, Verrucomicrobiae,* and *Hydrogenophilalia,* with significant differences for *Thermoflexia* ($p<0.05$). At the species level, *Faecalibacterium prausnitzii, Prevotella copri, Bacteroides dorei,* and *Bacteroides vulgatus* were most abundant, Specifically, certain Actinobacteria species were more significant ($p<0.05$).
Conclusions: The analysis showed significant differences in microbial taxa abundances between the CU Aβ+ and CU Aβ- groups at the phylum, class, and species levels. Understanding these microbiota shifts may help identify early therapeutic targets for managing AD progression, possibly assisting with preclinical AD diagnosis. Further research is needed to understand how the gut microbiome plays a role in the early stages of AD pathogenesis.

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SHIFT 01-237

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
2 - 3 April 2025

MEDICA ATTENUATE COGNITIVE DEFICITS AND NEUROINFLAMMATION.

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Aims: Alzheimer's disease (AD) is increasingly linked to alteration in the gut microbiota, particularly the reduction of certain *Bacteroides* strains and their metabolite, MEDICA, which is known for its anti-inflammatory properties. However, its direct influence on AD pathology remains unclear. This study explores whether MEDICA supplementation can improve cognitive function by modulating brain-gut axis.
Methods: We investigated the effects of MEDICA on amyloid plaque formation and neuroinflammation both in vitro, using microglial cells, and in vivo, using 5xFAD mice, a model of AD. MEDICA was administered orally to the mice, followed by behavioral testing and tissue analysis. Additionally, RNA sequencing was performed to identify changes in pathways and genes in the MEDICA-treated AD mice.
Results: Our results demonstrated that MEDICA reduces AD pathology. Specifically, we observed significant reductions in neuroinflammation in microglia and improved cognitive function in AD mice, as shown by Morris's water maze and novel object recognition tests. MEDICA also significantly decreased amyloid plaque formation compared to controls. Furthermore, gene expression analysis revealed that MEDICA treatment shifted the expression of genes related to apoptosis and neuroinflammation toward levels observed in healthy mice.
Conclusions: These results suggest that MEDICA can alleviate cognitive impairments and reduce amyloid plaque accumulation, highlighting the importance of the gut-brain axis in AD pathology. This study underscores the potential of targeting gut microbiota for novel AD treatment strategies and deepens our understanding of the gut-brain connection in neurodegenerative diseases.

SHIFT 01-240

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

MODULATION OF CATHEPSIN B AND D REGULATES LYSOSOMAL FUNCTION AND MICROGLIA MORPHOLOGY

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Aims: Cathepsin B and D are lysosomal hydrolases implicated in many cellular functions, including neuroinflammation, cell death, and the degradation of proteins such as beta-amyloid (Aβ). Biomarker studies in cerebrospinal fluid and blood have indicated that cathepsin levels differ in patients with Alzheimer's disease (AD) compared to controls. However, it is not yet clear how cathepsins contribute to microglia functions that may underlie the pathology of neurodegenerative diseases. Therefore, we aimed at investigating the role of cathepsin signaling in the living brain by using the zebrafish model system.
Methods: We explored cathepsin function in microglia and neurons of live larval zebrafish, using the transgenic *ApoE:GFP* zebrafish line. Lysosomal function was investigated using Lysotracker staining, and cell death was assessed with acridine orange staining. To manipulate cathepsin signaling, we used CA-074 and pepstatin A, two drugs that inhibit cathepsin B and D, respectively. Cell death levels, as well as microglia morphology, phagocytosis of fluorescent Aβ, and lysosomal function, were investigated *in vivo* using confocal microscopy.
Results: We found that inhibition of both cathepsin B and D significantly affected microglia morphology as well as lysosomal function in microglia in larval zebrafish. Baseline cell death levels appeared not to be impacted by the blockage of cathepsins.
Conclusions: Our study indicates that cathepsins play a vital role in regulating the function of microglia and their lysosomes *in vivo*. Future research needs to investigate the clinical implications of cathepsin dysregulation in human CNS diseases, such as AD.

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SHIFT 01-241

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

CHRONIC MILD STRESS REDUCES MICROGLIAL TOXICITY IN 5XFAD MICE

Yoel Shor[1], Reut Said[2], Nina Fainstein[1], Gilly Wolf[2], Lihi Sofer[1], Marva Lachish[1], Tal Ganz[1], Yara Shwaiky[1], Yarden Brock[2], Jonathan Gurevitz[2], Tzuri Lifschytz[2], Amit Lotan[2], Tamir Ben Hur[1]
[1]Hadassah - Hebrew University Medical Center, Neurology, Jerusalem, Israel, [2]Hadassah - Hebrew University Medical Center, Psychiatry, Jerusalem, Israel

Aims: Depression and anxiety are important risk factors for Alzheimer's disease (AD). Microglial activation via Toll-like receptors (TLR) 2 and 4 occur in both conditions, potentially exacerbating neurodegeneration in beta-amyloid afflicted brains. We studied whether chronic stress-induced depression accelerates AD pathology, and increases brain's susceptibility to environmental pathogens.
Methods: 32 transgenic 5xFAD and wild-type (wt) mice underwent a chronic mild stress (CMS) protocol to induce depression symptoms, parallel to an equal control group. Cognitive performance was assessed by behavioral tests, with both sexes represented. Half received intracerebroventricular (ICV) injections of Zymosan, a microbial TLR2 agonist, versus saline. Another control experiment excluded ICV injections. Following behavioral tests and injections, histopathological analysis evaluated neuronal and microglial density in behaviorally relevant areas using immunofluorescent staining. FACS and ROS production assays were performed *ex-vivo* on freshly-isolated microglia.
Results: CMS successfully induced depressive and anxious phenotypes in mice. Behavioral tests revealed sexual and genotypical differences under CMS, with females displaying better learning in the Radial arm water maze but compromised working memory in Y maze, compared to control females. CMS had no effect on Hippocampal and extra-hippocampal memory tests in 5xFAD and wt mice. CMS did not increase microgliosis or neuronal loss in behaviorally relevant regions (Pre-frontal cortex, Hippocampus, Amygdala) of transgenic mice. CMS did not increase brain vulnerability to TLR2 mediated neurotoxicity. FACS analysis revealed decreased activation markers in 5xFAD-extracted microglia and reduced ROS production.
Conclusions: Chronic stress does not worsen AD brain pathology and does not increase AD brain susceptibility to immune-mediated neurotoxicity, but rather induces a trend towards a neuroprotective effect.

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SHIFT 01-242

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

ISCHEMIC INJURY TRIGGERS A PROTECTIVE MICROGLIAL PHENOTYPE IN MODELS OF AMYLOID BETA PATHOLOGY

Michael James Candlish[1], Jan Hofmann[1], Desirée Brösamle[2], Annika Haessler[3], Murphy Demeglio[1], Angelos Skodras[2], Georgi Tushev[4], Eloah Dos Santos De Biasi[1], Stefan Günther[5], René Wiegandt[5], Heidi Theis[6], Elena De Domenico[6], K. Peter Nilsson[7], Marc Beyer[6], Mario Looso[5], Maike Windbergs[3], Jonas Neher[2], Andreas Chiocchetti[8], Jasmin Hefendehl[1]
[1]Goethe Uni Frankfurt, Neurovascular Disorders Group, Frankfurt am Main, Germany, [2]Hertie Institute for Clinical Brain Research, Department Of Cellular Neurology, Tübingen, Germany, [3]Institute of Pharmaceutical Technology, Frankfurt am Main, Germany, [4]Max Planck Institute for Brain Research, Frankfurt am Main, Germany, [5]Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany, [6]Platform for Single Cell Genomics and Epigenomics (PRECISE) at the German Center for Neurodegenerative Diseases and the University of Bonn, and West German Genome Center, Bonn, Germany, [7]Linköping University, Linköping, Sweden, [8]University Hospital, Goethe University Frankfurt Germany, Frankfurt am Main, Germany

Aims: Microglia are highly plastic cells that are capable of integrating subsequent insults. As the majority of Alzheimer's Disease (AD) patients also show cerebrovascular pathology, we here aimed to dissect the interactions between AD and ischemic brain injury on the microglial response to amyloid beta (Aβ) pathology.
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 murine co-morbidity model, we identify a microglia-dependent accumulation of Aβ plaques within the vulnerable peri-infarct region as rapidly as three weeks after stroke. This phenomenon occurred despite a well-established age/pathology-dependent cessation of *de novo* Aβ plaque formation. Notably, newly-formed peri-infarct Aβ plaques exhibit a relatively benign nature, and are encapsulated by an overabundance of phagocytotic microglia. Using spatial and single cell RNA sequencing (scRNA-seq), we identified a dramatic expansion of two microglial clusters in the co-morbid model that were virtually absent in all other conditions. These clusters are characterised by increased phagocytic pathways and additionally, we identified a stark microglial upregulation of several S100 proteins known to promote Aβ aggregation.
Conclusions: Taken together, our findings underscore that the pathological microenvironment created by ischemic stroke in AD triggers a functional switch in microglia that promotes the formation of highly compact Aβ plaques akin to those observed in patients that are resilient to the detrimental effects of AD pathology.

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SHIFT 01-243

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

ENHANCING MICROGLIAL TARGETING IN PRECLINICAL DRUG DISCOVERY VIA HUMAN MICROGLIA CHIMERIC MICE

Sofie Carmans, Wannes Dejonckheere, Tom Cornelissen
reMYND NV, Leuven, Belgium

Aims: Microglia, the central nervous system's immune cells, are critical to neuroinflammation and neurodegenerative diseases, particularly Alzheimer's disease. Given that several risk factors are predominantly expressed in human microglia, it is essential to develop models that mimic human microglial biology. This study aimed to develop a humanized mouse model with engrafted human microglia using an APP knock-in (APP-SAA) background, to better recapitulate human neuroinflammatory responses and evaluate its potential for preclinical efficacy and proof-of-concept studies.
Methods: Immunodeficient RAG2-/- mice, expressing human CSF1 to support human microglial survival, and harboring three familial APP mutations (APP-SAA), were used. Endogenous murine microglia were depleted using BLZ945 treatment, after which human microglial precursors were engrafted. Flow cytometry was used to assess engraftment efficiency. Amyloid pathology and microglial activation were evaluated by histological analyses, including human-CD9 and hCD45 staining, three months post-engraftment.
Results: Engraftment of human microglia was highly efficient, with flow cytometry indicating that approximately 80% of microglia were of human origin three months post-engraftment. By three months of age, these mice began to exhibit amyloid pathology similar to APP-SAA mice. Human microglia, activated around amyloid plaques, were confirmed through human-CD9 staining. In addition, hCD45 staining revealed widespread distribution of human microglia across the brain. These results demonstrate the successful creation of a humanized microglial environment in an AD model.
Conclusions: This humanized microglia-engrafted APP knock-in model closely mimics human neuroinflammatory responses and represents a valuable tool for investigating microglial function and therapeutic targets in neurodegenerative diseases. The robust human microglial engraftment and amyloid pathology observed underscore the model's potential for preclinical drug development. Ongoing refinements aim to further enhance the utility of this platform, accelerating the discovery of novel therapies that modulate microglial activity and mitigate disease progression.

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SHIFT 01-244

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

3D CONFOCAL MICROSCOPY UNRAVELS DETAILS IN AMYLOID PLAQUE – MICROGLIA INTERACTIONS

Maria Hanna Gotkiewicz[1], Janne Capra[2], Pasi Miettinen[1], Teemu Natunen[3], Heikki Tanila[1]
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Aims: Microglia clustering around amyloid plaques is well established but how they contact the plaque with processes is hard to see in conventional thin histological sections. We aimed to visualize details of amyloid plaque-microglia interactions in Alzheimer model mice at different stages of the amyloid plaque formation through a confocal 3D imaging approach
Methods: We cross-bred amyloid plaque forming APP/PS1 mice with CXCR1-GFP mice expressing GFP in microglia and examined their brains at 13 months of age. We took 35 or 100 µm coronal sections at the level of dentate gyrus and stained them with antibodies against amyloid-β, ApoE and CD68 (marker of phagocytosis) protein. The mounting medium contained DAPI, which besides nuclei stains the amyloid plaque core. Isolated amyloid plaques with the surrounding microglia were imaged in a 35 µm z-stack with ZEISS LSM 800 confocal microscope and 3D rendered and analysed with IMARISx64 10.0.1
Results: We imaged 61 clusters from three mice. We observed that enlarged microglia processes were not attracted to diffuse amyloid of the plaque shell but made contacts with the dense DAPI+ core and covered it. Enlarged microglia processes around amyloid plaques often displayed CD68+ lysosomes. We also noticed that dense-core plaques had a consistent layered structure like the Mozartkugel. The center consists of a DAPI+ core, wrapped in a thin layer of ApoE, which in turn is covered by enlarged microglia processes. The findings support the proposed role of ApoE in microglia chemoatraction.
Conclusions: Combining endogenous microglia fluorescence, confocal 3D imaging of thick sections and digital reconstruction gave us an unprecedented visibility of microglia interactions with an amyloid plaque. This approach help understand the role of microglia at different stages of Alzheimer pathology

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SHIFT 01-245

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2 - 3 April 2025

ALZHEIMER'S DISEASE POLYGENIC RISK SHAPES MICROGLIAL FUNCTION AND GENE EXPRESSION

Hazel Hall-Roberts[1], Emily Maguire[1], Atahualpa Castillo Morales[1], Bethany Shaw[1], Rachel O'Donoghue[1], Mateus Bernado-Harrington[1], Jincy Winston[1], Sarah Ellwood[2], Sally Cowley[2], Julie Williams[1]
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Aims: Late-onset Alzheimer's disease (LOAD) is driven by a complex genetic background, with over 75 risk loci identified through genome-wide association studies (GWAS). Many of these loci are highly expressed in microglia, yet the specific effects of LOAD's polygenic risk on individual cell types remain unclear. The IPMAR project leverages induced pluripotent stem cells (iPSCs) to explore this by capturing cases with very high polygenic risk for LOAD (HRLOAD) and comparing them to healthy, aged controls with extremely low risk (LRWELL). Participants were selected based on their polygenic risk score (PRS), a measure that summarizes their cumulative genetic risk, and were stratified by APOE genotype. Our hypothesis is that individuals with high polygenic risk share common microglial dysfunction. To test this, we aim to comprehensively profile microglia-like cells derived from iPSCs, with 'omics and functional assays, and link phenotypes to genetic risk levels.
Methods: 53 iPSC lines were generated with full quality control. iPSC were differentiated to microglia, and arrayed functional assays, single-cell transcriptomics and bulk proteomics were performed. Functional assays explored changes in phagocytosis, endocytosis, chemotaxis, mitochondrial health, purinergic signalling, cytokine release, and lipid accumulation. Statistical modelling was performed to correlate these phenotypes with PRS.
Results: We will showcase groundbreaking findings from the analysis of over 50 iPSC lines, representing the first detailed investigation into the impact of Alzheimer's disease polygenic risk on microglia.
Conclusions: The IPMAR resource, now available via the EBiSC2 biobank, is a valuable tool for unravelling how Alzheimer's polygenic risk shapes cellular behaviour, offering unprecedented opportunities for targeted research.

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SHIFT 01-260

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2 - 3 April 2025

BACE1-MEDIATED GABA SYSTEM DYSFUNCTION IN ALZHEIMER'S DISEASE

Hong Bao[1], Danlei Bi[1,2], Xiaoli Yang[1], Feng Gao[1], Yong Shen[1]
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Aims: Inhibitory currents via GABAA receptors are critical for regulating neural activity. Dysfunctional GABAA receptors contribute to hyperexcitability, a condition clinically linked to neurodegeneration and cognitive impairments. We hypothesize that GABAA receptors dysfunction caused by β-secretase (BACE1), impairing the GABA system, occurs before typical Alzheimer's disease (AD) pathology and aim to uncover potential mechanisms driving neural hyperexcitability in AD.
Methods: To investigate the role of neural BACE1 in GABA system impairments, we employed BACE1 transgenic and AD animal models. We combined cellular and molecular techniques, immunostaining, and functional assays to elucidate the potential pathological mechanisms underlying hyperexcitability in AD.
Results: In this study, we demonstrate that decreased levels of GABAAR β subunits correlate with increased BACE1 in both AD patients and animal models. Using BACE1 transgenic and AD models, we discover that neural BACE1 cleaves GABAAR β subunits, leading to their reduction in the brain. This BACE1-dependent cleavage reduces $GABA_AR$-mediated inhibitory currents, promoting neural hyperexcitability in AD mice. Notably, intervening in BACE1 cleavage of GABAAR β subunits restores inhibitory currents and alleviates neural hyperexcitability.
Conclusions: Our findings reveal a BACE1-dependent mechanism underlying GABA system dysfunction, providing insight into the neural hyperexcitability observed in AD.

SHIFT 01-261

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2 - 3 April 2025

THE ALZHEIMER'S GENE SORL1 IMPAIRS ENDOSOMAL TRAFFICKING AND AXONAL TRANSPORT IN HUMAN NEURONS

Dasa Bohaciakova
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Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, partly driven by genetic variations in the SORL1 gene, which is now recognized as the "fourth" major AD-causative gene. However, the precise role of different pathogenic SORL1 mutations in the development of AD-like pathology remains unclear. In this study, we aimed to investigate the mechanisms by which pathogenic SORL1 variants contribute to AD pathology.
Methods: Using CRISPR/Cas9 technology, we introduced several pathogenic mutations into induced pluripotent stem cells (iPSCs) and employed advanced in vitro models, including 2D inducible neurons (iNs) and 3D neural organoids (NOs), to explore their impact. We used Multielectrode array to measure the activity of neurons and live imaging to detect the axonal transport of selected proteins.
Results: Our findings reveal that pathogenic SORL1 variants disrupt SORLA protein function, leading to endosomal swelling, APP retention in endosomes, and increased cleavage of APP into Aβ40 and Aβ42 peptides. Notably, we also discovered that defective or deficient SORLA increases neuronal excitability and severely impairs axonal transport of the APP protein, likely due to disrupted trafficking of transport-related cargo proteins.
Conclusions: Together, these results provide novel insights into the cellular mechanisms by which SORL1 mutations drive AD pathology, offering potential targets for therapeutic intervention. Funding for this research was provided by the Czech Health Research Council - AZV NU22J-08-00075, and by the projects „SORLA-FIX“ (8F20009 D.B.), ADPriOMICS 2023-087, and ADDIT-CE 101087124 (all funded by MEYS/EU):

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SHIFT 01-262

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2 - 3 April 2025

SENSORY EVOKED GAMMA OSCILLATION CORRELATES WITH BRAIN MORPHOLOGY IN ALZHEIMER'S DISEAE

Mihaly Hajos, Brennan Jackson, Miguel Hernandez, Olivia Rowe, Chandran Seshagiri, Ralph Kern
Cognito Therapeutics, Cambridge, United States of America

Aims: Sensory evoked gamma oscillation is a promising novel therapeutic approach for Alzheimer's disease (AD). The present study evaluated whether age and brain morphology modify gamma responses by analyzing neurophysiological data collected in OVERTURE clinical trial participants with mild to moderate AD (Hajós et al., 2024).
Methods: The OVERTURE trial evaluated the safety, tolerability and efficacy estimates of Spectris™ treatment, which evokes 40Hz steady state oscillation via auditory and visual stimulation. Resting state and sensory-evoked steady-state gamma oscillations were recorded via electroencephalography with a 32-channel cap (ANT-Neuro) together with structural MRI at baseline. The relative power at 40Hz was computed for each channel. Global gamma response was computed by averaging the relative power at 40Hz across all channels, while frontal and occipital gamma responses were calculated by averaging local corresponding channels. Correlations were assessed between gamma response and age, as well as whole brain, whole cortical and white matter volume, and occipital cortical thickness (Pearson correlation).
Results: All participants responded with the required gamma oscillation to sensory stimulation for trial enrollment. Analysis of evoked gamma oscillation (n=25) showed that greater total brain cortical volume and broader occipital cortical thickness were associated with larger evoked global gamma power ($r=0.552$; $p<0.012$ and $r=0.517$; $p<0.040$, respectively). A trend was noticed between greater white matter volume and larger evoked global gamma power ($r=0.368$; $p<0.070$). Furthermore, global and occipital evoked gamma power showed a trend towards a diminished gamma response with age ($r=-0.356$; $p<0.080$ and $r=-0.352$; $p<0.085$, respectively).
Conclusions: Present findings contribute to our understanding of the association between sensory evoked neurophysiological responses and brain morphology in AD. Follow up studies with larger samples size will further delineate the most critical factors impacting evoked gamma oscillations in patients.

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SHIFT 01-263

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2 - 3 April 2025

DOES SLEEP-TIME SUBCLINICAL EPILEPTIFORM ACTIVITY IN ALZHEIMER'S DISEASE IMPAIR MEMORY CONSOLIDATION?

Sara Häkli[1], Henna Koivisto[1], Irina Gureviciene[1], Jonas Schimmel[2], Eric Castell Caubet[3], Maria Rozas Casero[4], Diana Beinert[2], Keerthana Malathi[5], Nanxiang Jin[1], Heikki Tanila[1]
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Aims: Objectives: Subclinical epileptiform activity (SEA) during sleep has been found to correlate with faster cognitive decline and memory impairment in Alzheimer's Disease (AD) patients. The systems consolidation theory suggests that during sleep, memories are transferred from temporary storage in the hippocampus to long-term storage in the cortex, which requires synchronization of hippocampal, cortical and thalamo-cortical oscillations. We set out to study whether there is a correlation between the amount of sleep-time epileptiform spikes and overnight memory consolidation in AD model mice.
Methods: Methods: APP/PS1 transgenic (n=8) and wild-type (n=12) male mice at 3.5-5.5 months of age were implanted with cortical, hippocampal and olfactory bulb EEG/LFP electrodes. An EMG electrode was used together with video recording to detect mobility. Each mouse underwent a weekly test session consisting of 1) memory training (Barnes circular platform or Novel object recognition (NOR)), 2) drug injection and 3) 3h video-EEG during the sleep period following the memory training. The amount of epileptiform spiking during the post-learning sleep period was manipulated with either Lamotrigine (increased spiking), Levetiracetam (decreased spiking) or vehicle (baseline). On the next day, the memory for the location or object was tested.
Results: Results: The interim analysis revealed lower preference towards the novel object in NOR by APP/PS1 mice ($p=0.012$) but no correlation with the treatment ($p=0.61$). The final results will be presented at the conference.
Conclusions: Conclusions: The preliminary results suggest that at an early phase of AD-like pathology mice are able to resist the effects of sleep associated SEA on memory consolidation.

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SHIFT 01-264

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2 - 3 April 2025

IN VIVO ANALYSIS OF THE DIRECT IMPACT OF AMYLOID BETA OLIGOMERS IN THE HIPPOCAMPUS ON NEURONAL ACTIVITY AND NEUROTRANSMITTER RELEASES

Vincent Hervé[1], Obaï Bin Ka'B Ali[2], Habib Benali[2], Jonathan Brouillette[1]
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Aims: One of the main neuropathological hallmarks of Alzheimer's disease (AD) is the accumulation of amyloid-beta oligomers (Aβo), which begins in the brain approximately 15 years prior to the onset of clinical symptoms. Aβo-induced neuronal hyperactivity has emerged as an early functional characteristic of AD, contributing to synaptic deficits, memory impairment, and neurodegeneration. Several studies suggest that Aβo reduce the inhibitory activity of the GABAergic system, leading to excessive activation of the glutamatergic system. The aim of this study is to investigate the impact of Aβo on neuronal activity and neurotransmitter release within the same animal model.
Methods: A microdialysis probe is implanted in the right hippocampus of a rat model to deliver Aβ oligomers over five consecutive days and to collect interstitial fluid (ISF) samples before, during, and after the injections. In addition, five electrodes are implanted within the hippocampi and default mode network of the rats to record neuronal activity.
Results: Our initial results demonstrate the ability to record local field potential (LFP) signals in five distinct brain areas and to detect several neurotransmitters (glutamate, GABA, serine, taurine, glutamine, and glycine) in ISF samples. Chronic Aβo injections resulted in a clear time-dependent increase in delta power and a progressive decrease in higher frequency bands (theta, alpha, beta, gamma) in the injected hippocampus. In the non-injected (left) hippocampus, stable trends were observed initially, with a late-onset increase in delta power and reduction in higher frequency power by day 5 in the Aβo group.
Conclusions: This study will provide novel insights into the relationship between Aβo-induced changes in neuronal activity and neurotransmitter release, contributing to a better understanding of the neurodegenerative processes involved in early AD.

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SHIFT 01-268

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEUROGENESIS
2 - 3 April 2025

AN ALTERED TIME COURSE OF NEUROGENESIS IN THE APPNL-F MOUSE MODEL

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[2]Karolinska University Hospital, Theme Inflammation And Aging, Huddinge, Sweden

Aims: The early disease mechanisms of Alzheimer's disease (AD) are poorly understood but studying changes in the brain before amyloid β-peptide plaque pathology and symptom onset could contribute to our understanding of the pathogenesis of the disease. In our previous studies of the AD knock-in *App*$^{NL-F}$ mouse model we noticed changes in neurogenesis early in the life span of the mouse. Doublecortin is a well-established marker of neuronal development and when it is phosphorylated, doublecortin plays a role in neuronal migration. In this study we aimed to further characterize neurogenesis in the *App*$^{NL-F}$ mouse model and AD brain by identifying a time course of doublecortin expression in brain tissue and in neurons.
Methods: We used brains of AD patients and of embryonic, 3-, 6-, and 12 months old *App*$^{NL-F}$ mice, which we stained for doublecortin and phosphorylated doublecortin using immunohistochemistry. Levels of doublecortin and phosphorylated doublecortin were assessed in neurons of different cortical regions in embryonic mouse brain by comparing total intensity of staining. Moreover, neurons positive for doublecortin signal were counted in the hippocampus of 3-, 6- and 12 months old mice.
Results: We found increased doublecortin but decreased phosphorylated doublecortin in the cortex of *App*$^{NL-F}$ mouse embryos. We also detected an increased cell count of doublecortin positive neurons in the hippocampus of 6- and 12 months old *App*$^{NL-F}$ mice.
Conclusions: We conclude that neurogenesis is altered in the early life span of the *App*$^{NL-F}$ mouse model, before symptom and pathology onset. These changes could lead to inefficient neuronal development and potentially contribute to AD disease pathogenesis.

SHIFT 01-269

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEUROGENESIS
2 - 3 April 2025

ADVANCED HIPPOCAMPAL 3D MODEL WITH SUBGRANULAR NEURAL STEM CELLS AND HIPPOCAMPAL NEURONS FOR IN VITRO NEURAL DIFFERENTIATION AND MIGRATION STUDIES

Chaejeong Heo
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Aims: The hippocampus is a primary brain area responding for memory formation and severely affected by Alzheimer's disease. Although hippocampus is important to study Alzheimer's disease and drug development, pathophysiological mechanism of the malfunctional hippocampus is not fully understood because of the lack of proper *in vitro* models that faithfully recapitulate physiological and pathological features depending on the progress of diseases.
Methods: Here, we introduce 2-layer hippocampus modeling using a microfluidic 3D spheroid culture platform. The 3D hippocampal spheroids were generated by 2 layered neurospheroid with adult subgranular zone-derived stem cells and hippocampal neurons subsequently with the microfluidic culture device. We proceed the spheroid culture for 3 weeks with over 90% of cell viability. The spheroids obtained from our platform exhibited high uniformity and the circularity of layered neurospheroids increased gradually overtime.
Results: The centric neural stem cells differentiated and migrated alongside the outer layered hippocampal neurons in 3D neurospheroid represented differently from 2D coculture. The centric neural stem cells showed differentiation ability in parallel to migration to give rise to newborn neuron and glial cells for the hippocampal model. In addition, the gene expression exhibited that gene sets related to neurogenesis, glial cell development and myelination, and neurotransmission significantly regulated during hippocampal spheroid development.
Conclusions: Our advanced hippocampal model using the 3D microfluidic platform is a robust solution for translational medical research of recapitulate hippocampus region of the brain.

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SHIFT 01-273

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2 - 3 April 2025

NANOBIT TAU BIOSENSORS BRING NEW INSIGHTS INTO THE MOLECULAR EVENTS TRIGGERING EARLY PATHOLOGICAL TAU TRANSFORMATION AND SEEDING ACTIVITY

Erika Cecon[1], Ludivine Houzé[1], Suzanne Lam[2], Fanny Petit[2], Marc Dhenain[2], François Mouton-Liger[3], Julie Dam[1], Claire Paquet[3], Ralf Jockers[1]
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Aims: Tau aggregates are well-characterized molecular hallmark of neurodegenerative diseases, including Alzheimer's disease (AD) and summarized as tauopathies. Yet, the initial cellular and molecular events that lead to tau transformation from physiological monomers into pathological oligomers and aggregates are still poorly known. Here we developed a series of inter- and intramolecular tau biosensors based on the highly sensitive Nanoluciferase (Nluc) binary technology (NanoBiT), in order to monitor the pathological conformational change and aggregation of tau in living cells.
Methods: We developed intra- and inter-molecular biosensors using the NanoBiT technology. In this system, the Nluc enzyme is split into a large 18 kDa fragment (LgBit) and a small 1.3 kDa fragment (SmBit), that are fused to tau. Biosensors were developed using full-length (2N4R) wild-type tau (WT-Tau), full-length mutated tau(P301L), and the pro-aggregating K18(P301L) central fragment of tau.
Results: We observed that the new biosensors reliably report: **i.** molecular proximity of physiological WT tau bound to microtubules; **ii.** changes in tau conformation and self-interaction upon phosphorylation; **iii.** the tau seeding activity induced by brain lysates of transgenic mouse and from human AD patients. The highly sensitive and quantitative properties of the tau NanoBiT sensors allow detection of interindividual differences in seeding potency of brain lysates and cerebrospinal fluids from AD patients. Seeding potency in brain lysates correlates well with the severity of tauopathy (AT8(phospho-tau)-positive aggregates) induced by the same samples when applied to neuronal cultures or to the brain of animal models.
Conclusions: Our NanoBiT tau biosensors are high-throughput-compatible and quantitative tools to monitor tau conformational changes, aggregation and seeding in response to a variety of chemical and biological challenges, providing new insights on the cellular mechanism driving tau pathological transformation processes.

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SHIFT 01-274

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2 - 3 April 2025

COMBINING SINGLE-MOLECULE IMAGING AND TRANSCRIPTOMICS TO CHARACTERISE TAU AGGREGATION IN ALZHEIMER'S DISEASE PROGRESSION

Elizabeth English[1,2], Nurun Fancy[3], Dorothea Boeken[1,2], Matthew Cheetham[1], John Danial[4], Johanna Jackson[5], Paul Matthews[3], David Klenerman[1,2]
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Aims: Tau aggregation is a hallmark of Alzheimer's disease (AD). This study characterises the tau aggregates formed at each Braak stage in single-molecule detail and combines this with transcriptomics to gain insights into the mechanisms leading to tau aggregation in AD.
Methods: Post-mortem brain samples were obtained from 13 donors and two brain regions, middle temporal gyrus (MTG) and primary somatosensory cortex (SOM), spanning each AD Braak stage. Aggregate-specific Simoa® assays measured aggregate quantity. Single-molecule pull-down (SiMPull) with super-resolution fluorescence microscopy determined tau aggregate shape and size. Single nucleus RNA sequencing (snRNA-seq) quantified microglial and neuronal gene expression of matched donor samples.
Results: Exponentially higher quantities of tau aggregates were detected from Braak stage 3, with increasing proportions phosphorylated. At all Braak stages, including non-AD, tau aggregates were detected across a range of sizes (20-500 nm). In advanced Braak stages, significantly increased quantities of long fibrillar aggregates (exceeding 0.9 eccentricity and 100 nm) were detected: with less than 5% at Braak stages 0-2, compared with up to 25%, but notably not all, of aggregates at Braak stages 5-6. Increased amyloid-beta aggregation and inflammatory damage-associated microglial (DAM) gene expression were detected in early Braak stages, proceeding tau aggregation.
Conclusions: Our data suggest a mechanism for AD whereby microglial inflammation, initiated firstly by amyloid-beta deposition and then by tau, triggers tau phosphorylation and aggregation. We propose this process occurs in increasing numbers of neurons, leading to the observed exponential increase in tau aggregates with Braak stage. Without evidence in this study to support prion-like spreading, regional differences in tau aggregation rates likely arise through distinct vulnerabilities to inflammation and aggregation.

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SHIFT 01-275

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2 - 3 April 2025

THE CYTOSKELETAL PROTEIN PLECTIN REGULATES TAU-INDUCED NEUROTOXICITY IN ALZHEIMER'S DISEASE

Tom Lee[1], Catherine Chen[1], Katherine Allison[2], Kelly Carter[1], Yarong Li[1], Pinghan Zhao[1], Pritha Bagchi[3], Ismael Al-Ramahi[4], Nicholas T. Seyfried[3], Juan Botas[4], Joshua Shulman[1]
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Aims: Proteomic analysis on Alzheimer's Disease (AD) brains identified a cytoskeletal-associated protein network upregulated in AD. Plectin is a network driver protein and functional analysis provides mechanistic insight on the underlying network biology. We aim to functionally characterize Plectin's role in tau-induced neurodegeneration in *Drosophila* and human neuronal cells. Moreover, we utilize genetic and biochemical analyses to identify and validate additonal protein network components.
Methods: Utilizing genetic and proteomic analyses, we validate Plectin as a potential AD risk factor. Moreover, we elucidate Plectin's role in Tau-induced neurotoxicity and dissect its mechanistic effect on tau dysfunction. Immunoprecipitation-mass spectrometry (IP-MS) analysis defined a *Drosophila* Plectin (dPLEC) interactome and complementary genetic screens have validated additional novel AD targets.
Results: In adult fly brain, *dPLEC* is ubiquitously expressed with strong enrichment in neuronal tissues. Using a *Drosophila* model of human tauopathy, *dPLEC* regulates age dependent Tau-induced neurotoxicity and locomotor dysfunction. Plus, *PLEC* functions to regulate Tau phosphorylation and aggregation in both fly and human cells. Continued mechanistic analysis in *Drosophila* and human cells will determine PLEC's role in AD neuropathogenesis and elucidate the underlying role of the cytoskeleton in AD susceptibility. To that end, we generated an dPLEC interactome and performed a secondary genetic screen to validate additonal network candidate proteins. Several cytoskeletal and synaptic proteins were identified and tested for their role in Tau-induced neurodegeneration and synaptic dysfunction.
Conclusions: Using cross-species analyses, we functionally validate PLEC as a regulator of Tau-induced neurodegeneration. We also identify PLEC as regulator of Tau phosphorylation, aggregation, and neuronal function. This data supports PLEC and its associated protein network as novel AD susceptibility targets and implicate cytoskeletal dysfunction as a regulator of AD susceptibility.

SHIFT 01-276

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2 - 3 April 2025

SINGLE-NUCLEUS MULTIOME ANALYSIS OF HUMAN CEREBELLUM IN ALZHEIMER'S DISEASE-RELATED DEMENTIA

Feixiong Cheng[1], Yayan Feng[1], Margaret Flanagan[2], Borna Bonakdarpour[3], James Leverenz[4], Andrew Pieper[5], Jeffrey Cummings[6]
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Aims: Although human cerebellum is known to be neuropathologically impaired in Alzheimer's disease (AD) and AD-related dementias (ADRD), the cell type-specific genomic and epigenomic changes that contribute to this pathology are not well understood.
Methods: We used 10x Genomics single-nucleus multiome (snRNA-seq and snATAC-seq) technology to profile gene expression and chromatin accessibility within the same nucleus isolated from human postmortem cerebellum and frontal cortex with AD/ADRD (n=3 donors with AD neuropathologic change, n=3 donors with diffuse Lewy body disease, and n=3 donors with progressive supranuclear palsy or frontotemporal lobar degeneration) and age- and sex-matched non-dementia control subjects (n = 8).
Results: Here, we report single-nucleus multiome (snRNA-seq and snATAC-seq) analysis of 103,861 nuclei isolated from cerebellum from 9 human cases of AD/ADRD and 8 controls, and with frontal cortex of 6 AD donors. We identified 431,834 significant linkages between gene expression and cell subtype-specific chromatin accessibility regions enriched for candidate *cis*-regulatory elements (cCREs) associated with AD/ADRD-specific transcriptomic changes and disease-related gene regulatory networks in cerebellar Purkinje cells and granule cells. Trajectory analysis of granule cell populations identified disease-relevant transcription factors (i.e., *RORA)*. We prioritized two likely causal genes, including *Seizure Related 6 Homolog Like 2* (*SEZ6L2*) in Purkinje cells and *KAT8 Regulatory NSL Complex Subunit 1* (*KANSL1*) in granule cells, via integrative analysis of cCREs derived from snATAC-seq, genome-wide AD/ADRD loci, and Hi-C looping data.
Conclusions: This first cell subtype-specific regulatory landscape in the human cerebellum identified here offer novel genomic and epigenomic insights into the neuropathology and pathobiology of AD/ADRD and other neurological disorders if broadly applied. This study aims to identify cell type-specific genomic and epigenomic signatures and associated genes/networks invovled in neuropathologies of AD/ADRD.

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SHIFT 01-277

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2 - 3 April 2025

THE BLOOD MICRORNAOME IN ADNI AND BEYOND: SIGNATURES TO AID THE SCREENING OF AT-RISK INDIVIDUALS FOR ALZHEIMER'S DISEASE (AD)

Andre Fischer
German Center for Neurodegenerative Diseases, Göttingen, Germany

Aims: Enhancing diagnostic tools for early detection of AD is crucial for advancing prevention and treatment strategies. MicroRNAs (miRNAs), short non-coding RNAs that regulate proteostasis, are emerging as promising biomarkers for AD. miRNAs are particularly powerful because each one can target multiple mRNAs, often functionally linked. This means that changes in a few miRNAs can signal disruptions across key cellular pathways. Moreover, miRNAs participate in inter-organ communication, which makes circulating miRNAs valuable indicators of brain pathology. Their stability in cell-free environments and resistance to freeze-thaw cycles also make miRNAs reliable for clinical diagnosis. Identifying miRNA biomarkers offers not only a means for earlier detection of AD-related neuropathology but also valuable prognostic and therapeutic insights.
Methods: Cross-sectional plasma samples from 803 ADNI participants (control = 165, early MCI = 272, late MCI = 217, AD = 149) were selected for small RNA sequencing. Similarly, we performed small RNA sequencing on blood samples from 1,056 participants in the DZNE DELCODE study. Data underwent quality control, and miRNA levels were associated with disease phenotypes and progression using AI-based approaches. Mechanistic studies were conducted on candidate miRNAs in relevant cell types.
Results: We identified microRNA signatures that correlate with diagnosis and predict conversion from mild cognitive impairment (MCI) to AD. Additionally, we analyzed the data in relation to a meta-analysis we conducted, which revealed robust miRNA signatures that could inform RNA therapies. Furthermore, we are developing approaches to transform the miRNA analysis into easier assay formats suitable for point-of-care settings
Conclusions: Blood microRNA signatures can diagnose MCI and, critically, predict conversion to AD. Combined with neuropsychological testing, miRNA profiling offers a promising approach to identifying at-risk individuals, potentially reducing reliance on costly and invasive tests.

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SHIFT 01-281

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS
2 - 3 April 2025

ADVANCING ALZHEIMER'S RESEARCH BY TARGETING DYSFUNCTIONAL ANGIOGENESIS

Jannis Heuer[1], Nine Kok[1], Rayman Tjokrodirijo[2], Yassene Mohammed[2], Peter Van Veelen[2], Annemieke Rozemuller[3], Helga De Vries[1], Nienke De Wit[1]
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Aims: In the majority of patients with Alzheimer's disease (AD), amyloid beta (Aβ) accumulates at the capillaries of the cerebral vasculature, a condition termed capillary cerebral amyloid angiopathy (capCAA). CapCAA correlates with the severity of AD pathology and is implicated in promoting vascular dysfunction and cognitive decline. Vascular dysfunction is an early pathological process and is recognized as a key player in disease progression. Identifying pathways that can restore cerebral vascular function is therefore an attractive target for treatment. However, we currently lack fundamental insights into the underlying mechanisms driving these detrimental vascular processes. Therefore, we aim to identify pathological changes in the cerebral vasculature of capCAA patients using a proteomic approach.
Methods: We isolated and characterized capillaries from post-mortem human brain tissue of capCAA patients and non-demented controls. The isolated vessels were subjected to proteomic analysis (e.g., mass spectrometry) to obtain a comprehensive profile of the pathological vascular changes in capCAA.
Results: Our proteomic data reveal a pro-angiogenic landscape in the vasculature of capCAA patients. We are currently validating these results and planning to perform in vitro studies using humanized cell models.
Conclusions: By unraveling the pro-angiogenic landscape in the brain during pathology, we aim to provide new insights into the crucial role of the vasculature in capCAA disease progression. This understanding may help us determine whether targeting angiogenesis can restore vascular function and combat AD.

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SHIFT 01-282

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS
2 - 3 April 2025

MULTI-ANCESTRAL GWAS IDENTIFIES NOVEL GENETIC LOCI ASSOCIATED WITH WHITE MATTER HYPERINTENSITIES AND THEIR LINK TO ALZHEIMER'S DISEASE

Tamil Iniyan Gunasekaran[1], Annie Lee[1,2,3], Clarissa Morales[3], Mohamad Alshikho[2,3], Patrick Lao[2,3,4], José Gutierrez[2], Jennifer Manly[2,3,4], Yian Gu[2,3,4], Adam Brickman[2,3,4], Lawrence Honig[2,3,4], Badri Vardarajan[2,3,4], Richard Mayeux[2,3,4]
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Aims: White matter hyperintensities (WMH) are frequently associated with Alzheimer's disease-related pathology. This study aimed to identify genetic loci linked to both WMH and AD.
Methods: We conducted a multi-ancestral GWAS of WMH from MRI in 1,578 WHICAP participants (428 non-Hispanic Whites (NHW), 550 African Americans (AA), 600 Caribbean Hispanics (CH)), adjusting for age, sex, three principal components, intracranial volume, and MRI magnetic field strength. Common variants with >1% allele frequency in any of the population were analyzed, and findings were replicated in 937 self-reported non-Hispanic Whites from ADNI with similar covariate adjustments. AD risk associations in ADNI were assessed using GWAS data from Kunkle et al (2021) and Bellenguez et al (2022).
Results: The multi-ancestral GWAS of WMH identified two loci with genome-wide significance for larger WMH: rs77570875 (P=2.01×10^{-8}) in *FTO* and rs660291 (P=3.77×10^{-8}) in *DNMT3B*, but did not replicate in the ADNI cohort. Focusing on loci with nominal significance (P<0.01), 23 loci were replicated in ADNI, including rs112343572 near *CYP51A1P1*, showing association in both the multi-ancestral WHICAP cohort (P=1.01×10^{-5}) and in ADNI (P=1.10×10^{-3}). Of these, 11 loci were also nominally associated with AD risk in the Kunkle et al. study based on 94,437 individuals. Additionally, two AD-associated loci (rs6489896 in *TPCN1* and rs1358782 in *RBCK1*) were also linked to WMH (P<0.05), which has genome-wide significance for AD risk in Bellenguez et al. study based on 788,989 individuals. We are in the process of evaluating these loci for their association with microbleeds.
Conclusions: Our study identified several putative genetic loci associated with increased WMH that are also linked to AD risk. Genetic risk factors shared between WMH and AD provide valuable insights into WMH-mediated AD pathology.

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SHIFT 01-284

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / AGGREGATION INHIBITORS
2 - 3 April 2025

INTERACTIONS OF POLYELECTROLYTES AND AMYLOID BETA PEPTIDES

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Aims: An imbalance between Aβ production and clearance results in the accumulation of Aβ, in particular Aβ42. We previously demonstrated that BACE1 is a major enzyme involved in clearance and can degrade Aβ42 to a shorter less aggregative form, i.e. Aβ34. However, Aβ42 aggregates can partially evade this BACE1-mediated degradation when it forms oligomers. We have previously demonstrated that synthetic dendritic polymers (dendrimers) have a high potential in modulating amyloid aggregation and rescuing amyloid toxicity. Dendritic polyglycerols (dPGs) are a subclass of dendrimers, which include dPG sulfate (dPGS) and dPG amine (dPGA). Notably, dPGS was shown to prevent Aβ42 fibril formation and mitigate damage at hippocampal excitatory synapses. Novel preliminary data indicate that dPGA can strongly inhibit protofibril formation. We hypothesize that dPGA has anti-amyloid properties, including the prevention of early Aβ aggregation, and the rescue of Aβ42 clearance through BACE1.
Methods: Using Thioflavin T assays we assessed the anti-amyloid activity of dPGS and dPGA against Aβ42 aggregation. Different concentrations (nanomolar range) and sizes of dPGA were used to assess the aggregation kinetics.
Results: We have demonstrated that dPGs such as dPGS and dPGA, modulate Aβ42 aggregation in a size and surface charge dependent manner, with larger positively charged dPGs exhibiting stronger anti-amyloid activity compared to smaller negatively charged dPGs. Our study shows that the large dPGA (550 kDa) molecules are most effective in comparison to smaller dPGA (10 and 80 kDa)
Conclusions: Synthetic polymers possess a significant therapeutic potential for targeting Aβ42 and open avenues for the development of effective treatments by inhibiting Aβ aggregation and promoting Aβ clearance.

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SHIFT 01-286

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2 - 3 April 2025

A SCALABLE WORKFLOW FOR THE SINGLE-CELL TRANSCRIPTOMICS-BASED SCREENING OF THERAPEUTICS IN ALZHEIMER'S DISEASE (AD) USING HUMAN IPSCS-DERIVED 3D NEUROIMMUNE CO-CULTURES

Caterina Carraro[1], Jessica Montgomery[1], Julien Klimmt[2], Carolina Gonçalves[2], Jonas Schulte-Schrepping[1], Elena De Domenico[3], Marc Beyer[1,3], Dominik Paquet[2,4], Joachim Schultze[1,3]
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Aims: The development of novel therapeutics for AD is particularly urgent and the increasing characterization of the underlying molecular hallmarks allows for new therapeutic avenues. Omics approaches have the potential to accelerate drug discovery[A] by offering a more comprehensive characterization of multiple pathomechanisms. To address such mechanisms, we propose the establishment of a single-cell transcriptomic workflow to accelerate the identification of drugs for AD and other neurodegenerative diseases.
Methods: Human iPSCs-derived cortical neurons, microglia, and astrocytes were co-cultured for 3 months before treatment. We set up a workflow for high-throughput drug screening optimizing the number of input 3D cultures, treatment timing, and dissociation coupled with single-cell transcriptomics using microwell or combinatorial indexing approaches.
Results: We established a workflow for single-cell transcriptomics-based drug screening on a iPSC-based 3D-culture (cortical neurons, microglia, astrocytes) model of AD[B]. This included optimization of treatment protocols, culturing and dissociation, coupled to strategies increasing reproducibility, throughput, miniaturization, cost-effectiveness, and scalability of single-cell readouts. With this workflow, we captured the expected heterogeneity of cell types and states as well as cell-type specific transcriptional dynamics of the drug response. From an initial screening, we identified drugs promoting a reversal of the AD phenotype.
Conclusions: We established an end-to-end single-cell transcriptomics platform using an advanced AD *in-vitro* model for i) the identification of AD multi-target drug candidates and for ii) screening of cell-type specific responses to drug perturbations ensuring high reproducibility, throughput, miniaturization and scalability. **A**. Carraro C, Beyer M et al., Tackling neurodegeneration in vitro with omics: a path towards new targets and drugs. doi: 10.3389/fnmol.2024.1414886. **B**. Klimmt J, Paquet D et al., A reproducible human brain tissue model to study physiological and disease-associated microglia phenotypes, Submitted for publication.

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SHIFT 01-287

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2 - 3 April 2025

COMBINING GENETICS WITH REAL-WORLD PATIENT DATA ENABLES ANCESTRY-SPECIFIC TARGET IDENTIFICATION AND DRUG DISCOVERY IN ALZHEIMER'S DISEASE

Feixiong Cheng[1], Yuan Hou[1], Pengyue Zhang[2], Yichen Li[1], Wenqiang Song[1], Andrew Pieper[3], James Leverenz[4], Jeffrey Cummings[5]
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Aims: Although high-throughput DNA/RNA sequencing technologies have generated massive genetic and genomic data in human disease, these findings have not been translated into new patient treatments. To address this problem, we utilized Mendelian randomization (MR) and large patient-level genetic and functional genomic data to evaluate druggable targets using Alzheimer's disease (AD) as a prototypical example.
Methods: We applied the genetic instruments from 9 expression quantitative trait loci (eQTL) and 3 protein quantitative trait loci (pQTL) datasets across five human brain regions from three human brain biobanks and performed MR in 7 genome-wide association study (GWAS) datasets of European ancestry (EA) and African ancestry (AA), with AD cases and controls.
Results: We identified 19 drug targets, including the inflammatory target of epoxide hydrolase 2 (EPHX2) as a potent AD target. We demonstrated that a genome-wide significant and protective variant of p.Arg287Gln in EPHX2 (P_{pQTL} = 5.50 × 10^{-16} and P_{GWAS} = 1.08 × 10^{-11}) significantly reduced level of phosphorylated-tau (p-tau181) and the ratio of p-tau181/total tau and increased neuron clump size in patient induced Pluripotent Stem Cells (iPSC)-derived neurons, mechanistically supporting MR results. Pharmacologic inhibition of EPHX2 significantly improved cognitive behaviors in AD transgenic animals. We further identified that 12 drugs (i.e., trazodone [ADRA1A] and baclofen [GABBR1]) harboring MR-supported targets are significantly associated with reduced incidence of AD in 111,680 mild cognitive impairment (MCI) patients from the Optum database. Using a target trial emulation design, we found that usage of trazodone was significantly associated with 23.5% reduced progression to AD (hazard ratio [HR] = 0.765, 95% confidence interval [CI] 0.703 – 0.828) in people with MCI in the MarketScan database.
Conclusions: We demonstrated that combining genetics and real-world patient data identified ancestry-specific therapeutic targets and medicines for AD and other neurodegenerative diseases if broadly applied.

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SHIFT 01-288

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2 - 3 April 2025

A NETWORK-BASED SYSTEMS GENETICS FRAMEWORK IDENTIFIES PATHOBIOLOGY AND DRUG REPURPOSING IN PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder. However, current treatments are directed at symptoms and lack ability to slow or prevent disease progression. Large-scale genome-wide association studies (GWAS) have identified numerous genomic loci associated with PD, which may guide the development of disease-modifying treatments.
Methods: We presented a systems genetics approach to identify potential risk genes and repurposable drugs for PD. First, we leveraged non-coding GWAS loci effects on multiple human brain-specific quantitative trait loci (xQTLs) under the protein-protein interactome (PPI) network. We then prioritized a set of PD likely risk genes (pdRGs) by integrating five types of molecular xQTLs: expression (eQTLs), protein (pQTLs), splicing (sQTLs), methylation (meQTLs), and histone acetylation (haQTLs). We also integrated network proximity-based drug repurposing and patient electronic health record (EHR) data observations to propose potential drug candidates for PD treatments.
Results: We identified 175 pdRGs from QTL-regulated GWAS findings, such as *SNCA*, *CTSB*, *LRRK2, DGKQ*, *CD38* and *CD44*. Multi-omics data validation revealed that the identified pdRGs are likely to be druggable targets, differentially expressed in multiple cell types and impact both the parkin ubiquitin-proteasome and alpha-synuclein (a-syn) pathways. Based on the network proximity-based drug repurposing followed by EHR data validation, we identified usage of simvastatin as being significantly associated with reduced incidence of PD (fall outcome: hazard ratio (HR) = 0.91, 95% confidence interval (CI): 0.87–0.94; for dementia outcome: HR = 0.88, 95% CI: 0.86-0.89), after adjusting for 267 covariates.
Conclusions: Our network-based systems genetics framework identifies potential risk genes and repurposable drugs for PD and other neurodegenerative diseases if broadly applied.

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SHIFT 01-292

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
2 - 3 April 2025

ORAL CURCUMIN FOR ALZHEIMER'S DISEASE: IMPACT ON CSF NEUROCHEMICAL PROFILE

Lorenzo Gaetani, Elisa Siena, Andrea Toja, Giovanni Bellomo, Alfredo Megaro, Giovanna Nardi, Federico Paolini Paoletti, Lucilla Parnetti
University of Perugia, Department Of Medicine And Surgery, Section Of Neurology, Perugia, Italy

Aims: Curcumin, the principal component of *Curcuma longa*, has shown to interfere with amyloidosis and tauopathy and to have anti-inflammatory and antioxidant properties in Alzheimer's disease (AD). This study aimed to evaluate the impact of oral curcumin on cerebrospinal fluid (CSF) and plasma AD biomarkers.
Methods: We conducted an 18-month, double-blind trial with individuals aged 55–90 with mild cognitive impairment or mild dementia due to AD, all with a CSF A+/T+ profile. Participants were randomized (1:1) to receive either a placebo or 200 mg/day of oral curcumin for 12 months, followed by a 6-month open-label extension where all participants received curcumin. CSF and blood samples were collected at baseline (T0) and 12 months (T12), with additional plasma sampling at 18 months (T18). Primary outcomes included changes in CSF Aβ42/Aβ40, sAPPα, sAPPβ, p-tau181, neurogranin, t-tau, NfL, sTREM2, and YKL40 at T12, and in plasma NfL at T12 and T18.
Results: Fifty participants (74.7±6.9 years, 64% female) were enrolled (curcumin: n=25, placebo: n=25). Between T0 and T12, CSF p-tau181 increased in both groups ($p<0.05$). In the placebo group, CSF t-tau and NfL levels significantly increased ($p<0.05$), while no changes were observed in the curcumin group. Other markers showed no significant differences. Plasma NfL levels remained stable across both groups at all time points.
Conclusions: Oral curcumin appeared to slow the increase of CSF t-tau and NfL over 12 months but had no effect on other markers, suggesting it may not target specific AD mechanisms but rather exert a broad, untargeted action. Larger studies are needed to further explore curcumin's role in neurodegenerative diseases.

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SHIFT 01-299

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
2 - 3 April 2025

A PILOT INTERVENTIONAL STUDY ON FEASIBILITY AND EFFECTIVENESS OF THE CUE1 DEVICE IN PARKINSON'S DISEASE.

Viktoria Azoidou[1], Kira Rowsell[2], Ellen Camboe[1], Kamalesh Dey[1], Alexandra Zirra[1], Corrine Quah[3], Thomas Boyle[4], David Gallagher[5], Cristina Simonet[1], Alastair Noyce[1]
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Aims: Current treatments for Parkinson's disease (PD) usually fail to address gait issues and falls, affecting quality of life. The CUE1 device delivers cueing with vibrotactile stimulation showing potential to alleviate motor symptoms and reduce falls based on preliminary user testing results. The aim is to evaluate the feasibility, safety, and tolerability of CUE1 and its effect on motor symptoms including gait issues, falls risk, and non-motor symptoms in PD.
Methods: Patients with PD used the CUE1 for 9-weeks and were assessed at weeks-0, -3, -6, and -9 on motor signs using MDS-UPDRS-III, Timed Up and Go (TUG), TUG with dual task (DT), Functional Gait Assessment (FGA), and Bradykinesia Akinesia Incoordination (BRAIN) tap. Patients reported outcomes through MDS-UPDRS-I, -II, and -IV and Pittsburgh Sleep Quality Index (PSQI).
Results: Ten people with PD (5 females, age range: 46-80; disease duration: 3-9 years) completed the CUE1 intervention with 100% compliance and no adverse events. CUE1 comfort and usability were rated highly (80%). Immediate CUE1 effect was observed on MDS-UPDRS-III(45.40±12.22 vs 39.60±11.74, p=0.008), TUG(11.53±1.92 vs 11.08±1.94, p=0.022), TUG DT(18.57±5.75 vs 17.61±6.28, p=0.037), and FGA(16.40±3.86 vs 18.60±3.92, p=0.007). Cumulative effect after 9-weeks was noted on MDS-UPDRS III(45.40±12.22 vs 27.80±12.32, p=0.005), FGA(18.60±3.92 vs 23.10± 2.85, p<0.001), TUG DT(18.57±5.75 vs 13.58±7.05, p=0.031) and BRAIN kinesia(45.10±14.39 vs 42.10±12.74, p<0.001) and incoordination(24331.09±38017.46 vs 14059.91±9030.96, p=0.016) scores. After a 9-week period, improvements were noted on PSQI(10.10±4.95 vs 6.90±3.81, p=0.002), and MDS-UPDRS-I(18.60±6.75 vs 12.20±3.68, p=0.011), -II(17.30±7.29 vs 11.90±8.67, p=0.002), and -IV(7.50±3.75 vs 3.40±2.95, p=0.003).
Conclusions: Cueing with vibrotactile stimulation via CUE1 appears to be a feasible and safe intervention for PD. It may improve motor features, balance, gait, and reduce fall risk, while also improving motor fluctuations, and non-motor symptoms including sleep.

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SHIFT 01-302

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / PERSONALIZED MEDICINES, SEX / RACE, AI, AND COMBINATION THERAPY
2 - 3 April 2025

A MULTIPLE-DRUG THERAPY BENEFITS COGNITION AND REDUCES AMYLOID PLAQUES IN APP NL-G-F KNOCK-IN MICE, IN A SEX-SPECIFIC MANNER

Francesca Eroli[1], Zeynep Acararicin[1], Christina Tsagkogianni[1], Stefania Zerial[1], Saverio Lancia[1], Felix Andersson[1], Maria Latorre Leal[1], Jonas Wastesson[2], Angel Cedazo-Minguez[1], Kristina Johnell[2], Silvia Maioli[1]
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Aims: Cardiovascular conditions like hypercholesterolemia and hypertension increase the risk for Alzheimer's Disease (AD). Thus, certain AD risk profiles may benefit from optimized multi-medication therapies including for example cholesterol-lowering and antihypertensive drugs. In this study we investigate the effects of two multiple-drug regimens in the APP^{NL-G-F} knock-in (APP KI) mouse model of AD and explore whether this could affect the disease progression at early stages. Our multiple-drug treatments consisted of the most frequently prescribed drugs in older patients in Sweden, such as compounds from cardiovascular drug classes like antithrombotic agents, lipid modifying agents, ACE inhibitors, selective calcium channel blockers, and psychotropic drugs, used in combination.
Methods: APP KI mice were fed for 2 months with a control or two different multi-medication diets. In addition to the drug regimens, mice were tested for specific monotherapies from the combinations. Animals were assessed for locomotion, cognition, and anxiety-like behavior. Brain tissues were collected for molecular biology experiments, while blood was analyzed for serum metabolomics.
Results: Multi-medication therapies differentially affected essential functions such as locomotion and memory in AD mice. Combination #1 rescued cognitive deficits in male APP KI mice but not in females, finding that positively correlated with a reduction in cortical Aβ plaques observed in treated males. Combination #2 did not improve cognitive outcomes. Monotherapies alone partially explained the effects induced by polypharmacy.

Conclusions: We show that multi-medication therapies including cardiovascular drugs like statins and β-blockers, or ACE inhibitors may impact AD progression depending on sex and drug combination, suggesting synergic effects deriving from the multi-medications. The present results can contribute to the development of more individualized therapies in aging and AD, with special attention on sex and gender factors.

SHIFT 01-303

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / PERSONALIZED MEDICINES, SEX / RACE, AI, AND COMBINATION THERAPY
2 - 3 April 2025

INTEGRATIVE FRAMEWORK FOR ALZHEIMER'S DISEASE DRUG REPURPOSING: GENETIC SUBTYPES, COGNITIVE EFFECTS, AND UNSUPERVISED LEARNING

Gyungah Jun
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Aims: This study aimed to develop a comprehensive framework for AD drug repurposing by integrating brain cell-type specific genetic subtypes and prioritized genes to identify existing compounds and explore medication effects across subtypes.
Methods: Based on previous research defining 4 genetic subtypes (Sahelijo et al., 2024), two main approaches were employed. First, we applied for an AI-based approach using PubChem data to identify compounds targeting these subtypes. Phase 2 clinical trial compounds were transformed into pharmacophore fingerprints using ChemmineR. Unsupervised learning algorithms (Agglomerative Clustering, Ensemble Clustering, Gaussian Mixture Models, Bayesian Gaussian Mixture Models). We clustered compounds, evaluated significance and similarity scores, and characterized targets. Second, medication data mining using the United Kingdom Biobank (UKB) data analyzed cognitive test scores (prospective memory, fluid intelligence, pairs matching, and numeric memory) among 487,409 participants, stratified into high-risk and low-risk groups based on genetic subtype profiles.
Results: Generated compound clusters for 4 genetic subtypes: Ast-M2 (3 clusters, 11 targets, 180 compounds), Ast-M9 (2 clusters, 14 targets, 341 compounds), Oli-M45 (4 clusters, 11 targets, 66 compounds), Oli-M50 (4 clusters, 18 genes, 431 compounds). Structural similarities seen in Ast-M2, Ast-M9, and Oli-M50; distinct signatures in Oli-M45. Oli-M45 subtype had highest significance (8.49) and mean similarity score (0.96), featuring Vinblastine formulations targeting TUBA1A/B. UKB analysis found 9 of 47 medications improved cognition significantly ($P < 0.05$). Amitriptyline, Fluoxetine, Glucosamine, and Atenolol showed differing responses by risk group within subtypes.
Conclusions: This study introduces an innovative approach to AD drug repurposing leveraging unsupervised learning algorithms, enabling precision medicine and subtype-driven strategies. Moreover, the observed differential medication responses across brain cell-type driven subtypes highlight the potential of genetic subtype-driven treatment strategies in advancing personalized therapies for AD.

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SHIFT 01-309

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / SECRETASE INHIBITORS & MODULATORS
2 - 3 April 2025

IDENTIFICATION OF A POTENTIAL Γ-SECRETASE MODULATOR THROUGH SMALL MOLECULE SCREENING AND ITS ROLE IN APP PROCESSING

Jongho Kim, Sunyoung Park, Dong-Gyu Jo
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Aims: The accumulation of amyloid-beta (Aβ) plaques in the brain is one of the hallmarks of Alzheimer's disease (AD) pathology. Aβ is generated through the proteolytic cleavage of amyloid precursor protein (APP) by β- and γ-secretase. Despite numerous attempts to regulate Aβ production through γ-secretase inhibition, most clinical trials have been unsuccessful due to severe side effects, primarily caused by the inhibition of Notch, a key γ-secretase substrate. Therefore, selectively modulating γ-secretase activity has emerged as a promising therapeutic strategy for treating AD.
Methods: In this study, we developed a cell-based reporter system to monitor γ-secretase-mediated APP cleavage activity. Using this system, we screened a library of 2,570 FDA-approved drugs and identified several compounds with potential γ-secretase modulating effects. We administered candidate compounds to AD mouse models, followed by various behavioral tests to evaluate cognitive function. Additionally, histochemical and biochemical analyses were conducted to verify the modulation of γ-secretase activity.
Results: One candidate, referred to as Compound A (Cpd A), significantly improved cognitive performance in 5xFAD mouse models. Further analyses revealed that Cpd A treatment reduced Aβ42 levels and Aβ plaque burden in the brains of the AD mice. Transcriptomic analysis identified significant changes in gene expression following Cpd A administration. In neuronal cells, the treatment of Cpd A reduced the interaction between γ-secretase and APP, leading to a decrease in APP cleavage.
Conclusions: Our findings demonstrate the therapeutic potential of Compound A as a selective γ-secretase modulator and provide insights into the roles of γ-secretase in Alzheimer's disease pathology.

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SHIFT 01-312

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
2 - 3 April 2025

APOE GENOTYPE AND POLYGENIC RISK SCORE (PRS) MODIFY AGE AT ONSET OF ALZHEIMER'S DISEASE IN APP DUPLICATION CARRIERS

Joan Groeneveld[1,2,3], Aude Nicolas[4], Lou Grangeon[5], Janna Dijkstra[1,2,3,6], Niccolo Tesi[2,3,7], Chenyang Jiang[1,2], Itziar De Rojas[8,9], David Wallon[5], Stéphane Rousseau[10], Jean-Charles Lambert[4], Yolande Pijnenburg[1,2], Marc Hulsman[1,2,3], Gael Nicolas[10], Henne Holstege[1,2,3], Floor Duits[1,2,6], Lisa Vermunt[1,2,6], Sven Van Der Lee[1,2,3]
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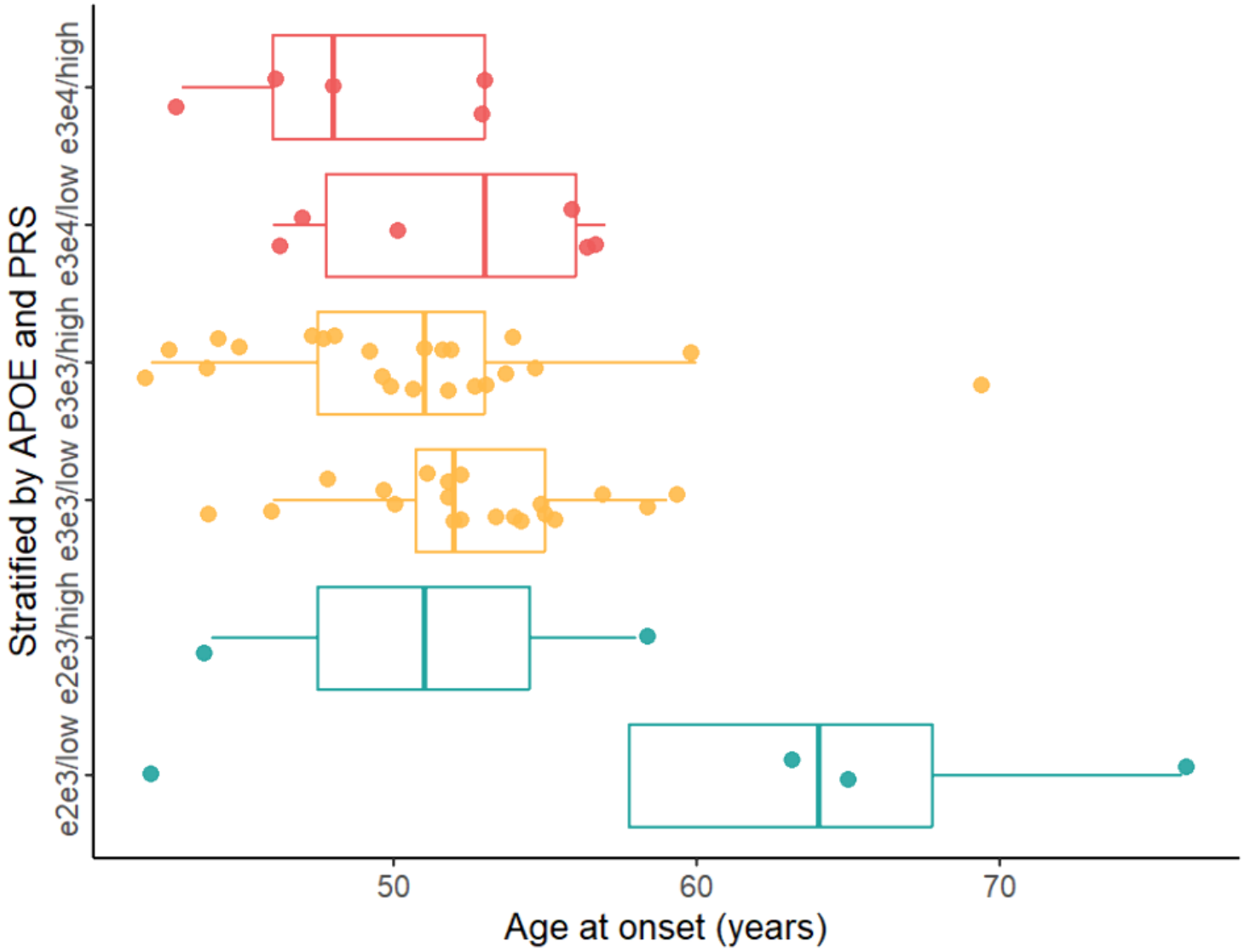
Aims: The age at onset (AAO) of autosomal dominant Alzheimer's disease (ADAD) caused by an *amyloid precursor protein (APP)* duplication varies widely (range 38-76 years). Genetic risk modifiers for sporadic Alzheimer's disease (AD) may partly cause the variation in AAO in these carriers. We aimed to investigate genetic modifiers of AAO in *APP* duplication carriers.
Methods: We analyzed genetic data from 92 *APP* duplication carriers, combining available data from 69 individuals with 23 cases from literature. We assessed the impact of the *APOE* genotype (ε2ε3, ε3ε3 and ε3ε4/ε2ε4 coded as 0, 1 and 2) and a standardized polygenic risk score (PRS) for AD on AAO using linear regression and Cox-proportional hazard models. With an exploratory Cox-model, we examined each genetic variant from the PRS, prioritizing genes determining the AAO (false discovery rate <0.2).
Results: Figure 1 shows the AAO of *APP* duplication carriers stratified by *APOE* genotype and low or high PRS. Using linear regression, the *APOE* genotype was associated with a 3.5-year reduction in AAO (p=0.012), while a 1-SD increase in PRS reduced AAO by 2.1 years (p=0.035). The *APOE* genotype had a hazard ratio (HR) of 1.75 for AAO (95% confidence interval (CI): 1.15-2.67, p=0.009), indicating that the *APOE* ε4 allele was linked to an earlier AAO, whereas the ε2 allele was associated with a later onset. The PRS was not significantly associated with AAO in the survival model (HR=1.33, 95% CI: 0.97-1.83, p=0.081). The exploratory analysis highlighted potential associations of AAO with variants near the *GRN* (HR=2.32, q=0.06) and *INPP5D* genes (HR=0.50, q=0.11).

Figure 1 – Boxplot of APP duplications carriers stratified by APOE genotype and PRS



Conclusions: *APOE* genotypes and common sporadic AD risk factors modify AAO in *APP* duplication carriers. These findings may improve AAO prediction and suggest potential targets for AAO modification.

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SHIFT 01-324

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2 - 3 April 2025

ATROPHY SUBTYPES IN ALZHEIMER'S DISEASE ARE DIFFERENTIALLY ASSOCIATED WITH ALZHEIMER'S DISEASE POLYGENIC RISK

Eleanor O'Brien[1], Chenyang Jiang[2], Vikram Venkatraghavan[2], Neil Oxtoby[3], Pierrick Bourgeat[4], Betty Tijms[5], Tenielle Porter[6], Simon Laws[7], Andre Altmann[8]
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Aims: Previous work has identified different gray matter atrophy subtypes in people with Alzheimer's disease (AD). We investigated the association between AD atrophy subtypes and polygenic genetic risk for AD.
Methods: Study participants originate from four cohorts: ADNI, AIBL, Amsterdam and UK BioBank comprising a total of 40,441 participants. Regional cortical and subcortical volumes were estimated using FreeSurfer 7.1.1. SuStaIn and Snowphlake were applied to the imaging data to obtain atrophy subtypes for each participant (https://doi.org/10.1101/2024.08.27.24312499). Polygenic risk scores (PRS) were computed using the PRSice software using Kunkle et al. (2019) as base GWAS and three P-value thresholds (P=5e-8, P=1e-05 and P=0.5). SNPs were limited to variants available in all cohorts; clumping and thresholding was conducted within the ADNI cohort. Genetic analyses were restricted to participants with European ancestry. We used logistic regression to test for an association between PRS and subtypes while adjusting for sex, age at imaging, and ten genetic principal components.
Results:

Table 1: Effect sizes (and standard errors) and resulting unadjusted p-values for the association between subtypes (columns) and PRS at specific thresholds (rows). Bold font indicates FDR-adjusted p-value < 0.05.

	SuStaIn				Snowphlake			
	Hippocampal sparing	Limbic predominant	Subcortical	Typical	Diffuse cortical	Frontal	Parieto-temporal	Subcortical
P=5e-8	-0.048 (0.021); P=0.028	0.040 (0.015); **P=0.008**	0.062 (0.022); **P=0.004**	0.006 (0.009); P=0.473	-0.025 (0.008); **P=0.002**	0.018 (0.009); P=0.058	-0.006 (0.020); P=0.752	0.021 (0.009); P=0.015
P=1e-5	-0.043 (0.019); P=0.025	0.043 (0.014); **P=0.002**	0.056 (0.020); **P=0.005**	0.003 (0.008); P=0.723	-0.022 (0.007); **P=0.003**	0.012 (0.009); P=0.158	-0.005 (0.018); P=0.790	0.018 (0.008); P=0.028
P=0.5	-0.004 (0.002); P=0.111	0.003 (0.002); P=0.078	0.001 (0.002); P=0.797	0.000 (0.001); P=0.786	-0.001 (0.001); P=0.365	0.002 (0.001); P=0.084	-0.001 (0.002); P=0.490	0.001 (0.001); P=0.253

Both subtyping methods identified four subtypes (SuStaIn: Hippocampal sparing, Limbic predominant, Subcortical, Typical; Snowphlake: Diffuse cortical, Frontal, Parieto-temporal, Subcortical). 34,687 subjects were included in the association analyses. 13,338 and 24,682 participants were assigned a subtype using SuStaIn and Snowphlake, respectively. The PRS at the P=0.5 threshold was not associated with any subtype (Table 1). Increased PRS at the other two thresholds, which comprise loci with strong associations with AD, was positively associated with the Limbic predominant (SuStaIn) and subcortical (SuStaIn) subtype and negatively associated with the Diffuse cortical subtype (Snowphlake) after FDR correction (Table 1).

Conclusions: AD polygenic risk comprising loci with strong association with AD was differentially associated with atrophy subtypes.

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β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2 - 3 April 2025

X CHROMOSOME GENETIC OVERLAP OF HORMONE, LIPID, AND BRAIN TRAITS WITH ALZHEIMER'S DISEASE REVEALS NOVEL MECHANISMS AND RISK GENES

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[1]Washington University School of Medicine, Neurogenomics And Informatics Center, St. Louis, United States of America, [2]Washington University in St. Louis, Neurology, St. Louis, United States of America

Aims: We recently completed the first large-scale X chromosome-wide association study (XWAS) of Alzheimer's disease (AD), revealing novel AD risk genes. Here, we aimed to integrate those results with XWASs of other AD-relevant traits to elucidate shared genetic signals and mechanisms contributing to AD risk and prioritize novel AD risk genes that previously lingered below significance thresholds.
Methods: The study design is shown in **Figure-1**. Non-sex-stratified and sex-stratified AD XWASs (Belloy et al. 2024) were integrated with XWASs from lipid, brain, and hormone-related traits (European ancestry). Locus-specific genetic colocalization analyses were evaluated for all AD-trait pairs when a respective variant in both traits was below a lenient threshold of P<1e-3. This ensured minimal signal was present in both traits, while allowing to explore signals below the typical X chromosome significance threshold (P<1e-5). Evidence of suggestive colocalization was denoted when colocalization posterior probability (PP4) ≥ 0.60.

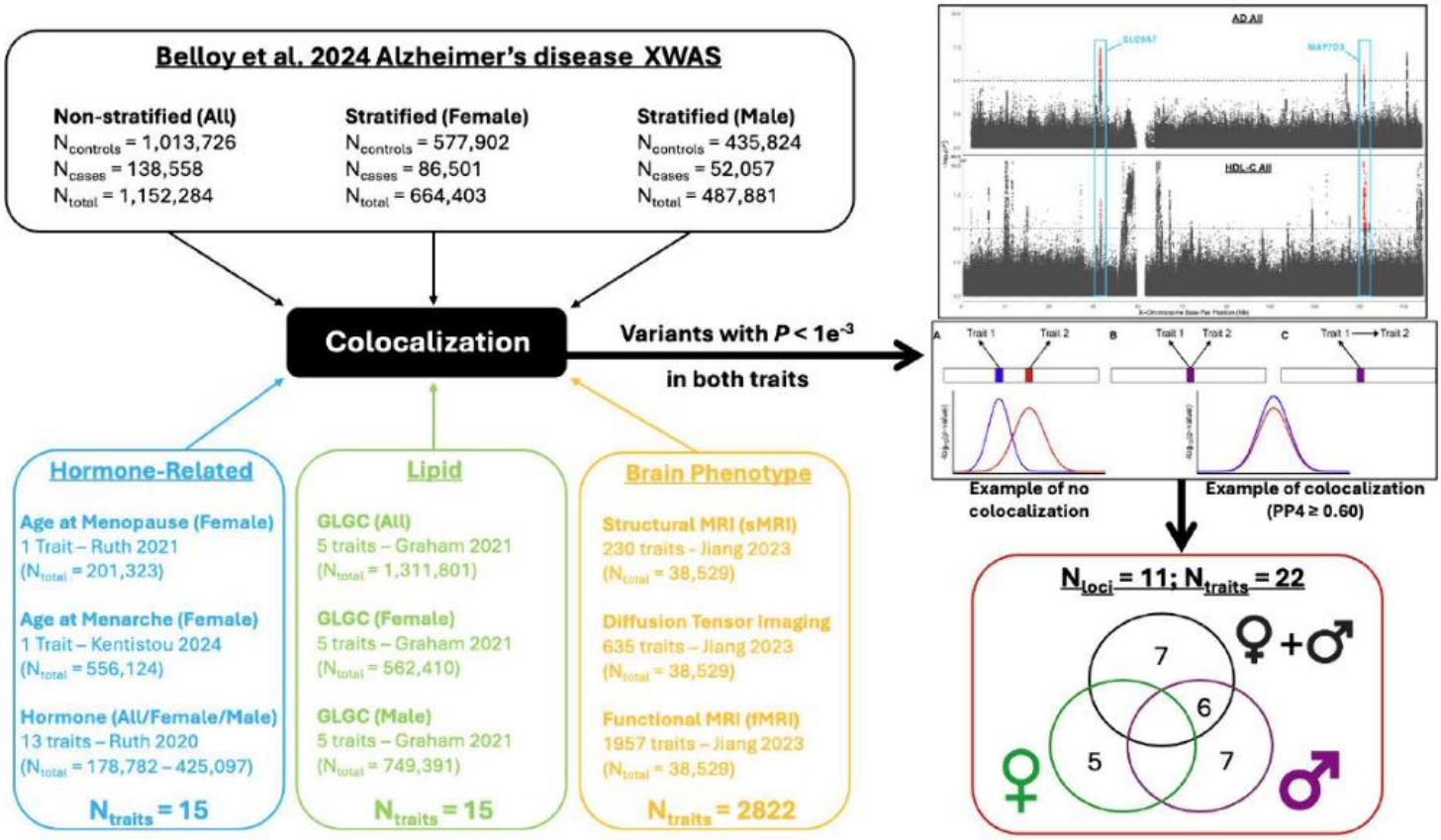

Figure-1. Study Design. Genetic colocalization was evaluated across AD X chromosome-wide association studies (XWASs) and multiple AD-relevant trait XWASs (left). Analyses were restricted to those loci/variants where there was at least minimal signals in both traits (center, right arrow; top right). A total of 10 loci across 22 AD-trait pairs were colocalized, including different AD-specific sex combinations (bottom right).

Results: We identified colocalization in 10 loci across 22 traits, including 4 previously identified AD risk loci (**Figure-2**): *SLC9A7* and *MAP7D3* colocalized with total testosterone and HDL-C, suggesting sex-specific mechanisms and cholesterol metabolism may tie into AD risk in these loci. *ZNF280C* and *MTM1* colocalized with multiple brain phenotypes, most notably brain network connectivity (**Figure-3**), suggesting potential AD resilience mechanisms. Importantly, we discovered 6 novel AD risk loci, including a female-specific AD risk locus on *DIAPH2*, which is linked to premature ovarian failure and has been shown to escape X chromosome inactivation.

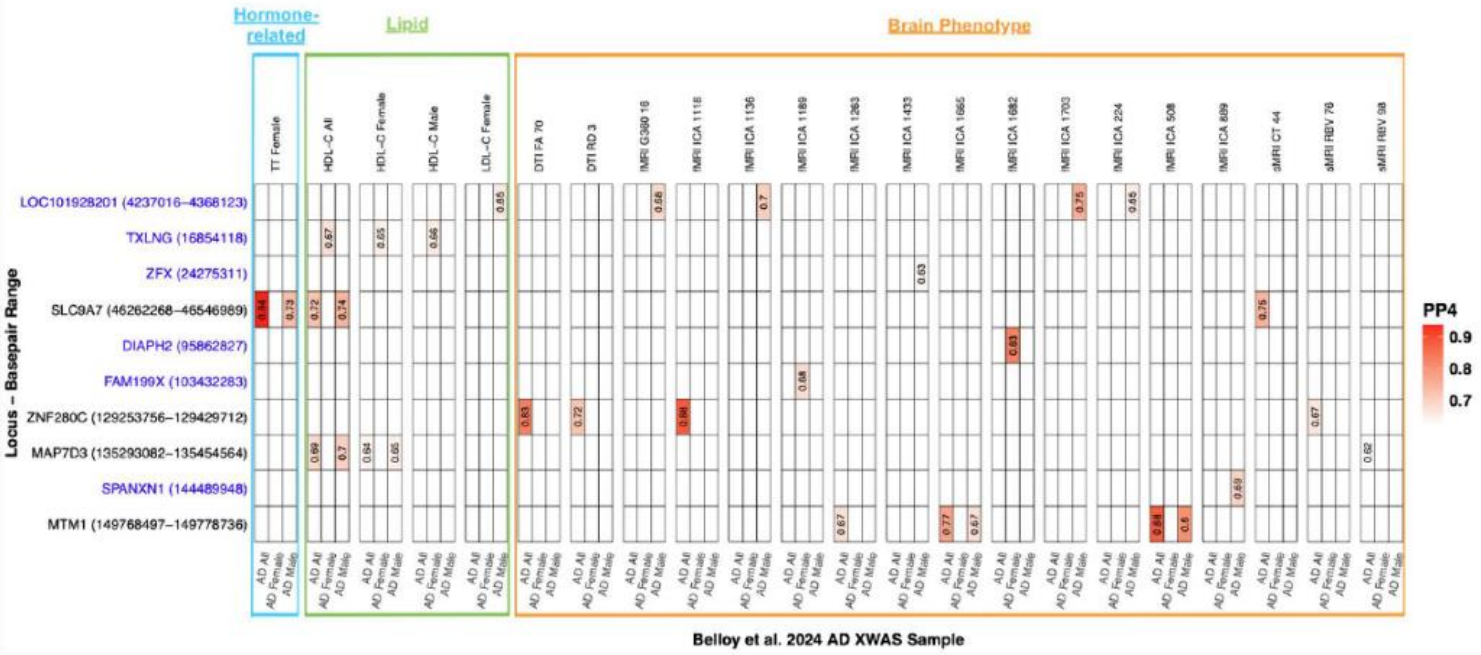

Figure-2. X chromosome AD genetic signals colocalized with other related traits. Colocalization heat map for all X-chromosome loci with PP4 ≥ 0.60. Loci denoted in black were previously identified in Belloy et al. 2024 AD XWAS, while blue colored loci represent novel AD-related X-chromosome loci. PP4 values from colocalization analysis are denoted within each cell.

Abbreviations: CT: Cortical thickness; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; fMRI: Functional magnetic resonance imaging; GLGC: Global Lipids Genetics Consortium; ICA: Independent component analysis; RBV: Regional brain volume; RD: Radial diffusivity; sMRI: Structural magnetic resonance imaging.

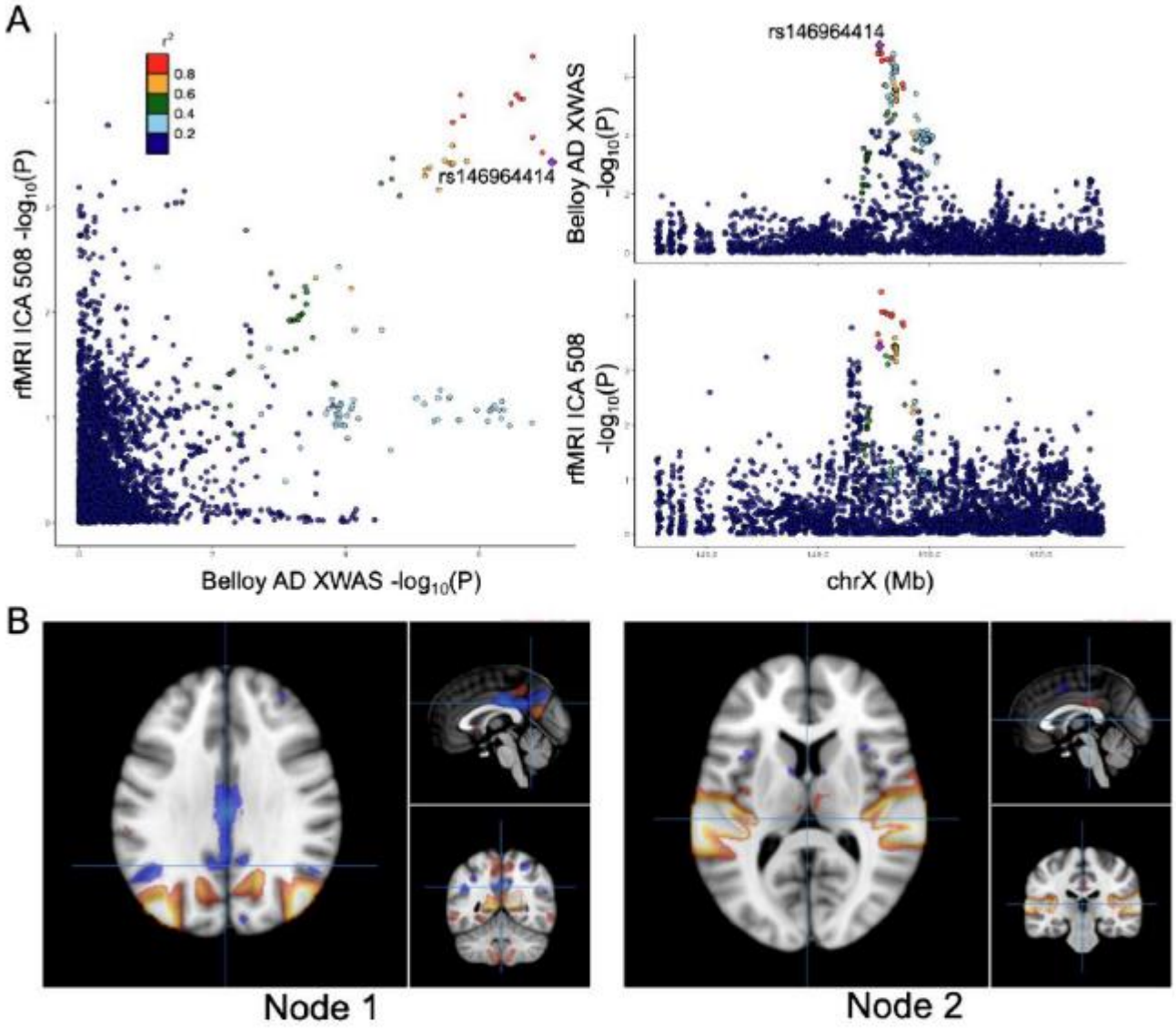

Figure-3. Illustration of genetic colocalization for MTM1 across AD and brain network connectivity. A) Strong colocalization was observed between the MTM1 AD risk locus and the brain connectivity phenotype "ICA-508". This corresponds to the connectivity between two brain networks, derived through independent component analyses (ICA) of brain resting state functional MRI scans across subjects in the UK Biobank. **B)** The two related brain networks are shown, with the left node (1) representing a component of the default-mode network (DMN), and the right node (2) representing components of auditory, cingulo-opercular, and somatomotor areas. Decreased DMN connectivity has been extensively linked to increased AD risk. Here we observed that decreased connectivity between the two networks was linked to increased AD risk.

Conclusions: This study provides novel insights into biological mechanisms that may contribute to X chromosome-linked genetic risk for AD, while also identifying several novel risk loci. In turn, this will help elucidate both sex-specific and sex-agnostic AD pathways and drug targets. Additional follow-up studies are ongoing.

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2 - 3 April 2025

GENETIC PLEIOTROPY ANALYSES ACROSS HORMONE-RELATED TRAITS AND ALZHEIMER'S DISEASE REVEAL SEX-SPECIFIC RELATIONSHIPS AND RISK GENES

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[1]Washington University School of Medicine, Neurogenomics And Informatics Center, St. Louis, United States of America, [2]Washington University in St. Louis, Neurology, St. Louis, United States of America

Aims: Sex differences are pervasive in Alzheimer's disease (AD). There is evidence for sex-specific genetic risk and a role of hormonal factors in AD, but there are limited understandings into their potential interplay. Here, we performed pleiotropy analyses on Genome-Wide Association Studies (GWASs) of hormone-related traits and AD risk to provide new insights into sex-specific AD mechanisms.
Methods: The study overview is presented in **Figure-1**. Briefly, we conducted pleiotropy analyses across sex-specific AD GWASs and hormone-related GWASs to identify (1) genome-wide genetic overlap/pleiotropy and (2) shared genetic variants/loci. For specific variants/loci, we used a tiered approach to prioritize the most promising discoveries.

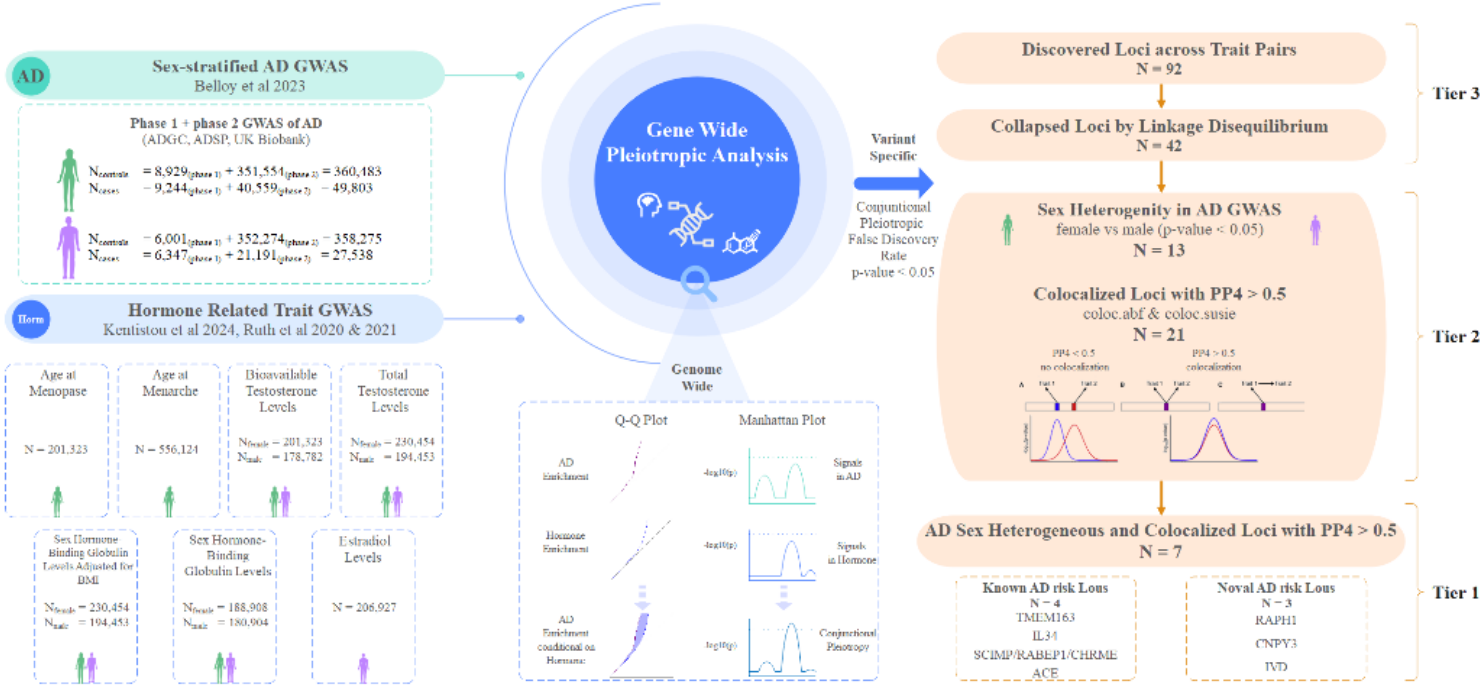

Figure-1. Schematic overview of the study design. Genome-wide pleiotropy analyses (center panel) were conducted across the largest sex-stratified AD GWASs to data (Belloy et al. 2023) and sex-stratified hormone-related trait GWASs (left panel). We sought to identify (1) genome-wide genetic overlap/pleiotropy and (2) shared genetic variants/loci (center). For specific variants/loci (right), we applied a pleiotropy false discovery rate (FDR) threshold of $P_{FDR}<0.05$ for each trait pair. We used a tiered approach to prioritize the most promising discoveries: Tier-3, locus displays significant pleiotropy, Tier-2, locus further displays sex heterogeneity in AD GWAS, or, shows genetic colocalization across trait pairs (implying not just a shared locus, but also a shared causal genetic signal), and Tier-1, locus further displays both sex heterogeneity in AD and genetic colocalization (representing the most promising discoveries).

Results: We observed enrichment of AD genetic signals when conditioned on any of the hormone-related traits, regardless of sex, indicating genome-wide pleiotropy (**Figure-2**). Further, we identified 42 Tier-3 pleiotropic loci (**Figure-3**). More pleiotropic loci overlapped with female AD signals, although female signals for total testosterone showed more overlap with male AD signals (N=9), including many

with sex heterogeneity in AD (N=6). AD loci shared with age-at-menopause (N=10) also included many with sex heterogeneity in AD (N=6). Finally, our prioritization approach identified 7 Tier-1 pleiotropic loci, including 3 not previously linked with AD but identified here through genetic overlap with age-at-menopause and testosterone (**Figure-1**). For example, one of the 3 novelly linked pleiotropic loci, *RAPH1*, has been linked to genetic risk for cardiovascular disease in men and increased aggressiveness of breast cancer in women, suggesting a broader role in sex-specific disease manifestation.

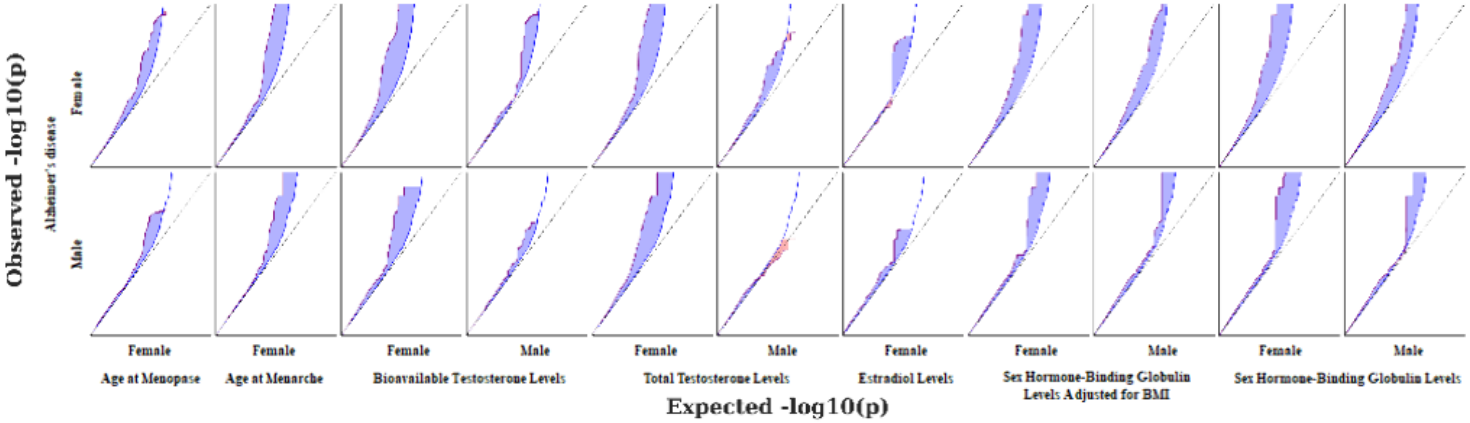

Figure-2. Genome-wide pleiotropy of AD signals conditional on hormone-related traits. Quantile-Quantile (QQ) plots show if observed genome-wide association signals deviate from expected null conditions. A signal close to the diagonal in the early quantile range (covering P-values < ~10-4) and subsequent upward signal, deviating from the diagonal, is a typical observation of significant associations with a given trait that deviates from random chance. The current QQ plots are additionally conditioned on variants that pass at least P-value<1e-3 in the indicated hormone trait. Blue shaded areas indicate the stronger deviation/ enrichment of the AD signal when condition on the hormone traits, implying the presence of genome-wide pleiotropy (red areas suggest deflation). One notable observation is that conditioned on the female signal for bioavailable testosterone or total testosterone displayed more AD signal enrichment, suggesting genetic regulation of testosterone in women may be specifically relevant to AD risk.

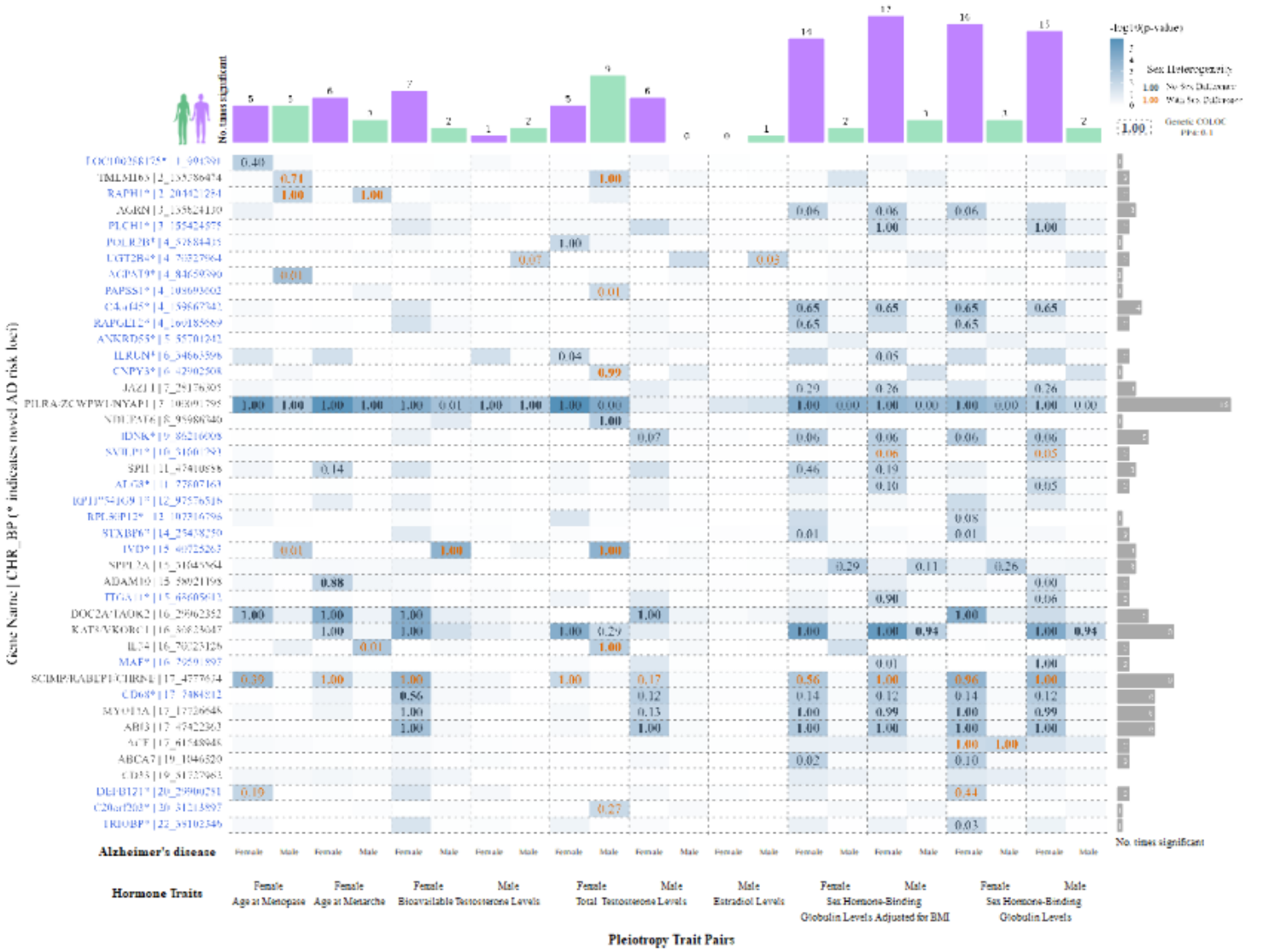

Figure- 3. Overview of 42 pleiotropic loci across AD and hormone-related traits. Loci are indicated in rows and sex-trait pairs in columns. AD loci are annotated with the nearest gene, where known AD loci are marked in black and novel ones are marked in blue(*). Cell colors reflect pleiotropy FDR P-values (-log10 scale). Genetic colocalization posterior probability (PP4) values are provided only in cells where pleiotropy FDR P<0.05, bolded values reflect PP4>0.5 (suggest reasonable colocalization), and pleiotropic loci with sex heterogeneity in the AD GWASs (P_{Het}<0.05) are further colored orange. The top histogram summarizes the total number of pleiotropic signals for a given sex-trait pair. The histogram on the right summarizes the total number of pleiotropic signals for a given locus. The most promising prioritized loci (Tier-1) are summarized in Figure-1.

Conclusions: This study highlights sex-specific genetic links between AD and hormone-related traits, prioritizing 7 compelling loci for further investigation. These findings provide an inroad to elucidate sex-specific AD pathways and drug targets.

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β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2 - 3 April 2025

AD-ASSOCIATED SRC RARE VARIANT IMPACTS APP METABOLISM AND NEURONAL ACTIVITY

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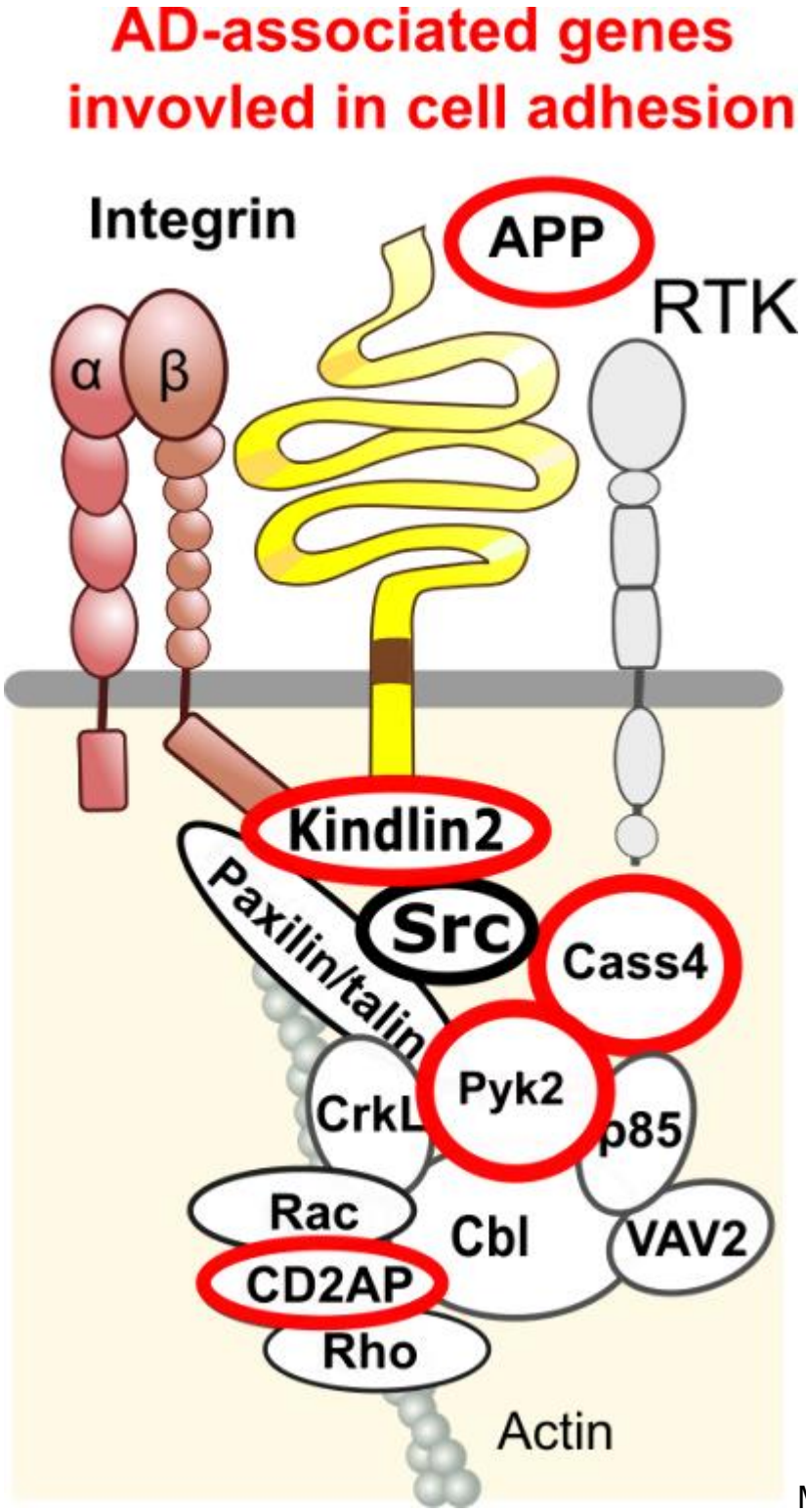
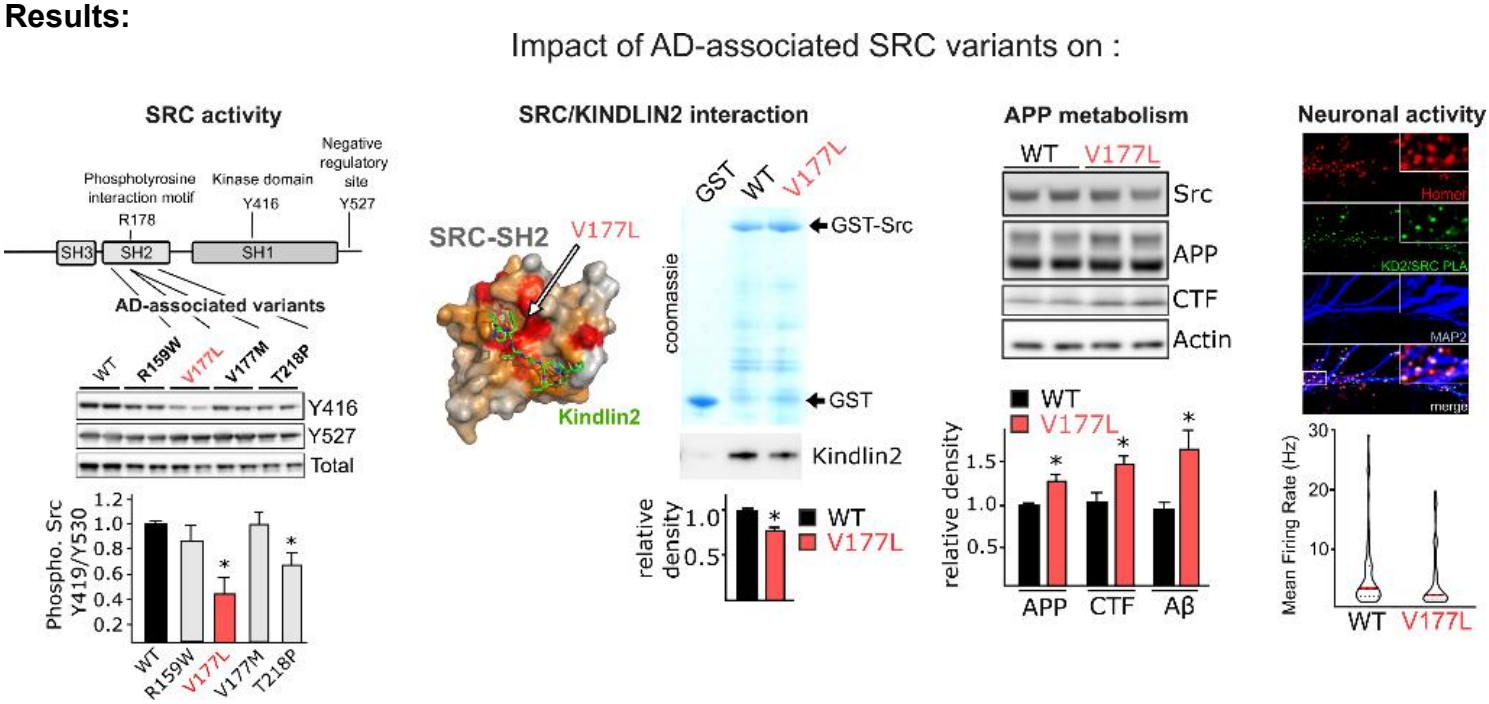
Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1167-RID-AGE Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Lille, France



Aims: Many genetic risk factors of AD are involved in cell adhesion pathways and among them, we identified KINDLIN2 (*FERMT2*) as a strong modulator of the APP metabolism. We have also reported that a KINDLIN2/APP interaction was necessary for KINDLIN2 to have an impact on APP metabolism and to control synaptic plasticity. Here, we identified the proto-oncogene tyrosine-protein kinase SRC, known to regulate KINLIND2 activity, also as strong regulator of the APP metabolism. Moreover, we investigated the functionality of *SRC* rare damaging variants, associated with AD risk, on SRC-dependent mechanisms.
Methods: Exome sequencing data from 32,558 individuals were used to perform a burden of predicted

damaging rare variants in SRC associated with AD risk. Then, we studied the functionality of these variants thought their capacity to modify (i) SRC/KINDLIN2 interaction by nuclear magnetic resonance, GST-pull down and Proximity Ligation Assay, (ii) APP metabolism and Aβ production in HEK299^{APP} cell, (iii) on neuronal activity using Microelectrode Array in primary neuronal culture (PNC).

Results:



SRC rare damaging variants were associated with the risk of AD (OR=6.1, 95% CI [1.4-26.7]). Among them, the SRC^{V117L} variant was associated with accumulation of APP-derived byproducts, including Aβ peptides. Moreover, the capacity of the SRC^{V177L} variant to bind KINDLIN2 is reduced when compared to the SRC^{WT}. Lasty, the overexpression of SRC^{V177L} in PNC was associated with a reduction in neuronal activity suggesting a harmful effect of this variant on synaptic plasticity.

Conclusions: *SRC* is a new genetic risk factor of AD and our data link this genetic determinant with two others, i.e. KINDLIN2 and APP, in common mechanisms affecting synaptic regulation. This knowledge should help to a better understanding of the synaptic dysfunctions that occur at the early stages of AD.

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2 - 3 April 2025

DISENTANGLING THE ROLES OF RACE, ETHNICITY, AND ANCESTRY IN APOE4-ASSOCIATED ALZHEIMER'S DISEASE

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[1]Case Western Reserve University, Population And Quantitative Health Sciences, Cleveland, United States of America, [2]Columbia University, Neurology, New York, United States of America, [3]University of Miami Miller School of Medicine, Dr. John T. Macdonald Foundation Department Of Human Genetics, Miami, United States of America

Aims: *APOE*'s ε4 haplotype (*APOE4*) is the strongest genetic risk factor for late onset Alzheimer's disease (LOAD), but its effect size varies by race and ethnicity (R/E). However, R/E is highly correlated with ancestry. This makes disentangling genetic and social constructs difficult, impeding the development of effective LOAD risk models. We address this gap by separately evaluating the roles of R/E and ancestry in LOAD.
Methods: We analyzed genetic and phenotypic data provided by the Alzheimer's Disease Genetic Consortium (ADGC) from 3,263 East Asian (EAS), 1,922 genetically admixed Hispanic/Latino (HIS), 7,663 genetically admixed non-Hispanic Black (NHB), and 31,518 non-Hispanic White (NHW) individuals. We stratified participants using R/E descriptors collected from primary, population targeted ADGC studies, assessing *APOE4* effects adjusted for age and sex. Next, K-means clustering generated four groups mapping to East Asian (EA), Hispanic/Latino (HI), African (AF), and European (EU) ancestry super-populations. We then built ancestry-stratified models, assessing *APOE4* effect adjusted for age and sex. Finally, we made ancestry adjustments to both regressions with the first two principal components. R/E descriptors were 97.8% concordant with corresponding ancestry super-population.
Results: *APOE4* ORs differed ($p<0.05$) between R/E groups similarly, whether PC adjusted or not. For PC-adjusted analyses, the results were: EAS OR_{APOE4} = 5.2; HIS OR_{APOE4} = 3.1; NHB OR_{APOE4} = 2.9; NHW OR_{APOE4} = 3.9. Ancestry-stratified estimates revealed virtually identical patterns of odds (EA OR_{APOE4}: 5.0; HI OR_{APOE4}: 3.2; AF OR_{APOE4}: 2.9; EU OR_{APOE4}: 3.9). R/E ORs did not differ significantly from their corresponding ancestry ORs.
Conclusions: R/E and ancestry *APOE4* effect estimates are indistinguishable in our data. This indicates that R/E and ancestry provide effectively interchangeable information when adjusting or stratifying to obtain *APOE4* effect estimates within the ADGC.

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2 - 3 April 2025

CELL STATE-DEPENDENT ALLELIC EFFECTS AND CONTEXTUAL MENDELIAN RANDOMISATION ANALYSIS FOR HUMAN BRAIN PHENOTYPES

Alexander Haglund[1], Verena Zuber[2], Julien Bryois[3], Dheeraj Malhotra[3], Leonardo Bottolo[4], Michael Johnson[1]
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Aims: This study aimed to map cell-type-specific expression quantitative trait loci (eQTL) in the post-mortem brain. We sought to uncover how the presence of disease affects eQTL associations and downstream inferences. Additionally, we aimed to infer relationships between cell-type-specific gene expression and brain phenotypic traits using genetic colocalisation and Mendelian randomisation (MR).
Methods: snRNA-seq was conducted on brain samples from 391 individuals. After cell-type annotation and pseudobulking, we conducted genome-wide *cis*-eQTL discovery at the cell-type level. We used interaction models to assess SNP-gene interactions with disease. Genetic colocalisation was used to identify eQTL/GWAS associations with 41 brain-related traits. We further applied MR in a controls-only subset (N = 183) to uncover putatively causal cell-type/gene/GWAS associations.
Results: We generated expression profiles for 2,348,438 single nuclei from 391 unique individuals. *Cis*-eQTL mapping across 8 major brain cell types identified 13,939 eGenes, 16.7-40.8% of which showed disease-dependent allelic effects. Colocalisation analysis revealed 501 colocalisations for 30 CNS traits, with 23.6% showing disease dependency. In the controls-only cohort (N = 183), we identified 91 additional colocalisations not found in the mixed cohort. Single-cell MR in control-only brains identified 140 putatively causal gene-trait associations of which 9 in AD and 5 in PD, including *EGFR* / Astrocytes and *GPNMB* / OPCs. A further 11 replicated at protein level in the UK Biobank, highlighting candidate biomarkers predictive of CNS outcomes.
Conclusions: This study provides a framework for conducting MR in single-cell expression in the brain, and enhances our understanding of disease effects on eQTLs associations and impact on colocalisation. We prioritize targets for brain disease and create a resource for unbiased interpretation of GWAS risk alleles, emphasizing the importance of using control brain tissue to improve the understanding of brain disease.

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SHIFT 01-330

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2 - 3 April 2025

NOVEL MACHINE LEANING METHOD IDENTIFIES ALZHEIMER'S DISEASE SUBTYPES USING LONGITUDINAL CLINICAL DATA AND HIGH-DIMENSIONAL OMICS DATA

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Aims: Heterogeneity of Alzheimer's Disease (AD) in older adults suggests subgroups with distinct biological profiles. Traditional methods may not capture clinically relevant subtypes and limit their ability to effectively incorporate longitudinal trajectory information. We developed a novel method that integrates longitudinal-clinical data and high-dimensional omics to identify AD subtypes with distinct time-varying risk factor effects.
Methods: We applied our model to 994 adults from the Religious Orders Study/Memory and Aging Project, incorporating brain transcriptomics and longitudinal cognitive data, adjusting for sex, *APOEe4*, and vascular risk factors. Our model identified four subgroups. We investigated clinico-pathological differences among groups and time-varying effect of vascular risk factors on cognitive function within each group. Differential gene expression and GO enrichment analyses were performed to reveal molecular pathways among groups.
Results: Table 1. Participants characteristics by group

	Group 1	Group 2	Group 3	Group 4
Cohort size, n	164	179	217	434
Age at visit (mean, SD)	88.16 (6.12)	87.67 (6.94)	87.74 (6.41)	88.15 (7.33)
Global cognitive function (mean, SD)	-2 (1.13)	-1.19 (0.96)	-0.73 (0.82)	-0.09 (0.56)
Pathological diagnosis of AD, n (%)	128 (78%)	140 (78%)	157 (72%)	204 (47%)
Diagnosis of AD dementia, n (%)	122 (95%)	101 (81%)	89 (64%)	53 (18%)
Women, n (%)	125 (24%)	123 (31%)	141 (35%)	287 (34%)
APOEe4	57 (35%)	62 (35%)	59 (27%)	76 (18%)
Hypertension, n (%)	145 (88%)	158 (88%)	193 (89%)	404 (93%)
Diabetes, n (%)	18 (11%)	34 (19%)	32 (15%)	84 (19%)
Stroke, n (%)	44 (27%)	41 (23%)	41 (19%)	86 (20%)
Frailty, n (%)	74 (45%)	56 (31%)	69 (32%)	117 (27%)

Figure 1. Trajectories of global cognitive function by group

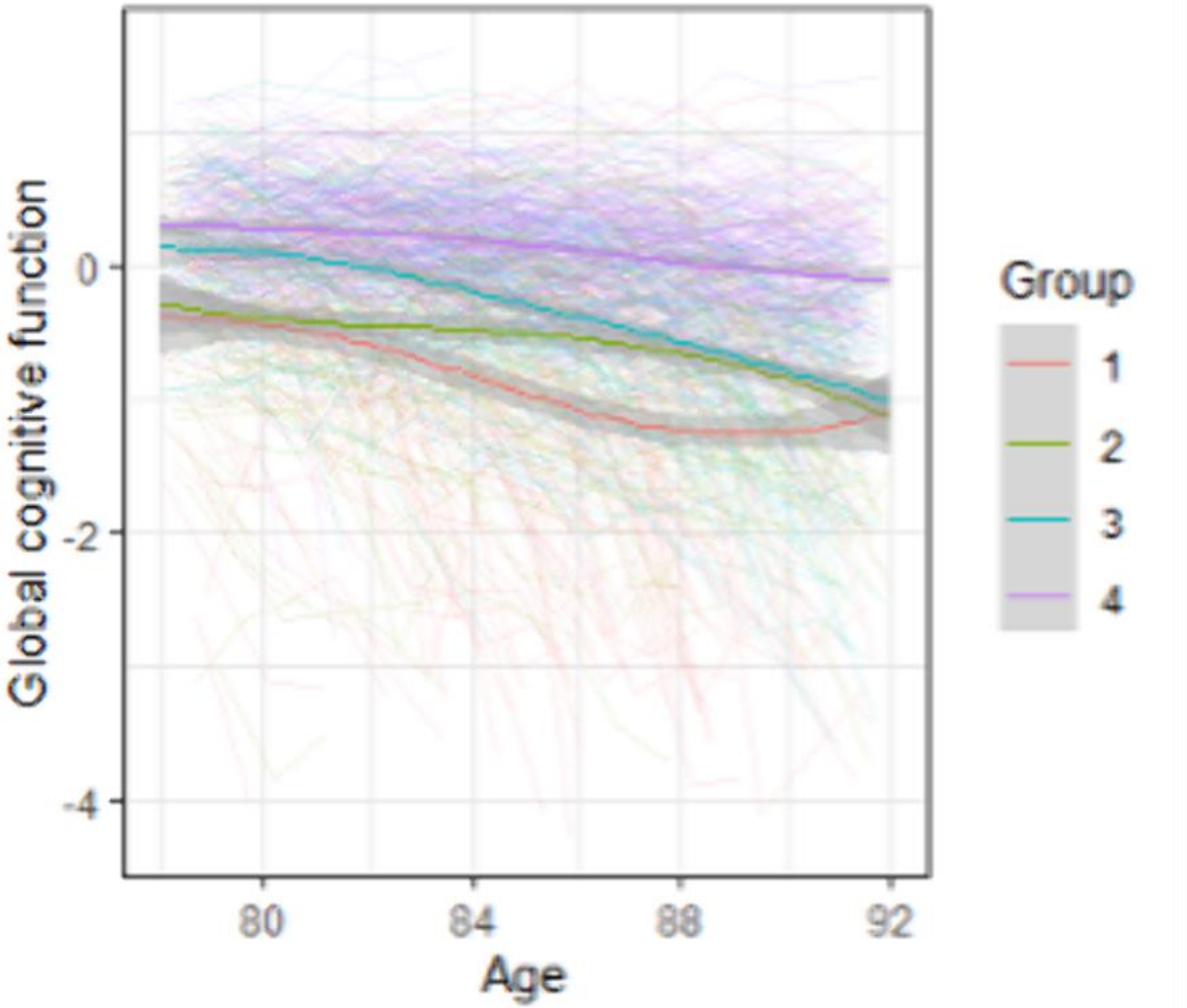


Figure 2. Clinico-pathological differences among groups

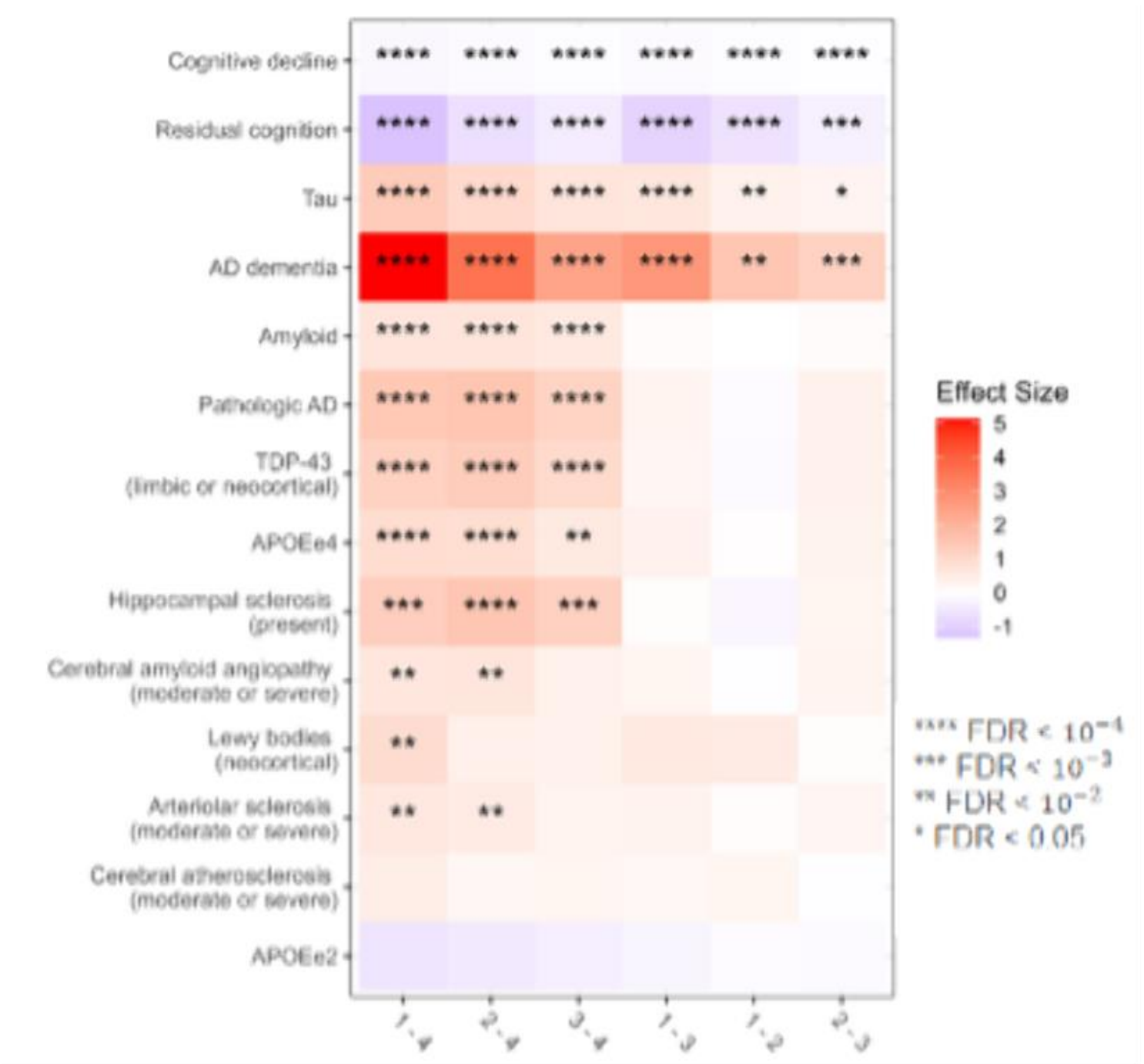
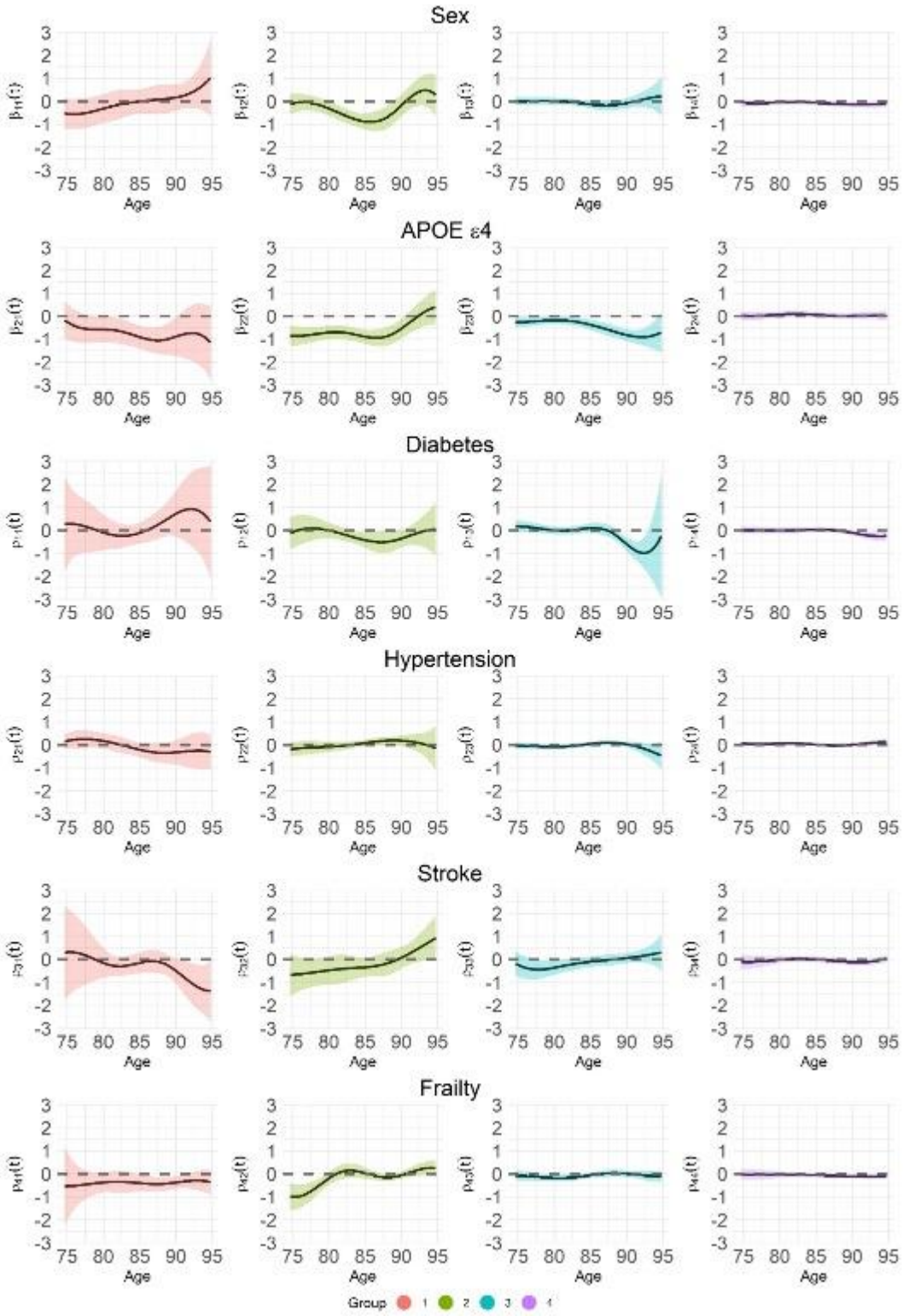


Figure 3. Effect of time-varying risk factors on global cognitive function for each group.



Participants had a mean age of 81 years (Table 1). Cognitive decline followed a gradient from Group 1 (fastest decline) to Group 4 (slowest decline) (Figure 1). Groups 1–3 showed steeper cognitive decline, higher risk of AD dementia, prevalence of AD pathological hallmarks compared to Group 4 (Figure 2). In Group 1, participants with *APOEe4* (ages 78-90), stroke (age>92), and frailty (ages 85-92) had a lower cognitive function (Figure 3). Compared to Group 4, Group 1 was involved in Golgi vesicle transport, oxidoreductase activity, tubulin binding, and vesicle tethering complex.

Conclusions: Our novel approach identified clinically meaningful AD subgroups with distinct cognitive

trajectories, vascular profiles, and molecular signatures. This work is crucial for design of therapeutics and trials that focus on precise molecular targets.

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SHIFT 01-339

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
2 - 3 April 2025

CELL TYPE SPECIFIC CHARACTERIZATION OF MRNA, LNCRNA, CIRCRNA, AND PSEUDOGENES EXPRESSED IN POSTMORTEM BRAIN IN ALZHEIMER'S AND CONTROLS

Elizabeth Hutchins[1,2], Jerry Antone[2], Eric Alsop[1,2], Jennifer Nolz[3], Qi Wang[3], Rebecca Reiman[4], Winnie Liang[4], Geidy Serrano[5], Thomas Beach[5], Diego Mastroeni[3], Ben Readhead[3], Andrew Singleton[2,6], Michael Nalls[1,2], Eric Reiman[7], Kendall Van Keuren-Jensen[2]
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Aims: Long non-coding RNA are cell type specific, regulators at the transcriptional and post-transcriptional level, expressed in the central nervous system, and implicated in the development and progression of neurodegenerative disease. CircRNA regulate gene expression, can be enriched in synapses, dynamically expressed during neuronal development, and accumulate in the brain during aging. Laser capture microscopy (LCM) is utilized to analyze cell populations without tissue dissociation and includes cytoplasmic RNAs, in addition to RNA found in nuclei. We characterized the non-coding RNA landscape in Alzheimer's disease and controls in three cell types (microglia, astrocytes, and neurons) isolated with LCM in two brain regions (posterior cingulate and superior frontal gyrus).
Methods: Postmortem brain from participants with AD (n = 35), mild cognitive impairment (n = 15), non-demented (n = 35), and ND with AD pathology (n = 15) was embedded in OCT and sectioned at 10 microns for laser capture microscopy (LCM). 300 cells per subject of the following cell types were LCM isolated: microglia, astrocytes, and neurons, from both the posterior cingulate and the superior frontal gyrus. RNA was isolated for whole transcriptome RNA sequencing. A custom genome annotation featuring additional lncRNAs was developed by adding lncRNA from the LncBook and LNCipedia databases to what is already available in v45 of GENCODE.
Results: An additional 108,718 lncRNA genes were added to the 19,375 lncRNA already available in v45 of GENCODE. About 10,000 – 15,000 mRNA and 1,000 – 17,000 lncRNA are consistently expressed, depending on cell type and region. LncRNA and circRNA are enriched in neurons compared to astrocytes and microglia.
Conclusions: We identified cell-type enriched non-coding RNA, including lncRNA and circRNA, in the human brain in AD and controls to better understand disease biology.

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SHIFT 01-342

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
2 - 3 April 2025

LOOKING BEYOND THE REFERENCE: USING GENOME ASSEMBLY AND PANGENOME GRAPHS TO INVESTIGATE AN AFRICAN-ORIGIN PROTECTIVE HAPLOTYPE FOR ALZHEIMER'S DISEASE

Luciana Bertholim Nasciben[1], Karen Nuytemans[1,2], Marina Lipkin-Vasquez[1], Derek Van Booven[1], Farid Rajabli[1,2], Sofia Moura[1], Aura Ramirez[1], Derek Dykxhoorn[1,2], Liyong Wang[1,2], William Scott[1,2], David Davis[3], Regina Vontell[3], Katalina Mcinerney[4], Michael Cuccaro[1,2], Goldie Byrd[5], Jonathan Haines[6], Larry Adams[1], Margaret Pericak-Vance[1,2], Juan Young[1,2], Anthony Griswold[1,2], Jeffery Vance[1,2]
[1]University of Miami, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]University of Miami Miller School of Medicine, Dr. John T. Macdonald Foundation Department Of Human Genetics, Miami, United States of America, [3]University of Miami Miller School of Medicine, Brain Endowment Bank, Department Of Neurology, Miami, United States of America, [4]University of Miami Miller School of Medicine, Department Of Neurology, Miami, United States of America, [5]Wake Forest School of Medicine, Maya Angelou Center For Health Equity, Winston-Salem, United States of America, [6]Case Western Reserve University, Institute For Computational Biology, Department Of Population & Quantitative Health Sciences, Cleveland, United States of America

Aims: *APOE*ε4 is the strongest genetic risk factor for Alzheimer's disease (AD). Recently, our group described a protective locus from African origin (rs10423769_A) that has a statistical interaction with *APOE*ε4 reducing the risk of AD up to 75% in *APOE*ε4 homozygotes. The locus is located 2 MB upstream from *APOE* in an area of segmental duplications (SD) in a cluster of pregnancy-specific glycoproteins (*PSGs*) and lncRNA genes. The aim of this study is to get insights into the mechanism of protection involved in this locus using long-read sequencing and genome assembly techniques to resolve the area of SD.
Methods: We performed whole-genome sequencing (WGS) with the Oxford Nanopore PromethION in carriers and non-carriers of rs10423769_A (n=38), followed by local genome assembly of reads with TREAT/Otter. We also performed PacBio Revio WGS (n=6), followed by assembly using hifiasm, and building of pangenome graphs and structural variation (SV) calling with minigraph.
Results: Nanopore data indicated that the protective allele is associated with an expanded variable number of tandem repeats (VNTR) region 32 kb of rs10423769_A. Motif analysis showed that the 29bp repetitive sequence, which occurs in a higher number with the protective allele, carries predicted binding sites for the MEF2 family of transcription factors, which are involved in neuronal development. PacBio sequencing and genome assembly confirmed the co-occurrence of the expanded VNTR with the protective allele, and overall detected a higher number of SVs in the 1 mb SD region surrounding the A haplotype when compared to the reference, which are currently under investigation.
Conclusions: We speculate that the differences identified between the protective and reference haplotype contribute to changes in binding of regulatory elements or chromatin structure, which could ultimately change *APOE*ε4 expression.

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SHIFT 01-343

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
2 - 3 April 2025

PROGNOSTIC VALUE OF LIGHT REFLEX PUPILLOMETRY AND ACTIGRAPHY IN EARLY ALZHEIMER'S DISEASE – A LONGITUDINAL COHORT STUDY

Mathias Holsey Gramkow[1], Frederikke Kragh Clemmensen[1], Andreas Brink-Kjær[2,3], Ulrich Lindberg[4], Ian Law[5,6], Otto Mølby Henriksen[5], Gunhild Waldemar[1,6], Poul Jørgen Jennum[3,6], Steen Gregers Hasselbalch[1,6], Kristian Steen Frederiksen[1,6]
[1]Danish Dementia Research Centre, Dept. of Neurology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [2]Department of Health Technology,Technical University of Denmark, Kongens Lyngby, Denmark, [3]Department of Clinical Neurophysiology, Copenhagen University Hospital - Rigshospitalet, Glostrup, Denmark, [4]Functional Imaging Unit, Department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital - Rigshospitalet, Glostrup, Denmark, [5]Department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, [6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Aims: Easily applied biomarkers for the prognosis of Alzheimer's disease are crucial in the current paradigm of disease-modifying therapies. Wearable and portable digital health technologies allow unobtrusive monitoring and remote testing of clinical features and may be used for disease tracking. Hand-held quantitative light reflex pupillometry measures distinct midbrain functions that receive cortical modulatory inputs, and actigraphy can measure circadian rhythm and activity levels, both shown to be altered in Alzheimer's disease. We aimed to determine the prognostic value of quantitative light reflex pupillometry and actigraphy in early Alzheimer's disease and evaluate neuroimaging (MRI and [18F]FDG-PET) changes associated with the biomarkers.
Methods: Single-center longitudinal cohort study. A total of 105 patients with Alzheimer's disease were recruited and followed for 18-24 months since diagnosis. Quantitative light reflex pupillometry (PLR-3000, NeurOptics) and dual sensor, body-worn actigraphy (SENS Motion) were performed at baseline and follow-up. Disease progression was evaluated with the Clinical Dementia Rating Scale. Region-of-interest MRI volumetry and standardized uptake value ratios for [18F]FDG-PET were derived using FreeSurfer for 1-year follow-up changes. To study associations between changes in the light reflex and actigraphy, clinical progression and neuroimaging, linear regression models and logistic regression will be used. Machine learning will be applied to actigraphy data to build a classifier for progression vs. non-progression.
Results: The results of the present study will elucidate the prognostic value of two promising digital biomarkers, which may be used for guiding treatment selection and direct planning of care in Alzheimer's disease. Completion of follow-up is finished in the last quarter of 2024, and the study results will be presented at the conference.
Conclusions: This study will show whether the investigated markers may ease prognostication in Alzheimer's disease.

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SHIFT 01-344

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
2 - 3 April 2025

PREDICTIVE POWER OF SELF- AND INFORMANT-REPORTED COMPLAINTS IN SUBJECTIVE COGNITIVE DECLINE: A CLINICALLY BASED LONGITUDINAL STUDY

Hana Horakova[1], Dylan Jester[2], Terezie Zuntychova[1], Veronika Matuskova[1], Kateřina Veverová[1], Tomas Nikolai[1], Katerina Sheardova[3], Jan Laczo[1], Ross Andel[3,4], Jakub Hort[1,3], Martin Vyhnálek[1]
[1]Second Faculty of Medicine, Charles University and Motol University Hospital, Memory Clinic, Department Of Neurology, Prague, Czech Republic, [2]Women's Operational Military Exposure Network (WOMEN), Va Palo Alto Health Care System, Palo Alto, United States of America, [3]International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic, [4]Arizona State University, Edson College Of Nursing And Health Innovation, Phoenix, United States of America

Aims: Subjective cognitive complaints (SCCs) in cognitively normal older adults may be an early clinical indicator of Alzheimer's disease and related disorders. However, it remains unclear which SCCs are most strongly associated with cognitive decline and whether this differs between patient and informant reports. We aimed to evaluate the ability of specific SCCs, from both patient and informant versions of the Questionnaire of Cognitive Complaints (QPC), to predict cognitive decline in individuals with subjective cognitive decline (SCD).
Methods: A total of 262 patients with SCD ($mean_{age}$=67.2, SD=7.4) from the Czech Brain Aging Study were included. Participants underwent comprehensive neuropsychological assessment at baseline and at least one annual follow-up visit ($mean_{follow\text{-}up}$=4 years). Self-report and informant-report versions of the 10-item QPC were administered at baseline. Linear mixed models controlling for sex, age, and education assessed the effect of the QPC-SCCs on the rates of change in global cognition, memory, and executive function/processing speed, presented as standardized z-scores. Baseline means, and standard deviations were used as references for follow-up z-scores.
Results: Informant-reported complaints were less frequent than self-reports on all QPC items. Both self- and informant-reports of *memory change*, *worse memory compared to peers*, and *limitations in daily activities* significantly predicted decline in global cognition, memory, or executive function/processing speed. However, informant-reports generally predicted a steeper slope of cognitive decline. Only informant-reports of *spatial orientation difficulties* and *forgetting past experiences*, and only self-reports of *personality change*, predicted decline in global cognition.
Conclusions: Only a subset of patient- and informant-reported SCCs predicted objective cognitive decline in SCD. Our findings suggest that patients and their informants provide different insights into the cognitive changes experienced, with informant-reports generally predicting a steeper rate of cognitive decline, emphasizing their greater efficiency.

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SHIFT 01-345

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
2 - 3 April 2025

UNLOCKING THE BEHAVIOURAL IMPAIRMENTS OF HUMANIZED APP KNOCK-IN MICE THROUGH MACHINE LEARNING ANALYSIS

Loukia Katsouri, Angela Misak, Stephen Burton, John O'Keefe
UCL, Sainsbury Wellcome Centre, London, United Kingdom

Aims: Alzheimer's disease is a neurodegenerative disorder that is the most common cause of dementia in the elderly population. One promising mouse model of AD is the humanised *App*$^{NL\text{-}G\text{-}F}$ knock-in model. Aims: To find a sensitive behavioural task to detect an early behavioural deficit in App knock-in mice and evaluate how it changes with ageing using 6-, 12- and 21-month-old A*pp*$^{NL\text{-}G\text{-}F}$ mice. Objectives: To assess recognition, working, and short-term spatial memory, as well as anxiety-like behaviours and locomotion in mice, using machine learning algorithms for data analysis.
Methods: We utilized male and female AppNL-G-F mice and their wild-type littermates at 6 months, 12 months, and 21-22 months of age. The mice underwent a comprehensive behavioral assessment as illustrated in Figure 1. Following this, we rigorously analyzed the videos using DeepLabCut and advanced machine learning techniques to accurately estimate their performance (Figure 2).

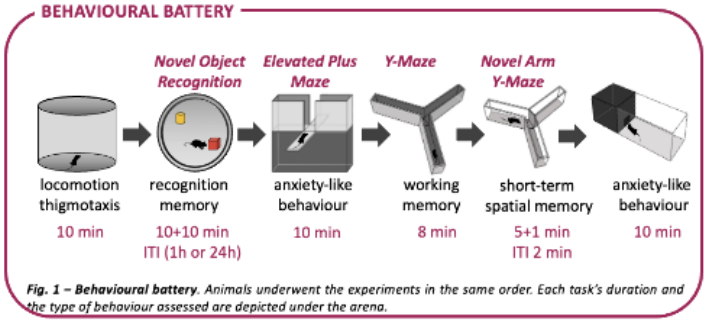

Fig. 1 – Behavioural battery. Animals underwent the experiments in the same order. Each task's duration and the type of behaviour assessed are depicted under the arena.

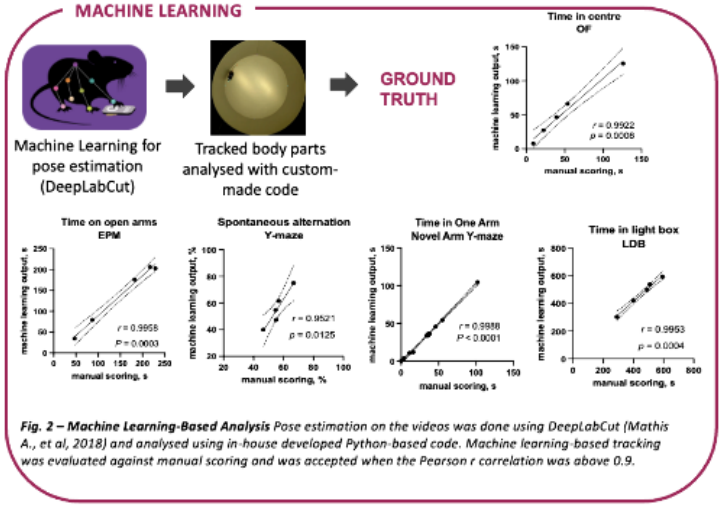

Fig. 2 – Machine Learning-Based Analysis Pose estimation on the videos was done using DeepLabCut (Mathis A., et al, 2018) and analysed using in-house developed Python-based code. Machine learning-based tracking was evaluated against manual scoring and was accepted when the Pearson r correlation was above 0.9.

Results:

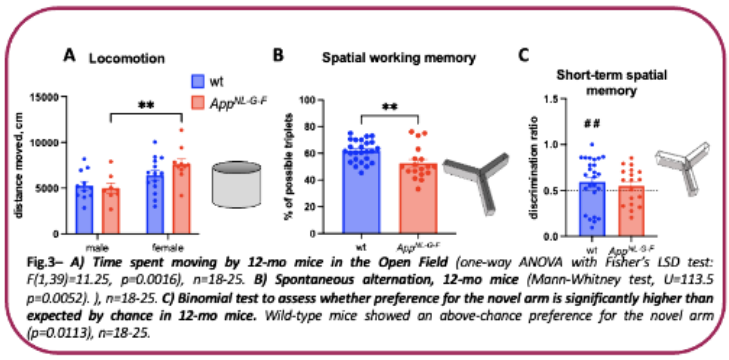

Fig.3– *A) Time spent moving by 12-mo mice in the Open Field* *(one-way ANOVA with Fisher's LSD test: F(1,39)=11.25, p=0.0016), n=18-25.* ***B) Spontaneous alternation, 12-mo mice*** *(Mann-Whitney test, U=113.5 p=0.0052).), n=18-25.* ***C) Binomial test to assess whether preference for the novel arm is significantly higher than expected by chance in 12-mo mice.*** *Wild-type mice showed an above-chance preference for the novel arm (p=0.0113), n=18-25.*

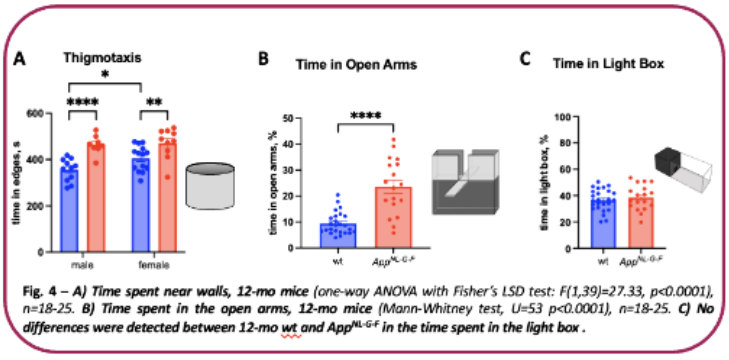

Fig. 4 – *A) Time spent near walls, 12-mo mice* *(one-way ANOVA with Fisher's LSD test: F(1,39)=27.33, p<0.0001), n=18-25.* ***B) Time spent in the open arms, 12-mo mice*** *(Mann-Whitney test, U=53 p<0.0001), n=18-25.* ***C) No differences were detected between 12-mo wt and AppNL-G-F in the time spent in the light box .***

We found that 6-mo AppNL-G-F animals have decreased locomotion and possible short-term spatial memory impairments as well as increased anxiety-like behaviour. Moreover, 12-mo AppNL-G-F animals also have spatial working and short-term memory impairments (Figure 3) and altered anxiety-like behaviour (Figure 4). Conversely, aged animals have working and recognition memory impairment irrespective of their genotype and their anxiety-like behaviour is not modified further in 22-mo App^{NL-G-F} animals (Figures 5-6)

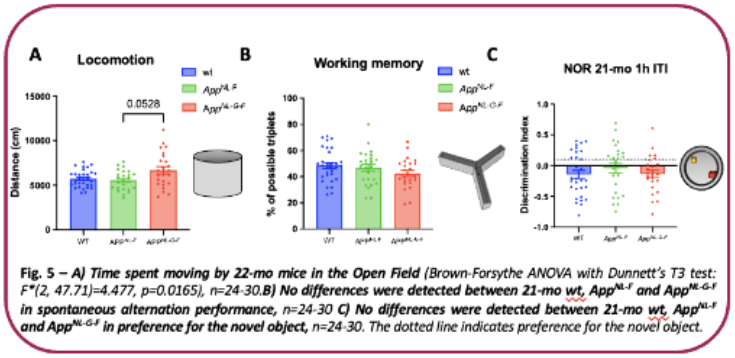

Fig. 5 – *A) Time spent moving by 22-mo mice in the Open Field* *(Brown-Forsythe ANOVA with Dunnett's T3 test: F*(2, 47.71)=4.477, p=0.0165), n=24-30.* ***B) No differences were detected between 21-mo wt, AppNL-F and AppNL-G-F in spontaneous alternation performance,*** *n=24-30* ***C) No differences were detected between 21-mo wt, AppNL-F and AppNL-G-F in preference for the novel object,*** *n=24-30. The dotted line indicates preference for the novel object.*

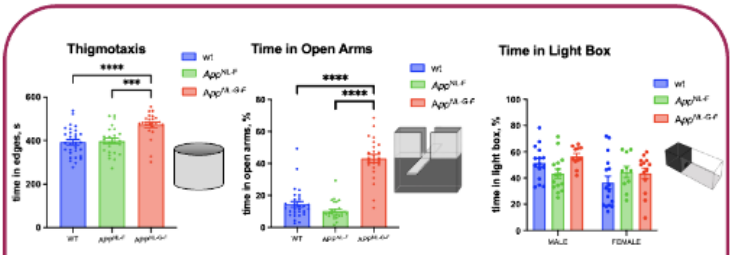

Fig. 6 – *A) Time spent near walls, 22-mo mice* *(one-way ANOVA with Tukey's post-hoc: F(2,76)=6.622, p=0.0022), n=24-30.* ***B) Time spent in the open arms, 22-mo mice*** *(Kruskal-Wallis test with Dunn's post-hoc test: H(3)=46.06 p<0.0001), n=24-30.* ***C) No differences were detected between 22-mo wt, AppNL-F and AppNL-G-F in the time spent in the light box,*** *n=24-30.*

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Conclusions: AppNL-G-F mice: •Are hyperactive in the Open Field and have increased thigmotaxis indicating high arousal and hyperactivity. •Exhibit decreased anxiety in the EPM and do not show increased anxiogenic behaviour in the Light/Dark box. •Have Y-maze deficit at 12 months but differences disappear in aged mice. •App^{NL-F} mice are performing similarly to wild-type mice and don't exhibit any further impairments at 22-mo.

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SHIFT 01-346

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
2 - 3 April 2025

SCREENING FOR AD STAGES IN THE BIOFINDER PRIMARY CARE COHORT USING A DIGITAL SPEECH BIOMARKER FOR COGNITION (SB-C)

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Aims: This study explores the potential of a digital speech biomarker for cognition (SB-C) to discriminate between the following FDA-recognised AD stages: 2 (asymptomatic, CDR=0, Aβ42/p-tau181-positive), 3 (subtle cognitive symptoms,CDR=0.5, Aβ42/p-tau181-positive) and 4 (mild cognitive impairment, CDR ≥1, Aβ42/p-tau181-positive), in order to provide an accessible screening solution in real-life clinical settings.
Methods: We utilized data from the Swedish BioFINDER-Primary Care study (N=144).Participants were classified into AD stages following the FDA Guidance for Industry definition based on amyloid and tau pathology confirmed through CSF, along with clinical assessments. The SB-C and subscores (executive function, memory, processing speed) were automatically extracted from recordings of Semantic Verbal Fluency (SVF) and RBANS List Learning tasks applying speech recognition and feature extraction.The SB-C is a z-score corrected for age and education. We found pairwise optimal cut-offs for the SB-C between the AD stages and evaluated discriminative performance by assessing sensitivity, specificity and balanced accuracy.
Results: Participants' characteristics are presented in Table1. The SB-C demonstrated robust discriminatory power across all three FDA stages. The cutoff analysis showed optimal cut-offs of the SB-C normed z-scores of -0.8 to separate stage 2 and 3 and -1.3 to separate stage 3 and 4 respectively. With those cut-offs classification performance was at 77% accuracy (sens =.88, spec=.67) for stage 2 vs. 3 and for stage 3 vs. 4 (sens= .66, spec = .77) respectively. Combining FDA stage 2 and 3 and separating it from stage 4 yielded a balanced accuracy of 75% (sens = .75,spec =.77).

Table 1. Characteristics of participants

FDA Stages	2	3	4
N	32	82	30
Age	75.31 (5.96)	77.49 (6.38)	80.84 (5.56)
Education	11.72 (2.89)	11.16 (2.98)	10.47 (3.2)
MMSE	26.91 (5.21)	25.17 (2.94)	20.53 (4.95)
ki:e SB-C Cognition Score	-0.3 (0.75)	-1.21 (0.83)	-1.85 (0.91)
ki:e SB-C Executive Score	0.11 (1.12)	-0.32 (1.04)	-1.16 (1.03)
ki:e SB-C Memory Score	-0.72 (0.52)	-1.41 (0.56)	-1.62 (0.35)
ki:e SB-C Processing Score	0.07 (0.82)	-1.02 (0.92)	-1.6 (1.28)

Table 2. Classify between FDA Stage 2 vs. 3

	Cut off	BAL	Sensitivity	Specificity
ki:e SB-C Cognition Score	-0.832	0.772	0.875	0.670
ki:e SB-C Executive Score	-0.563	0.579	0.781	0.378
ki:e SB-C Memory Score	-1.457	0.740	0.968	0.512
ki:e SB-C Processing Score	-0.489	0.766	0.812	0.719

Table 3. Classify between FDA Stage 3 vs. 4

	Cut off	BAL	Sensitivity	Specificity
ki:e SB-C Cognition Score	-1.341	0.713	0.658	0.766
ki:e SB-C Executive Score	-0.855	0.689	0.744	0.633
ki:e SB-C Memory Score	-1.472	0.639	0.512	0.767
ki:e SB-C Processing Score	-0.672	0.624	0.414	0.833

Table 4. Classify between FDA Stage 2 & 3 vs. 4

	Cut off	BAL	Sensitivity	Specificity
ki:e SB-C Cognition Score	-1.395	0.751	0.766	0.767
ki:e SB-C Executive Score	-0.784	0.706	0.667	0.746
ki:e SB-C Memory Score	-1.309	0.709	0.867	0.552
ki:e SB-C Processing Score	-0.946	0.696	0.733	0.658

Conclusions: The SB-C demonstrates potential as a non-invasive tool for differentiating between AD stages, offering a practical and accessible solution for broader application in clinical settings and specifically primary care, where automated speech extraction could provide cost and time benefits.

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2 - 3 April 2025

DIAGNOSTIC PERFORMANCE OF ABTEST-MS IN MILD COGNITIVE IMPAIRMENT: FINDINGS FROM THE CLINICAL VALIDATION STUDY.

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Aims: Plasma Aβ42/Aβ40, as measured with an antibody-free method (ABtest-MS) has previously demonstrated clinical utility for both cognitively unimpaired and impaired (mild cognitive impairment - MCI) populations, as highlighted in prior studies. However, the initial research faced limitations due to a small sample size of MCI individuals, potentially affecting the generalizability of its conclusions. To address this, an extension of the original validation study has been designed to include a larger number of MCI individuals, aiming to enhance the robustness of the findings and ensure closer alignment with real-world scenarios. The primary objective of this extension study is to validate the ABtest-MS against cerebrospinal fluid (CSF) amyloid status (Aβ42/Aβ40) as the gold standard for amyloid pathology in MCI populations.
Methods: The study comprises two independent cohorts: 500 participants from Hospital de Santa Maria (Lleida, Spain) and 200 participants from Hospital Clínico San Carlos (Madrid, Spain), all diagnosed with MCI. The study's secondary objective is to define two diagnostic cutoff values to maximize diagnostic performance by balancing positive and negative predictive values (PPV and NPV) and minimizing the uncertainty zone. The analysis will follow a three-part validation strategy: **Part A**: Calculate key diagnostic parameters (AUC, sensitivity, specificity, accuracy, PPV, NPV) for each cohort individually. **Part B**: Apply logistic regression models from Cohort 1 to Cohort 2 for external validation, and recalculate the diagnostic metrics. **Part C**: Perform an overall analysis combining both cohorts and calculate two distinct cutoff values to minimize uncertainty and maximize predictive performance.
Results: from these analyses will be presented at the congress. Preliminary results suggest potential improvements in clinical decision-making for MCI populations, offering a more accurate tool for assessing amyloid deposition risk.
Conclusions: To be disclosed at the conference.

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2 - 3 April 2025

KIDNEY FUNCTION AND ALZHEIMER'S DISEASE: IMPACT ON PLASMA BIOMARKERS AND CORRECTION FACTORS

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Aims: Our aim was to quantify the impact of kidney function on plasma Aβ42/40, pTau181, pTau217, and NfL and to determine correction factors for these biomarkers in a cohort of patients with available estimated glomerular filtration rate (e-GFR) at the time of lumbar puncture (LP) and collection of blood samples
Methods: Our cohort included 112 patients with CSF, serum, and plasma samples collected on the same day. Participants were classified by their A/T/N profile based on CSF (n=52 A+/T+, n=5 A+/T-, n=15 A-/T+, n=40 A-/T-). AD biomarkers (Aβ42/40, pTau181, pTau217, and NfL) were measured using the Lumipulse G1200. Serum creatinine and e-GFR were assessed in serum collected at LP. Linear and logistic regressions were applied to to log-transformed data obtain correction factors based on renal parameters.
Results: Out of 112 patients, 58 exhibited kidney dysfunction (KD, e-GFR < 60 mL/min/1.73 m²). KD correlated with increased plasma concentrations of Aβ42, Aβ40, pTau181, pTau217, and NfL ($p<0.01$). Ratios of pTau isoforms to Aβ42 did not fully offset the KD effect. Correcting for e-GFR and age improved the CSF and plasma NfL correlation (from r=0.69 to r=0.83). A sex- and creatinine-based correction removed KD-related effects on plasma pTau181 and pTau217 distributions and enhanced the accuracy in detecting the CSF A+/T+ profile at pre-determined cutoff values.
Conclusions: KD significantly affects plasma AD biomarkers. Corrections for age, sex, e-GFR, and creatinine eliminate this effect, enhancing diagnostic performance and cutoff transferability.

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2 - 3 April 2025

CARDIOVASCULAR RISK AND ITS ASSOCIATION WITH PLASMA BIOMARKERS ALONG THE ALZHEIMER'S DISEASE TRAJECTORY

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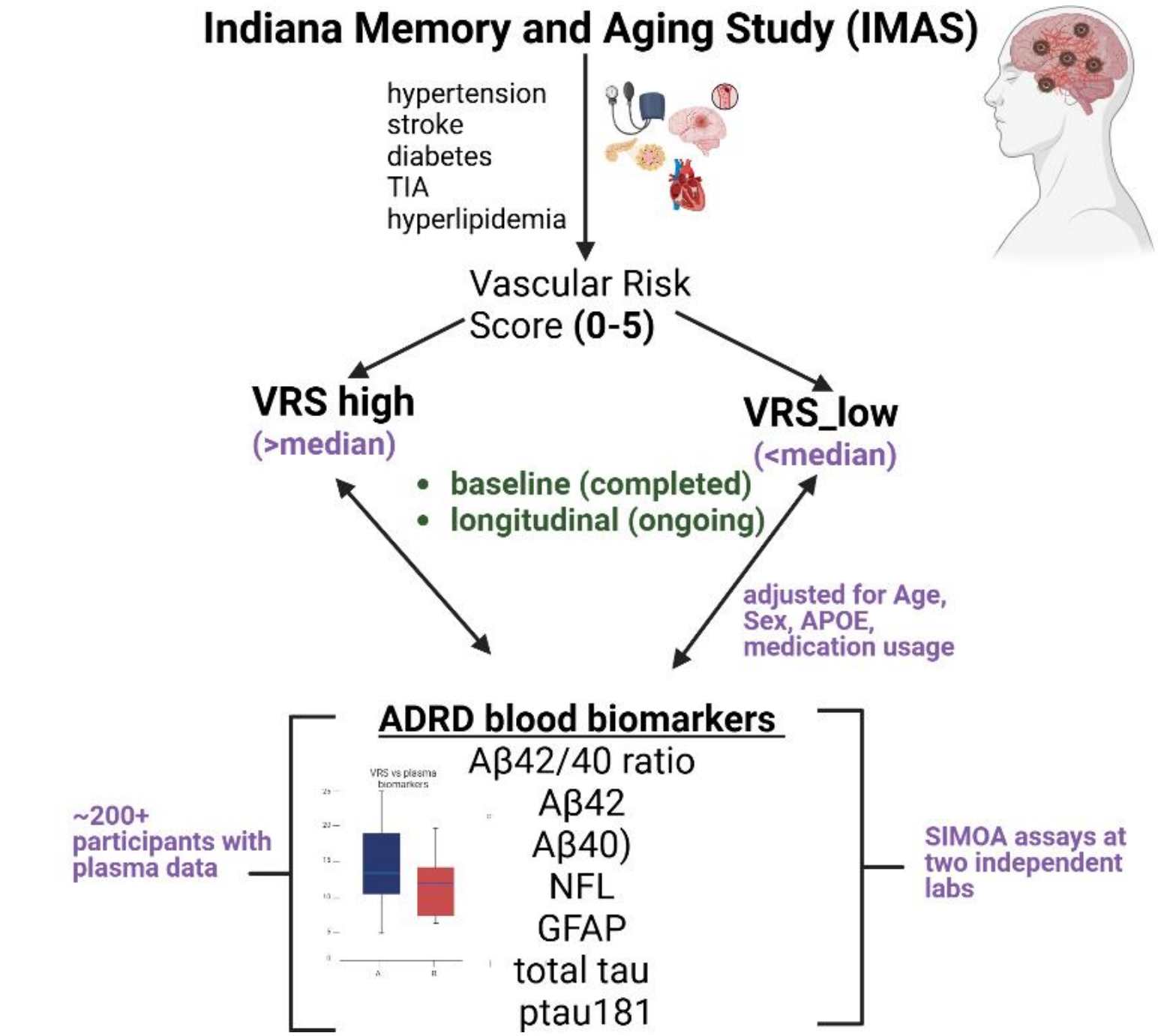
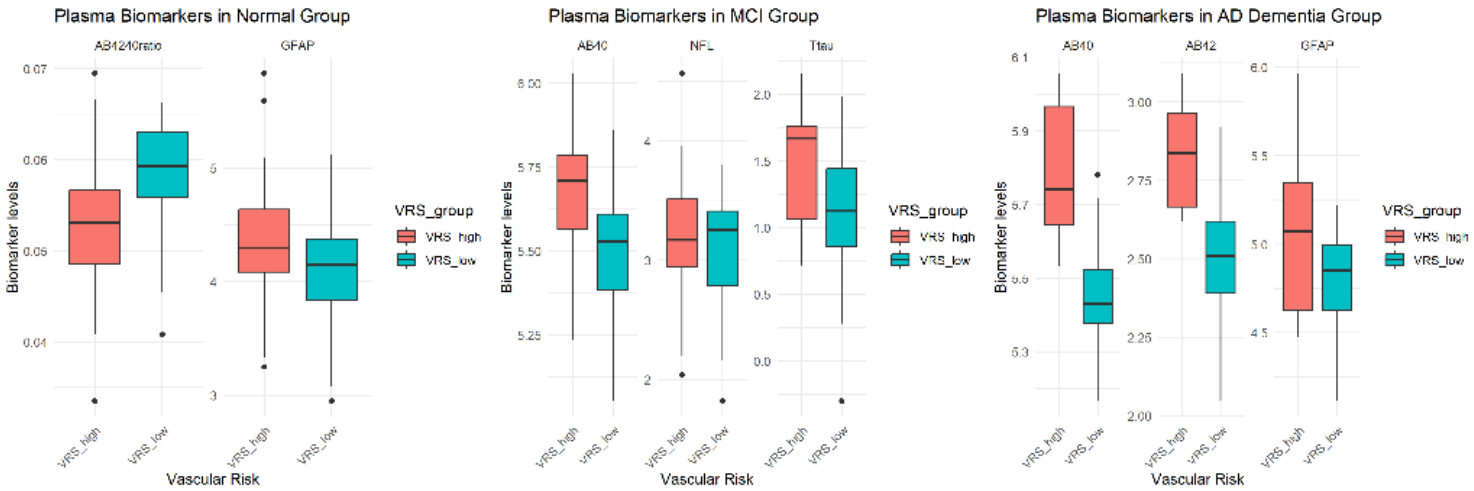
Aims: Altered plasma biomarker signatures associated with cardiovascular health may serve as indicators of early cognitive decline in asymptomatic individuals. This study aims to identify blood-based ADRD biomarkers associated with high cardiovascular risk in cognitively unimpaired individuals (CN) and those in earlier stages, such as mild cognitive impairment (MCI), at the Indiana Alzheimer's Disease Research Center (IADRC).
Methods:



We used cross-sectional multivariable linear regression models to explore the relationship between vascular burden and plasma biomarkers for AD. Cardiovascular risk was assessed with a vascular risk score (VRS) including hypertension, diabetes, hypercholesterolemia, transient ischemic attack (TIA), and stroke. Plasma levels of amyloid-β (Aβ42/40 ratio, Aβ42, Aβ40), NFL, GFAP, and total tau (N=151) and ptau181 (N=108) were measured using SIMOA assays at two independent labs in Indiana University School of Medicine or University of Gothenburg. Covariates included age, sex, and *APOE4* carrier status.

Results:



In the CN group, elevated cardiovascular risk was significantly associated with lower Aβ42/40 ratios ($p < 0.05$, $\beta = -1.87$) and lower Aβ42 levels ($p < 0.05$, $\beta = -1.43$). In the MCI group, higher cardiovascular risk was significantly associated with higher Aβ40 ($p < 0.05$, $\beta = 1.93$) and t-tau levels ($p < 0.01$, $\beta = 0.83$). Stratification by median VRS value revealed significantly altered biomarker signatures (Aβ42/40, NFL, t-tau, GFAP) between those with high and low vascular risk profiles in each diagnostic group (Figure).

Conclusions: The observed baseline associations between vascular burden and changes in key AD biomarkers highlight the importance of considering cardiovascular health in the context of neurodegenerative risk. Ongoing studies in this cohort continue to investigate how cardiovascular burden and plasma biomarkers may interact to influence cognitive decline in cognitively unimpaired and non-demented individuals, longitudinally.

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2 - 3 April 2025

BIOLOGICAL VARIATION OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS IN A MIXED MEMORY CLINIC COHORT

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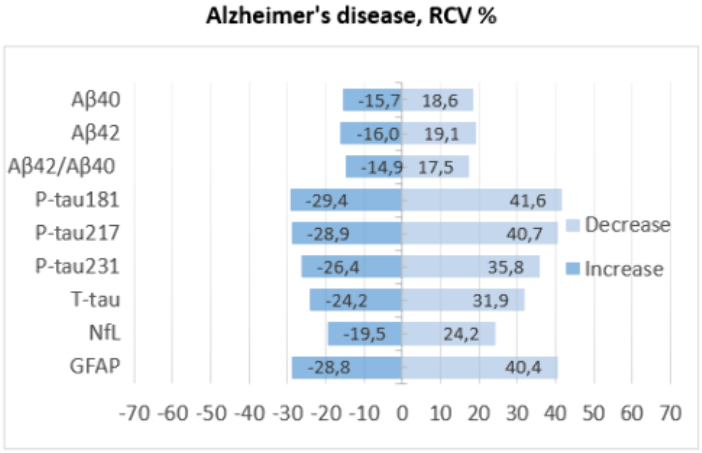
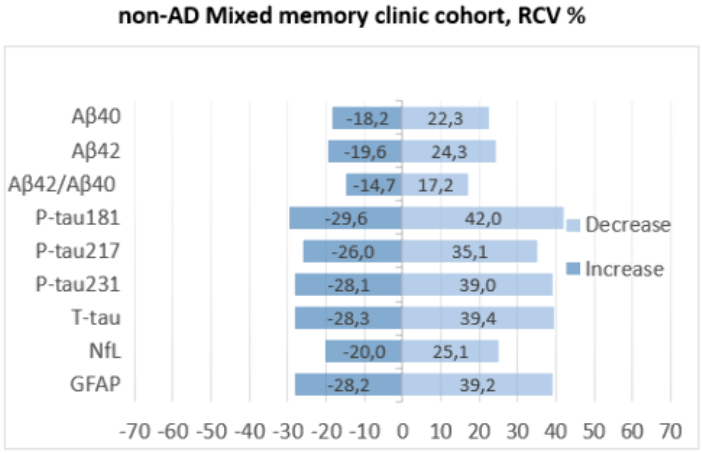
Aims: For clinical implementation of Alzheimer's disease (AD) blood-based biomarkers (BBMs), knowledge of biological variation (BV), determined by a patient's physiology, is crucial to ensure safe and correct biomarker interpretation, i.e., to capture changes or treatment effects that lie beyond BV. In this study we investigated BV in AD biomarkers for the intended use population, memory clinic patients.
Methods: In a consecutive sample of memory clinic patients (AD n=27, non-AD n=20), blood samples were collected on three separate days within a period of 36 days and analysed for plasma Aβ40, Aβ42, p-tau181, p-tau217, p-tau231, T-tau, neurofilament light (NfL), and glial fibrillary acidic protein (GFAP). We measured biological variation within- and between-subject and explored if BV could be affected by confounding factors. Secondly, we established the minimum change required to detect a difference between two given blood samples that exceeds biological and analytical variation (reference change value, RCV). Finally, we tested if classification accuracy varied across the three visits.
Results: Within-subject BV ranged from ~3% (Aβ42/40) to ~12% (T-tau). Between-subject BV ranged from ~7% (Aβ40) to ~39% (NfL). Adding time, eGFR Hba1c, and BMI to the models did not affect the variation. RCV was lowest for Aβ42/Aβ40 (-~15%/+~17%) and highest in P-tau181 (-~30/+~42%). No variation in classification accuracies was found across visits.





Conclusions: We found low within-subject BV, robust to various factors, appropriate to capture

individual changes in AD BBMs, while moderate between-subject BV may give rise to caution in diagnostic contexts. High RCVs may pose challenges for AD BBMs with low fold changes and consequently, biological variation is important to take into consideration when, e.g., estimating intervention effect and longitudinal changes of AD BBM levels.

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2 - 3 April 2025

PLASMA AND CSF BIOMARKERS IN SUBJECTIVE COGNITIVE DECLINE: THE BBRC ALZHEIMER AT-RISK (B-AARC) COHORT

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Aims: To investigate the main blood-based and relevant cerebrospinal fluid-based (CSF) biomarkers in individuals with Subjective Cognitive Decline (SCD) from the β-AARC cohort, which enrolled individuals seeking medical advice for cognitive complaints.
Methods: The β-AARC study includes a set of clinical and biomarker evaluations, including Alzheimer's disease (AD)-related blood-based and CSF-based biomarkers. Aβ42/Aβ40, p-tau181 and t-tau were analyzed in CSF (Lumipulse, Fujirebio), and Aβ42/Aβ40, p-tau217 (both Lumipulse), p-tau181, GFAP (both NeuroToolKit [Roche Diagnostics International Ltd]) and NfL (Simoa N4PE) in plasma. Amyloid positivity (A+) was defined as CSF Aβ42/Aβ40 ratio<0.071. Group differences were analyzed using t-tests, Mann-Whitney U test, or chi-square tests. We evaluated the performance of plasma biomarkers in detecting A+ using Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC). Finally, we calculated sensitivity, specificity, positive (PPV), and negative predictive values (NPV) at different cut-offs.
Results: We analyzed 143 individuals with SCD (A+=20%). Table1 summarizes participants' characteristics and CSF biomarkers' levels. A+ individuals had higher plasma p-tau217, p-tau181, GFAP and NfL concentrations, and lower plasma Aβ42/Aβ40 ratio (all p≤0.001) (Table2). The highest AUCs for detecting A+ were achieved with plasma Aβ42/Aβ40 (AUC=0.93) and p-tau217 (AUC=0.92) (Table3), but only the last remained stable up to a coefficient of variation of 0.20. Using the Youden's index cut-off, plasma p-tau217 showed sensitivity=0.93, specificity=0.87, NPV=0.98, and PPV=0.64. All plasma biomarkers had an NPV>0.90, but PPVs ranged from 0.33 to 0.64. Setting the sensitivity to 0.95, plasma p-tau217 achieved a specificity=0.61, PPV=0.38 and NPV=0.98, while at a specificity=0.95 cut-off, obtained a sensitivity=0.48, PPV=0.70 and NPV=0.88.
Conclusions: Plasma biomarkers can detect amyloid pathology in SCD, but its low prevalence in this cohort results in higher NPVs than PPVs, making them more useful for ruling-out pathology.

Table 1. Summary of SCD participants characteristics.

	Total sample (n=143)		Amyloid negative (A-, n=114)		Amyloid positive (A+, n=29)		
	n		n		n		p value
Age (years±sd)	143	66.58 ± 6.26	114	65.27 ± 5.9	29	71.73 ± 4.89	<0.001
Education (years±sd)	143	14.99 ± 3.49	114	15.19 ± 3.38	29	14.17 ± 3.86	0.170
Sex (Female)	143	84 (58.7%)	114	66 (57.9%)	29	18 (62.1%)	0.840
Duration of symptoms (n)							
< 1 year	143	8 (5.8%)	114	8 (7.0%)	29	0 (0.0%)	0.032
1-2 years		22 (15.4%)		16 (14.0%)		6 (20.7%)	
2-5 years		67 (46.9%)		58 (50.9%)		9 (31.0%)	
5-10 years		29 (20.3%)		23 (20.2%)		6 (20.7%)	
> 10 years		17 (11.9%)		7 (7.9%)		8 (27.6%)	
Familial history of dementia (n)	143	72 (50.3%)	114	57 (50%)	29	15 (51.7%)	1
MICOG (total score±sd)	143	12.01 ± 5.17	114	12.09 ± 5.27	29	11.69 ± 4.83	0.711
SUCOG (total score±sd)	143	6.25 ± 5.35	114	6.06 ± 5.54	29	7 ± 4.52	0.397
HADS (total score±sd)	142	9.82 ± 5.88	114	9.76 ± 6.04	28	10.07 ± 5.28	0.794
MMSE (total score±sd)	142	28.64 ± 1.31	113	28.68 ± 1.3	29	28.48 ± 1.35	0.470[a]
M@T (total score±sd)	143	45.23 ± 2.96	114	45.39 ± 2.87	29	44.59 ± 3.24	0.194[a]
Diabetes (n)	137	14 (10.2%)	108	9 (8.3%)	29	5 (17.2%)	0.330
Dyslipidemia (n)	137	73 (53.3%)	108	52 (48.1%)	29	21 (72.4%)	0.030
Major depression (n)	137	9 (6.6%)	108	8 (7.4%)	29	1 (3.4%)	0.730
Insomnia (n)	137	11 (8%)	108	5 (4.6%)	29	6 (20.7%)	0.010
Obstructive sleep apnea (n)	137	14 (10.2%)	108	11 (10.2%)	29	3 (10.3%)	1
CSF Aβ42/Aβ40 (ratio±sd)	143	0.08 ± 0.02	114	0.09 ± 0.01	29	0.04 ± 0.01	<0.001[b]
CSF p-tau181 (pg/ml±sd)	143	44.13 ± 29.76	114	36.32 ± 12.06	29	74.83 ± 51.77	<0.001[b]
CSF t-tau (pg/ml±sd)	143	322.2 ± 180.55	114	279.83 ± 108.64	29	488.76 ± 285.75	<0.001[b]

Table 1 summarizes the main characteristics of the participants with SCD, including demographic, clinical and cognitive variables, and CSF biomarkers levels. CSF Aβ42/Aβ40 ratio, p-tau181 and t-tau were measured using the Lumipulse platform (Fujirebio) and a CSF Aβ42/Aβ40 ratio <0.071 was used to defined amyloid positivity (A+). Key: a.: adjusted by age, sex and education. b.: Adjusted by age and sex.

Abbreviations: HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; SCD, Subjective Cognitive Decline; sd, standard deviation; M@T, Memory Alteration Test.

Table 2. Plasma biomarkers levels in SCD

	Total sample (n=143)		Amyloid negative (A-, n=114)		Amyloid positive (A+, n=29)			
	n	mean ± sd	n	mean ± sd	n	mean ± sd	p value	Adjusted by age and sex p value
Plasma Aβ42/Aβ40 ratio	138	0.09 ± 0.01	111	0.09 ± 0.01	27	0.08 ± 0.01	<0.001	<0.001
Plasma p-tau217 (pg/ml)	143	0.16 ± 0.15	114	0.12 ± 0.08	29	0.32 ± 0.23	<0.001	<0.001
Plasma p-tau181 (pg/ml)	96	0.72 ± 0.2	78	0.67 ± 0.15	18	0.94 ± 0.22	<0.001	<0.001
Plasma GFAP (pg/ml)	96	76.73 ± 35.33	78	69.21 ± 32.52	18	109.32 ± 28.29	<0.001	<0.001
Plasma NfL (pg/ml)	132	15.49 ± 7.09	103	14.44 ± 6.14	29	19.2 ± 8.93	0.002	0.001

Table 2 summarizes plasma biomarkers levels. In plasma, Aβ42/Aβ40and p-tau217 were determined with Lumipulse, p-tau181 and GFAP with NeuroToolKit, a panel of exploratory robust prototype assays [Roche Diagnostics International Ltd], and NfL with Simoa N4PE. Age and sex were included as covariates to calculate adjusted by age and sex p-values. CSF Aβ42/Aβ40 ratio levels were used to determine amyloid status, with amyloid positivity (A+) defined as <0.071.

Abbreviations: Aβ42/Aβ40, amyloid beta 42/40 ratio; CI, confidence interval; CSF, cerebrospinal fluid GFAP; glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau181, phosphorylated tau 181; SCD, Subjective Cognitive Decline; sd, standard deviation; t-tau, total tau.

Table 3. Performance of plasma biomarkers for amyloid detection in SCD using Youden's index cut-offs

	Standardized coefficient	Standardized coefficient p-value	Youden's index cut-off	AUC [95% CI]	Sensitivity	Specificity	PPV	NPV
Plasma Aβ42/40	-2.09	<0.001	0.09	0.93 [0.88. 0.97]	0.96	0.83	0.58	0.99
Plasma p-tau217	1.97	<0.001	0.14	0.92 [0.85. 0.98]	0.93	0.87	0.64	0.98
Plasma p-tau181	1.45	<0.001	0.75	0.85 [0.74. 0.95]	0.89	0.69	0.40	0.96
Plasma GFAP	1.16	<0.001	83.5	0.86 [0.77. 0.95]	0.89	0.82	0.53	0.97
Plasma NfL	0.61	0.004	16.69	0.69 [0.59. 0.79]	0.83	0.53	0.33	0.92

Table 3 presents results from logistic regression models and ROC analyses of plasma biomarkers for amyloid detection (CSF Aβ42/Aβ40 ratio<0.071).

Abbreviations: Aβ42/Aβ40, amyloid beta 42/40 ratio; AUC, area under the curve; CI, confidence interval; CSF, cerebrospinal fluid GFAP; glial fibrillary acidic protein; NfL, neurofilament light chain; PPV, positive predictive value; NPV p-tau181, phosphorylated tau 181; SCD, Subjective Cognitive Decline; t-tau, total tau.

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SHIFT 01-358

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

INVESTIGATION OF PLASMA BIOMARKERS FOR THE DETECTION OF AUTOPSY CONFIRMED CO-PATHOLOGIES IN ALZHEIMER'S DISEASE

Jennifer Cooper[1], Andrew Agbay[1], Sophie Stukas[1], Naomi Futhey[1], Imogene Scott[1], Ian Mackenzie[1], Veronica Hirsch-Reinshagen[1], Robin Hsiung[1], Cheryl Wellington[2]
[1]University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada, [2]The University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada

Aims: To compare the plasma biomarker profile in patients with autopsy-confirmed Alzheimer's disease (AD) in the presence or absence of co-pathologies to identify differentially expressed biomarker patterns capable of separating these groups.
Methods: Plasma samples were obtained from the UBC Hospital Clinic for Alzheimer Disease and Related Disorders from patients clinically diagnosed with dementia with subsequent post-mortem neuropathological analysis. Biomarkers were analysed on the Quanterix HD-X analyzer using Simoa assays (Neurology 4-plex E, p-tau-181, and AlzPATH p-tau-217) and Alamer ARGO HT analyzer using the NULISAseq CNS panel-120. Group comparisons were performed using a Mann-Whitney or Kruskal-Wallis test with FDR adjustment for multiple comparisons where appropriate.
Results: Out of 86 participants, 31 (36%) had no AD pathology, 8 (9.3%) had pure AD pathology and 47 (55%) had AD with at least one co-pathology (**figure 1**). Both Simoa and NULISA analysis demonstrated elevated plasma GFAP, p-tau-181 and p-tau-217 in AD compared to those without, irrespective of co-pathologies. When comparing pure AD to AD with co-pathology, none of the biomarkers measured by Simoa could differentiate groups. However, NULISA analysis revealed novel biomarkers patterns. When comparing pure AD (n=8) versus AD plus TPD-43 co-pathology (n=8), brain derived neurotrophic factor and inflammatory markers (CCL17, CD63) were lower in the AD + TDP-43 group and SRFP1 (cell signaling regulator) was higher. When comparing pure AD (n=8) versus AD plus cerebrovascular disease (CVD) (n=5), Aβ42 and Aβ38 were higher in the AD + CVD group.

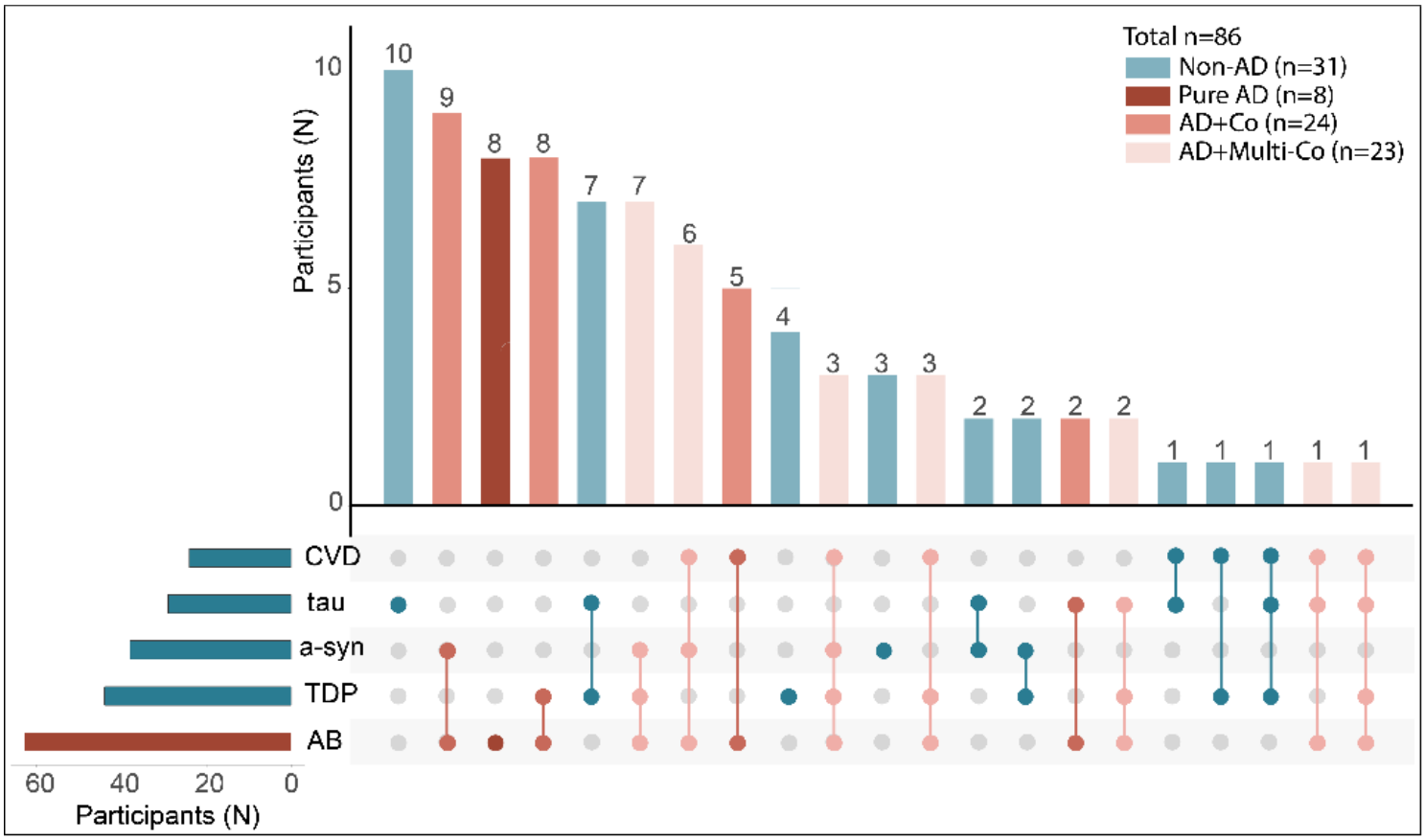

Figure 1. Upset plot showing distribution of neuropathological characterizations of CARD clinic cohort. Abbreviations: AD, Alzheimer's disease; Co, co-pathology; Multi-Co, multiple mixed co-pathologies; CVD, cerebrovascular disease; a-syn, alpha synuclein; TDP, TDP-43; AB, amyloid beta.

Conclusions: P-tau-217, p-tau-181, and GFAP are sensitive markers of AD pathology but they lack the specificity to detect co-pathologies. Discovery analysis identified unique biomarker patterns to detect co-pathologies such as TDP-43 and CVD.

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On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

SOBA: A SOLUBLE OLIGOMER BINDING ASSAY FOR DETECTION OF TOXIC OLIGOMERS

Valerie Daggett
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Aims: The formation of toxic Abeta peptide oligomers is one of the earliest events in the molecular pathology of Alzheimer's Disease. These oligomers lead to a variety of downstream effects, including impaired neuronal signaling, neuroinflammation, and tau phosphorylation, It's estimated this begins 10-20 years before symptoms. Toxic Abeta oligomers contain a nonstandard protein structure we call alpha-sheet. We have rationally designed peptides to selectively bind alpha-sheet oligomers. The aim is to use this technology to detect Abeta and alpha-synuclein oligomers in brain lysates, CSF, blood and stool samples.
Methods: We have developed an ELISA-like sandwich assay to detect alpha-sheet toxic oligomers in CSF, but instead of an antibody as the capture agent, we use an alpha-sheet peptide. The immobilized capture peptide binds to the alpha-sheet structure in the oligomers, and they are captured based on their complementary structure, not sequence.
Results: Initial proof of concept for SOBA was achieved by testing of 379 blinded banked human plasma samples. SOBA detected Abeta toxic oligomers in all patients on the AD continuum, including non-cognitively impaired controls who later progressed to MCI. ISOBA also discriminates AD from other forms of dementia, yielding sensitivity and specificity of 99% relative to clinical and neuropathological diagnoses via ROC analyses. Additional independent cohorts (n = 265) yield similar results.
Conclusions: The presence of alpha-sheet toxic oligomers is detected iin MCI and AD cases, in addition to non-cognitively impaired subjects who later convert to MCI, suggesting that it may provide standalone, preclinical detection of AD. SOBA is not reliant on invasive sample collection procedures, multistep processing and enrichment, proprietary equipment, patient information, or inclusion of risk factors, making it potentially easy to deploy in standard labs and clinics.

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On-Demand Oral Poster on Board - Shift 01
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2 - 3 April 2025

DEVELOPMENT OF A NOVEL B-SYNUCLEIN SPECIFIC DIGITAL IMMUNOASSAY IN CEREBROSPINAL FLUID AND BLOOD

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Aims: Synaptic loss is a hallmark of Alzheimer's disease (AD). Recent data suggests that presynaptic brain-specific protein beta-synuclein (β-syn) is a promising biomarker of synaptopathy in cerebrospinal fluid (CSF) and blood. A previous QTX SIMOA homebrew immunoassay has been described using α/β-syn antibodies,[1] but we aimed to develop a novel β-syn specific immunoassay, to eliminate cross-reactivity with α-syn in blood.
Methods: Rabbits were immunized with peptides targeting mid-region and two different C-terminal regions of the β-syn protein. Alongside commercially available β-specific antibody RD-120 (mid-region), these antibodies were characterized and tested for β-syn specificity using peptide mapping with α-syn residues, SDS-page and Western blot. QTX SIMOA homebrew assays were developed and evaluated for spike-recovery using recombinant β-syn and CSF. One format was used in a paired CSF-plasma cohort of patients with AD (n=5), mild cognitive impairment (n=2) and controls (n=3).
Results: Two novel rabbit monoclonal antibodies (RD-116, RD-123) with complementary epitopes, as well as RD-120 were identified as β-specific. Two SIMOA formats were developed with RD-123 as capture and RD-116 or RD-120 as detector antibody. The RD-123/RD-120 format achieved LLOQ of 0.019 pg/mL with a calibrator range of 200-0.002 pg/mL and measured all clinical samples (CSF: 2.17-10.22 pg/mL (%CV=2.95%), plasma: 0.14-0.58 pg/mL (%CV =7.18%)). Spike recovery experiments did not meet predefined specifications (80-120%), highlighting the need for sample diluent optimization. Nevertheless, increased plasma β-syn concentrations were observed in AD.
Conclusions: Two highly β-syn specific antibodies were developed and can be used on the QTX SIMOA platform and potentially other immunoassay platforms. Development of β-syn specific immunoassays, e.g. optimization of the current SIMOA formats, and larger clinical cohorts are necessary and to understand the role of β-syn in AD. 1. Halbgebauer S, et al. Neurology 2022.

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2 - 3 April 2025

DAVOS ALZHEIMER'S COLLABORATIVE HEALTHCARE SYSTEM PREPAREDNESS: ACCURATE DIAGNOSIS IMPLEMENTATION PROJECT METHODOLOGY

Amy Deckert, Monica Zigman Suchsland, Karen Weyrauch, Tim Macleod, Alissa Kurzman, Katherine Selzler
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Aims: Timely and accurate diagnosis of cognitive impairment and Alzheimer's disease is a major barrier to providing optimal care and access to treatments and supportive services. Blood biomarker (BBM) tests show promise for early detection, but healthcare systems are not prepared to integrate them into routine practice. The Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) program launched the Accurate Diagnosis implementation research project in eight sites across five countries to identify factors contributing to successful implementation of BBMs in the Alzheimer's diagnostic pathway.
Methods: The DAC-SP Accurate Diagnosis project uses a mixed methods design to evaluate the implementation process (e.g., acceptability, feasibility) and outcomes (e.g., BBM adoption, clinical and health services outcomes) of using BBMs in existing care pathways. Sites developed independent study protocols to optimize feasibility, while collecting and sharing a common clinical dataset for cross-site analyses.
Results: The mixed methods evaluation is guided by the revised Consolidated Framework for Implementation Research (CFIR; Damschroder et al., 2022) to identify barriers and facilitators to BBM adoption and sustainability in clinical practice. The role of site-specific influential factors will be assessed at baseline, mid-point, and post-program through questionnaires and qualitative interviews. Sites will convene as a Community of Practice to co-create a digital blueprint with practical implementation guidance for other healthcare systems.
Conclusions: Key learnings from cross-site data analysis planning for sites with diverse settings and protocols will be reported. The DAC-SP Accurate Diagnosis project is the first global implementation study of the real-world use of BBMs for triaging patients with suspected Alzheimer's disease. Findings will accelerate development of standard processes and uptake of new innovations in clinical pathways, so that patients and families can benefit from a timely and accurate diagnosis.

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2 - 3 April 2025

LUMINEV, SEMI HIGH-THROUGHPUT (96-WELL) ANALYSIS OF EXTRACELLULAR VESICLES IN PLASMA SAMPLES.

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Aims: Extracellular vesicles (EV) incorporate proteins and nucleic acids from the parent cell. Proteins exposed on EV surface are dictated by their cellular origin and biogenesis pathway. To better understand the EV origin and function, it is important to develop methods that reveal EV surface protein composition of heterogeneous EV populations in culture supernatants and in biofluids.
Methods: LuminEV is a Luminex assay we developed to detect CD9, CD63, and CD81 (common and abundant EV markers) on intact EVs from plasma and cell culture, directly bypassing the EV isolation steps. LuminEV was used to analyze EV markers with an IgG control, thus ensuring that background signal was subtracted.
Results: LuminEV assay for CD9, CD63, and CD81 was validated by comparing single-plex and multi-plex, linearity, spike-in recovery, inter- and intra-assay precision, and reproducibility between operators. LuminEV measurement of CD9, CD63, and CD81 in conditioned media from 15 cell lines revealed strong variations between cell types. Using tetraspanin levels as a readout, we noted suppression of EV in cells treated with GW6869 and elevation following Monensin, Bafilomycin-A, and Apilimod treatments. In plasma samples, CD9 is the most common marker at 72%, followed by CD63 and CD81 at 16% and 12%, respectively (N=72 healthy individuals). CD63 displayed a weak, albeit significant, correlation with age and was slightly lower in female samples. All tetraspanins are significantly higher in plasma samples from neurodegenerative patients, but CD81 shows the most significant change (1. Fold $P<0.001$).
Conclusions: LuminEV is a sensitive, multiplexed assay for measuring EV surface proteins in cell culture media and plasma samples. The current results verify the specificity of the assay, provide a reference standard in healthy individuals, and suggest elevated EV secretion in neurodegenerative patients.

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On-Demand Oral Poster on Board - Shift 01
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2 - 3 April 2025

INFLUENCE OF CO-PATHOLOGY ON CSF AND PLASMA SYNAPTIC MARKERS SNAP25 AND VAMP2 IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

Lorenzo Gaetani[1], Giovanni Bellomo[1], Julie Goossens[2], Andrea Toja[1], Federico Paolini Paoletti[1], Eugeen Vanmechelen[2], Lucilla Parnetti[1]
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Aims: Synaptic dysfunction is a relevant feature of Alzheimer's disease (AD) and Parkinson's disease (PD) and protein misfolding may affect synaptic functionality. Amyloidosis (A), tauopathy (T), and α-synucleinopathy (S) can be detected in cerebrospinal fluid (CSF). This study aimed to determine: i) whether CSF α-synuclein seed amplification assay positivity (S+) influences levels of the synaptic markers synaptosomal-associated protein 25 (SNAP25) and vesicle-associated membrane protein 2 (VAMP2) in the CSF and plasma of AD patients; ii) how CSF A/T positivity affects SNAP25 and VAMP2 levels in PD patients.
Methods: We included 80 AD, divided into preclinical (pre-AD), mild cognitive impairment (MCI-AD), and dementia (dem-AD) stages, 47 PD and 41 controls for whom the CSF A/T/S profile was available. All AD and 5/47 PD patients were CSF A+/T+; 26/80 AD and all PD patients were CSF S+. All controls were CSF A−/T−/S−. SNAP25 and VAMP2 levels in CSF and plasma were measured using novel Simoa-based immunoassays.
Results: CSF SNAP25 and VAMP2 were significantly higher in AD (167.7±41.3; 369.7±147.2 pg/mL) compared to PD (109.9±33.4; 253.5±119.9 pg/mL) and controls (117.6±41.6; 295.2±182.1 pg/mL) ($p<0.001$). Plasma SNAP25 was also elevated in AD (1.9±0.6 pg/mL), while VAMP2 levels showed no differences between groups. Synaptic markers were elevated already in pre-AD and did not differ between pre-AD, MCI-AD and dem-AD. AD S+ and S− had no difference in synaptic markers, independent of the clinical stage, while PD A+/T+ had higher levels of CSF and plasma SNAP25 (132.3±41.6; 1.9±0.5) compared to non-A+/T+ PD (105.4±34.2; 1.3±0.3) ($p<0.05$).
Conclusions: SNAP25 and VAMP2 seem to be primarily altered in presence of AD pathology, being not significantly influenced by neuronal α-synucleinopathy. SNAP25 is a promising synaptic marker that can be reliably measured in both CSF and plasma.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

PLASMA P-TAU217 PREDICTS COGNITIVE DECLINE IN PRECLINICAL ALZHEIMER'S DISEASE: A 7-YEAR LONGITUDINAL STUDY

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Aims: To **determine whether blood biomarkers can predict longitudinal cognitive changes** over a 7-year mean follow-up in **individuals at-risk of Alzheimer Disease** (AD), and to evaluate whether **amyloid-β (Aβ) status modifies** these associations.
Methods: We analyzed **313 cognitively unimpaired participants** from the **longitudinal ALFA+ study** with **three cognitive visits** available (average follow-up: 7.24±0.79 years) (Table 1). We tested the association of **plasma biomarkers** (p-tau181, p-tau217, Aβ42/40, GFAP and NfL) with **subsequent longitudinal changes** of a modified preclinical Alzheimer's cognitive composite (mPACC) **using linear mixed effects models**. Furthermore, we assessed whether **Aβ status (as defined by CSF Aβ42/40) modified these associations**.

Table 1. Demographics of the sample used for the analysis, stratified by amyloid status

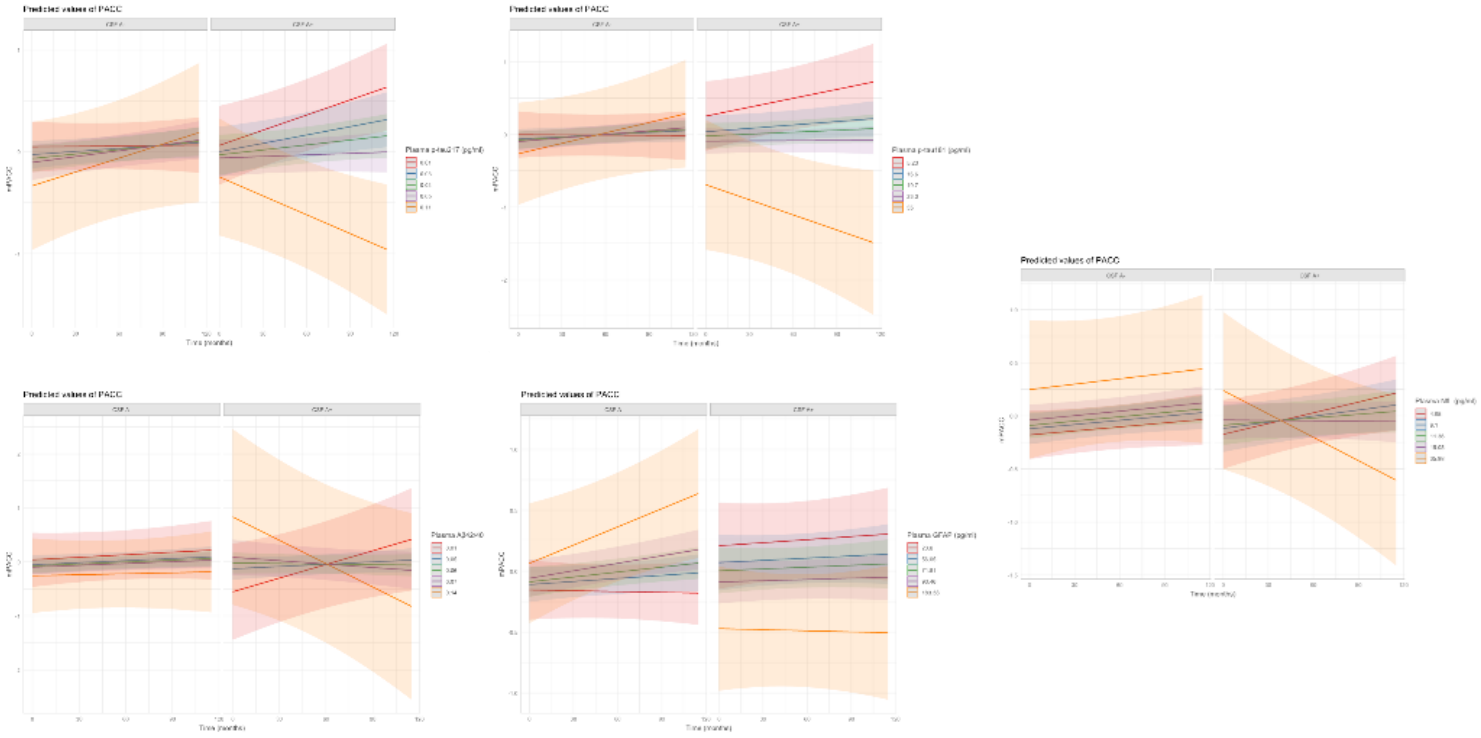
Characteristic	N	CSF A-, N = 201	CSF A+, N = 98
mPACC (baseline)	313	-0.01 (-0.40, 0.49)	-0.11 (-0.61, 0.43)
Education (years)	313	13.0 (11.0, 17.0)	12.5 (11.0, 17.0)
Age at the second visit (years)	313	59.9 (56.4, 63.7)	62.6 (58.4, 65.3)
Women	313	129 (64%)	60 (61%)
Plasma Aβ42/40	308	0.065 (0.057, 0.071)	0.057 (0.050, 0.062)
Plasma GFAP (pg/ml)	311	69 (54, 85)	82 (63, 108)
Plasma NfL (pg/ml)	312	11.1 (8.8, 14.1)	13.1 (9.7, 16.2)
Plasma p-tau181 (pg/ml)	313	19 (16, 23)	21 (18, 24)
Plasma p-tau217 (pg/ml)	287	0.033 (0.025, 0.042)	0.046 (0.035, 0.061)

Amyloid status was defined by CSF Aβ42/40 ratio, Amyloid-positive (A+) was defined as CSF Aβ42/40 <0.071. CSF determination was performed in the second visit. Data are represented as median (IQR) in case of continuous variables or n (proportion %) in case of categorical.

Abbreviations: Aβ, amyloid-β; GFAP, glial fibrillary acidic protein; mPACC, modified preclinical Alzheimer's cognitive composite; NfL, neurofilament light; p-tau, phosphorylated tau.

Results: No plasma biomarker was associated with longitudinal cognitive changes in the **overall sample**. However, **Aβ status significantly modified the association** between baseline plasma **p-tau217 and cognitive decline (β = -0.10, $p_{adj.}$ = 0.03)**, while **p-tau181, Aβ42/40 and NfL showed trends towards interaction ($p_{adj.}$ ≈ 0.07).** In **Aβ-positive (A+)** individuals, **all plasma biomarkers except GFAP** were **nominally associated** with cognitive decline (Figure 1, Table 2).

Fig. 1 Plasma biomarkers (p-tau181, p-tau217, Aβ42, NfL, and GFAP) and predicted cognitive trajectories (modified PACC scores) over 7-year mean follow-up



The lines represent predicted changes in cognitive performance (y-axis) across different time points (x-axis), adjusted for relevant covariates (age, sex, and years of education). Plasma biomarker values are displayed in distinct color gradients to illustrate their impact on cognitive decline over time. The shaded areas represent the 95% confidence intervals for each predicted trajectory. The values selected include the minimum, Q1, median, Q3 and maximum of each biomarker. Each panel compares amyloid-negative (CSF A-) and amyloid-positive (CSF A+) individuals, showing the differential effects of the biomarkers on cognitive decline.

Table 2. Association between baseline plasma biomarkers and longitudinal cognitive change (mPACC) in 7 years mean follow-up time

Biomarkers	Global		Plasma biomarker x CSF amyloid status		CSF A-		CSF A+	
	β	p.adj	β	p.adj	β	p.adj	β	p.adj
p-tau217	-0.02	0.553	-0.10	0.030	0.02	0.356	-0.08	0.065
p-tau181	0.00	0.866	-0.07	0.070	0.02	0.356	-0.05	0.144
GFAP	0.01	0.673	-0.05	0.184	0.04	0.356	-0.01	0.767
NfL	-0.02	0.553	-0.06	0.075	0.00	0.902	-0.07	0.073
Aβ42/Aβ40	0.01	0.740	-0.08	0.193	0.00	0.937	-0.05	0.115

The association between plasma biomarkers and mPACC change was assessed with a linear mixed effects models adjusted for sex, age and education (years). Analyses were performed after stratifying for Aβ-negative (A) and Aβ-positive (A) groups, as defined by CSF Aβ42/40 ratio. We report the linear regression standardized coefficients (β) and p values. We also calculated the p value for the interaction term "plasma biomarker × Aβ status". The formula fitted was (*mPACC ~ Time + plasma biomarker + CSF status + Sex + Age + Years of education + Time:plasma biomarker + plasma biomarker:CSF status + Time:CSF status + Time:plasma biomarker:CSF status* for the interaction models and *mPACC ~ Time + plasma biomarker + Sex + Age + Years of education + Time:plasma biomarker)* for the rest of models. All models were adjusted for multiple comparisons by controlling the false discovery rate at 0.05 using the Benjamini-Hochberg method.

Conclusions: <u>Plasma p-tau217 is a reliable predictor of long-term cognitive decline in individuals at the preclinical stage of AD</u>. These findings **highlight the potential of plasma p-tau217** for use in **early screening and targeted prevention strategies** in clinical trials, although futher work is needed to

see if the **magnitude of the mPACC change** observed is meaningful in the context of standard phase 2 clinical trials.

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On-Demand Oral Poster on Board - Shift 01
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2 - 3 April 2025

PLASMA P-TAU T217 LEVELS CORRELATE WITH NEOCORTICAL NEURITIC PLAQUE DENSITY.

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Aims: Alzheimer disease (AD) and primary age-related tauopathy (PART) commonly display co-pathologies, such as cerebrovascular disease (CVD), Lewy body disease (LBD), and limbic predominant age-related TDP-43 encephalopathy (LATE). We analyzed Texas Alzheimer's Research and Care Consortium (TARCC) participant post-mortem tissue and ante-mortem plasma (sample closest to death) to assess the correlation between various pathologic changes and plasma biomarkers. We also quantified p-tau burden in the hippocampal subregions, entorhinal cortex, and frontal neocortex, and compared this to plasma biomarkers.
Methods: Using the Quanterix HD-X platform, we analyzed the plasma levels of p-tau T181, p-tau T217, NfL, GFAP, Aβ-40, and Aβ-42 in the TARCC participants with AD, PART, LBD, LATE, CVD and combinations of these pathologies (n=16) (Table 1). P-tau burden in the tissue was quantified using Aperio ImageScope (Figure 1).

CLINICAL DX	AGE	SEX	NEUROPATH DX	Braak stage	Thal phase	CERAD NP score	CVD	synuclein	TDP-43 (Y/N)	LATE stage	HS (Y/N)	CAA (Y/N)	Other dx
MCI	94	M	ADNC-HIGH and LATE	V	5	2			Y	2	N	Y	ARTAG
NC	78	M	ADNC-INT, CVD, BS LB	III	5	2	microinfarcts	BS	N	N/A	N	Y	AGD
NC	88	M	ADNC-INT	III	4	0			N	N/A	N	N	
NC	78	M	PART, possible	I	2	0			N	N/A	N	N	
NC	93	I	PART,definite	III	0	0			N	N/A	N	Y	ARTAG
PR	90	I	ADNC-INT, LATE and HS	V	3	0			Y	3	Y	N	
PR	80	M	ADNC-HIGH, LATE, HS and AM+OB LB	VI	5	3		AM+OB	Y	1	Y	N	
PR	87	M	ADNC-HIGH, CVD	V	4	2	remote infarct		N	N/A	N	N	
PR	81	M	ADNC-INT and LATE	IV	5	1			Y	2	N	Y	
PR	87	F	ADNC-INT and LATE	IV	5	2			Y	2	Y	Y	
PR	86	M	ADNC-INT, LATE, HS and BS LB	II	4	2		BS	Y	3	Y	N	
PR	70	F	ADNC-HIGH	VI	5	3			N	N/A	N	Y	
PR	80	F	ADNC-HIGH, AM+OB LB	VI	5	3		AM+OB	N	N/A	Y	Y	
PR	75	M	ADNC-HIGH and LATE	VI	5	3			Y	2	N	Y	ARTAG
PR	88	M	ADNC-HIGH	VI	4	3			N	N/A	N	N	ARTAG
PR	105	F	ADNC-HIGH, LATE, CVD and limbic LB	V	4	3	infarcts	limbic	Y	2	N	Y	

MCI: mild cognitive impairment, PR: probable AD, NC: normal control, BS: brainstem, AM: amygdala, OB: olfactory bulb, HS: hippocampal sclerosis

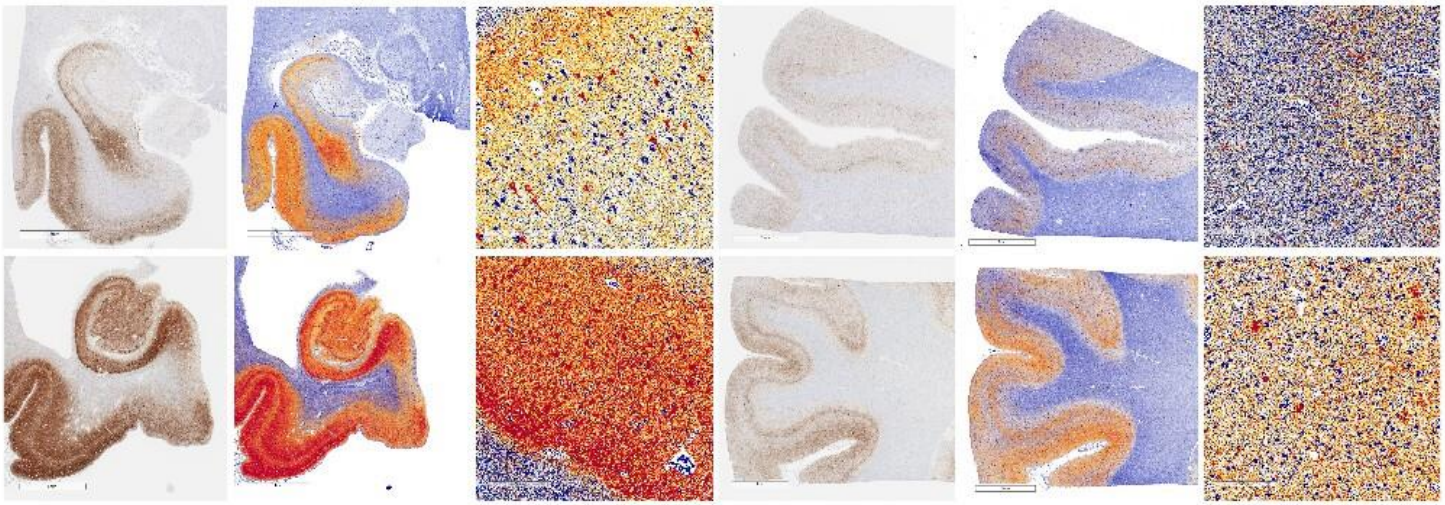
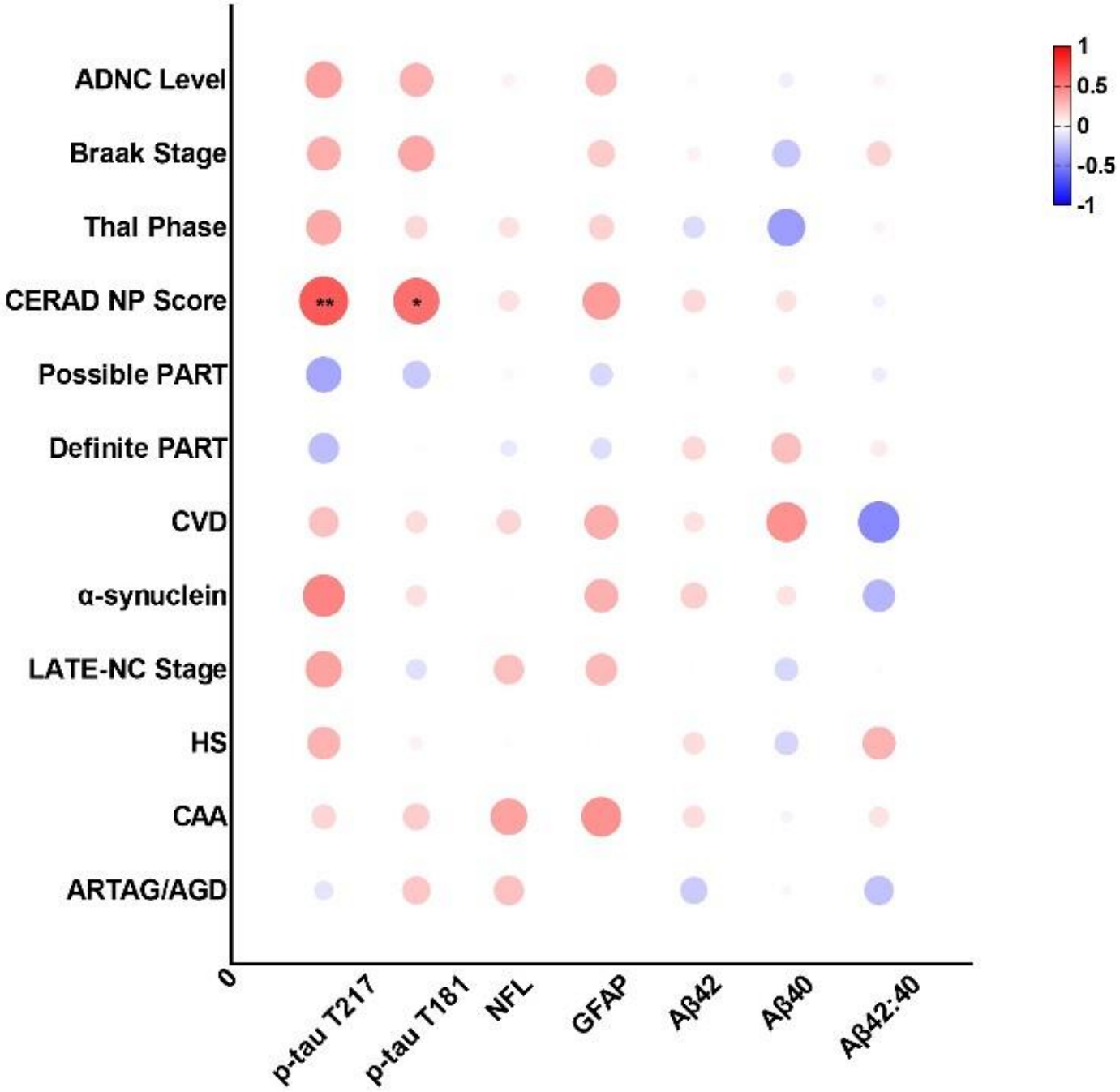


Figure 1. Examples of Aperio ImageScope quantification of p-tau burden.

Results: Analyses demonstrated a strong correlation between CERAD neuritic plaque score and plasma p-tau T217 levels. There was also a significant correlation between p-tau T181 levels and neuritic plaque density, but less significant than T217. Plasma p-tau T217 levels, however, did not correlate with the Braak stage, Thal phase or overall p-tau burden in the frontal neocortex or hippocampus (Figure 2).



Conclusions: In conclusion, we found a strong correlation between plasma p-tau T217 levels and CERAD neuritic plaque score, but no correlation between plasma p-tau T217 and overall p-tau (AT8) burden in the frontal neocortex or hippocampus. This suggests that T217 correlates more specifically with neuritic plaques (which are composed of β-amyloid *and* p-tau) rather than neurofibrillary tangles and neuropil threads, explaining the previously described clinical correlation between plasma p-tau T217 levels and the presence of β-amyloid *and* tau in the brain (measured by amyloid- and tau-PET, as well as other plasma and CSF biomarkers).

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SHIFT 01-366

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

THE PROGNOSTIC VALUE OF PLASMA PTAU217 FOR SYMPTOM PROGRESSION IN OLDER PRIMARY CARE PATIENTS – A REAL WORLD STUDY

Luca Kleineidam[1,2], Pamela Martino-Adami[3], Selcuk Özdemir[2,4], Leonie Weinhold[5], David Koehler[5], Madhurima Chatterjee[2], Michael Pentzek[6], Siegfried Weyerer[7], Horst Bickel[8], Birgitt Wiese[9], Steffi Riedel-Heller[10], Martin Scherer[11], Agustín Ruiz[12,13], Oliver Peters[14,15], Matthias Schmid[2,5], Kaj Blennow[16,17], Henrik Zetterberg[16,18,19,20,21], Andreas Jeromin[22], Michael Wagner[1,2], Alfredo Ramirez[1,2,3,23,24], Anja Schneider[1,2]
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Aims: Blood-based biomarkers (BBM) detect Alzheimer's disease pathology with high precision and can identify primary care patients eligible for disease-modifying therapies. We assessed the prognostic value of BBM for symptomatic progression in primary care, which is still understudied.
Methods: We measured plasma BBM (ALZpath pTau217, pTau181, Abeta42/40, NfL, GFAP) using SIMOA technology in 1523 primary care patients (79-97 years) from the AgeCoDe cohort (up to eight years of follow-up). Using ROC analyses and linear mixed models, we investigated the associations of BBM with incident dementia and the decline in cognition and activities of daily living (ADL).

Results: Plasma pTau217 showed the highest prognostic value for incident dementia (AUC[95%-CI]=0.773[0.744-0.822]), and considering other BBM, demographics, or confounders offered no substantial improvements of prognosis. The performance of pTau217 was higher in younger (AUC[95%-CI]=0.804[0.764-0.845]) compared to older individuals (AUC[95%-CI]=0.729[0.686-0.772]), who showed a higher risk of dying before dementia onset. Two-point reference ranges for pTau217 showed a high positive predictive value for dementia in younger MCI patients (PPV[95%-CI]=81.4[65.0-97.8], NPV[95%-CI]=72.0[55.1-88.9]) but lower values in older MCI patients (PPV[95%-CI]=59.3[44.4-74.3], NPV[95%-CI]=74.4[61.8-87.0]) and cognitively unimpaired individuals (PPV[95%-CI]=43.8[37.9-49.8], NPV[95%-CI]=93.1[91.1-95.2]), who showed a lower dementia incidence before death. In individuals with MCI or dementia at blood collection (N=321), high plasma pTau217 predicted a faster decline in cognition and ADL and a higher risk for institutionalization, independent of initial cognition.
Conclusions: ALZpath plasma pTau217 provided the highest prognostic value for future disease progression among examined BBM and identified a high-risk group for a faster decline in cognition and independence among older cognitively impaired primary care patients, who will benefit from treatments. When using BBM for the prognosis of future symptom development, the risk of death before symptom onset should be considered.

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SHIFT 01-367

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

CSF PROGRANULIN CORRELATES WITH ALZHEIMER DISEASE AND CSF AMYLOID STATUS

Peter Koertvelyessy[1], Wenzel Glanz[2], Emrah Düzel[2], Daniel Bittner[3], Stefan Vielhaber[4], Laura Göschel[1], Jonah Nietiet[1]
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Aims: Progranulin (PGRN) has numerous functions in the CNS including microglial activation, synaptic pruning and neuroprotection in neurons. Giving these functions Progranulin has been become of interest in neurodegenerative diseases, such as Alzheimer´s Disease (AD) or Frontotemporal Dementia (FTD). Progranulin levels in Cerebrospinal fluid (CSF) levels have been measured in smaller cohorts in AD with ambiguous results. Our aim is to look at a larger AD cohort to test the Hypotheses of higher CSF-PGRN mirroring the neuroprotective efforts in AD.
Methods: We retrospectively analyzed the routine data from the memory clinic at the university of Magdeburg for CSF AD biomarker and CSF PGRN. The AD diagnosis was made via CSF biomarker (pathological Core1 biomarker (Amyloid)). Our AD cohort comprises 136 patients and were correlated with non-neurodegenerative, non-inflammatory controls (n=28), patients (n=54) with vascular dementia (Fazekas 3 and higher) and 54 patients with mixed vascular (Fazekas 2 and higher) and AD pathology.
Results: Thus, AD patients had the highest CSF-PGRN levels compared with all other groups. CSF-PGRN levels are significantly ($p<0.01$) higher in AD, vascular dementia and mixed pathology patients than in our controls. Alzheimer patients had higher CSF-PGRN levels compared to mixed pathology patients ($p=0.015$) but not to vascular dementia patients ($p=0.108$). There was no significant correlation to biomarkers of neuronal damage such as Total-Tau nor Neurofilament light Chain.
Conclusions: Giving the high number of biomarkers for AD and CSF-PGRN not being able to distinct between vascular dementia and AD, CSF-PGRN is not a reasonable marker for AD. One may conclude that the reason for the robust increase of CSF-PGRN is due to a general reaction of the brain to neuronal damage. A comparison study with other diseases is necessary.

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SHIFT 01-368

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

IN-VITRO DIAGNOSTIC TEST BASED ON EXOSOMES FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE AND RISK STRATIFICATION OF PATIENTS

Rosanna Rossi[1], Amanda Cano[2], Agustín Ruiz[3,4], Mercè Marti Ripoll[5], Maria Isabel Pividori Gurgo[1]
[1]Universitat Autonoma de Barcelona, Institute Of Biotechnology And Biomedicine Ibb/department Of Chemistry, Barcelona, Spain, [2]Ace Alzheimer Center Barcelona_International University of Catalunya (UIC), Barcelona, Spain, [3]Universitat Internacional de Catalunya, Research Center And Memory Clinic, Fundació Ace, Barcelone, Spain, [4]Instituto de Salud Carlos III, Networking Research Center On Neurodegenerative Diseases (ciberned), Madrid, Spain, [5]Institute of Biotechnology and Biomedicine (IBB-UAB), Immunology, Barcelona, Spain

Aims: Exosomes, nano-sized extracellular vesicles secreted by most cell types, have been shown to carry Alzheimer's-related molecules and are promising candidates for early diagnosis biomarkers. Although the full molecular mechanisms of Alzheimer's disease are not completely understood, early pathological changes in the brain might be reflected by the amount and characteristics of brain derived exosomes (BDEs). There is evidence that exosomes can pass the brain blood barrier and be found in several body fluids, including blood, representing a huge advantage to the current diagnostic targets. This study aimed to explore the use of BDEs in plasma as biomarkers for Alzheimer's disease, by developing in-vitro diagnostic test (IVD) for early detection and risk-stratification of the patients.
Methods: We optimized our method using exosomes from the SH-SY5Y neuroblastoma cell line, obtained through differential ultracentrifugation. Tosyl-activated magnetic nanoparticles functionalized with an anti-NLGN3 antibody were used to isolate neuronal-derived exosomes by targeting the NLGN3 neuronal marker. Subsequently, we targeted the AD biomarker β-site APP cleaving enzyme 1 (BACE-1) on the surface of the captured exosomes. BACE-1 is closely linked to the production of β-amyloid peptides, a hallmark of Alzheimer's dosease. We developed immunoassay platforms with optical, chemiluminescent, and electrochemical readouts to detect BACE-1, as depicted in Figure 1.
Results: We got very promising results with the 3 platforms, especially with the electrochemical one, which had a lower LOD (Figure 1, B). A screen-printed electrode integrated with electrochemical reader has been used for the analysis of plasma patients with Mild Cognitive Impairment and suspected Alzheimer's Disease, compared to plasma of healthy donors used as control.
Conclusions: Preliminary results showed the capability of the method for risk stratification of the patients.

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SHIFT 01-404

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

ENHANCED DIAGNOSTIC ACCURACY OF PLASMA MIRNA-BASED ALZHEIMER'S DETECTION USING THE APO-EASY® IVD KIT AND NEURODEGENE V2

Seval Kul[1], Nicolas Scalzitti[1], Dany Mukesha[1], Miguel Casanova[2], Lucas Pham-Van[1], Çetin Kocaefe[1,3], Stéphanie Boutillier[2], Hüseyin Firat[2]
[1]Firalis, S.A., Huningue, France, [2]Amoneta Diagnostics, Huningue, France, [3]Hacettepe University School of Medicine, Dept. Of Medical Biology, Sıhhiye, Turkey

Aims: We evaluated the clinical performance of a novel multimodal blood-based diagnostic approach for early-stage Alzheimer's disease (AD) detection. This method integrates multiple data types, including the expression of three plasma miRNAs, lncRNA transcriptomics, *APOE* genotyping, and NeuroDeGene V2, a comprehensive panel of genetic variants, to improve diagnostic accuracy.
Methods: Total RNA was extracted from 600µl of Plasma-EDTA samples for miRNA quantification via qPCR. For lncRNA transcriptomic analysis, total RNA sequencing was performed on peripheral blood mononuclear cells (PBMCs). *APOE* haplotyping was assessed using the APO-Easy kit. In addition, we have used the NeuroDeGene V2 panel to genotype 15,533 genetic variants associated with dementia and neurodegenerative diseases. Diagnostic performance was evaluated on 1000 samples from the ADDIA cohort, collected across 13 European clinical centers. Multimodal integration of the miRNA expression, lncRNAs transcriptomic data, *APOE* haplotyping, and the NeuroDeGene V2 panel was analyzed using five predictive models: Lasso, Random Forest, XGBoost, Naïve bayes and Partial least squares (PLS) regression. This analysis employed five-fold cross-validation and 20 replicates, generating 100 models in total.
Results: In the training set, the mean area under the curve (AUC) for miRNA-based diagnostics using the lasso model was 0.71 (95% CI=0.68-0.72). Remarkably, the incorporation of the top 5 SNPs from NeuroDeGene V2, combined with *APOE* genotyping using the APO-Easy® kit, improved the AUC to over 0.90, significantly enhancing diagnostic accuracy.
Conclusions: The multimodal integration of plasma miRNAs, lncRNA transcriptomics, *APOE* genotyping, and the NeuroDeGene V2 panel represents a highly effective blood-based diagnostic tool for distinguishing AD from healthy controls and non-AD dementias. This approach shows great promise for improving differential diagnosis in clinical settings and advancing precision medicine in AD.

SHIFT 01-405

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

SIMULTANEOUS PREDICTION OF CONTINUOUS BRAIN AMYLOID AND TAU PET LEVELS USING PLASMA PTAU217 RATIO IN PRECLINICAL AND EARLY ALZHEIMER'S DISEASE

Viswanath Devanarayan, Arnaud Charil, Kanta Horie, Pallavi Sachdev, Yuanqing Ye, Thomas Doherty, Harald Hampel, Lynn Kramer, Shobha Dhadda, Michael Irizarry
Eisai Inc., Clinical Evidence Generation, Nutley, United States of America

Aims: PET imaging quantifies amyloid and tau pathology for Alzheimer's disease (AD) staging. This study assesses whether the plasma phosphorylated to non-phosphorylated Tau217 ratio (pTau217R) can simultaneously predict brain amyloid and tau PET levels using a single model, identifying individuals with varying pathology.
Methods: Plasma pTau217R was measured via immunoprecipitation-mass spectrometry. A joint model predicting amyloid PET Centiloid (CL) and tau PET standardized uptake value ratio (SUVR) in cortical grey matter was developed in a training set (TS) of 144 early AD participants from ClarityAD and validated in two cohorts: VS1 (98 early AD, ClarityAD) and VS2 (139 preclinical/early AD, ADNI). TS and VS1 participants were Aβ+ (visual read), while VS2 included Aβ+ and Aβ- participants. Amyloid PET tracers were predominantly Florbetaben in TS and VS1, and Florbetapir in VS2, while tau PET tracers were [18F]MK6240 in TS/VS1 and Flortaucipir in VS2. The model, incorporating pTau217R and demographics (age, sex), is tracer-agnostic and built using stochastic gradient boosting.
Results: The pTau217R-based model simultaneously predicted amyloid levels (up to 89 CL) and tau levels (SUVR up to 2), explaining 47.8% and 54.3% of the variance in VS1, and 42% and 48.2% in VS2, respectively. The area under the receiver operating characteristic curve (AUROC) for identifying subjects at different amyloid and tau thresholds ranged from 0.89 to 0.95. Adding clinical assessments (ADAS-Cog-13, CDR-SB, MMSE) did not improve performance. Using the model to rule out patients with no/low amyloid and tau reduced the need for PET scans by up to 70% for amyloid and 65% for tau.
Conclusions: The pTau217R-based model reliably predicts amyloid and tau PET levels simultaneously, regardless of the tracer used, reducing the reliance on PET scans and broadening clinical utility.

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SHIFT 01-406

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

PLASMA PTAU181 PREDICTS CLINICAL PROGRESSION IN MILD ALZHEIMER'S DISEASE IN A RANDOMIZED CONTROLLED TRIAL.

Jack Taylor[1], Mark Jaros[2], John Harrison[3,4,5], Christopher Chen[6], Dana Hilt[1]
[1]Actinogen Medical, SYDNEY, Australia, [2]Summit Analytical, Denver, United States of America, [3]Scottish Brain Sciences, Edinburgh, United Kingdom, [4]King's College, London, United Kingdom, [5]fAlzheimercentrum, AUmc, Amsterdam, Netherlands, [6]Memory Aging and Cognition Centre, Yong Loo Lin School of Medicine, National University of Singapore, Department Of Pharmacology, Singapore, Singapore

Aims: Plasma pTau181 is a biomarker with high diagnostic accuracy, disease sensitivity, and correlation with pathologically proven Alzheimer's Disease (AD) as well as rate of future progression. The Phase 2a XanADu biomarker trial aimed to identify patients with elevated plasma pTau181 and explore the natural histories of their clinical progression and potential efficacy of Xanamem in these patients.
Methods: The XanADu biomarker trial used a prespecified, double-blind analysis. 72 participants with clinically diagnosed AD and available plasma samples from baseline and/or Week 12 of the "XanADu" phase 2a trial of Xanamem vs. placebo. The analysis prespecified plasma pTau181 >median to identify patients more likely to have AD ("H", >6.74pg/mL, n=34). Efficacy variables assessed included four clinical scales: ADAS-Cogv14, ADCOMS, CDR-SB, and MMSE, as well as cognitive and behavioral endpoints. Cohen's d (*d*) of ≥0.2 defined potential clinical significance.
Results: In H pTau181 placebo group, participants displayed clinically significant worsening over 12 weeks compared to the low (L) pTau181 group on all clinical scales: CDR-SB (*d*=0.63), ADCOMS (*d*=0.55), MMSE (*d*=0.52), and ADAS-Cog (*d*=0.53). Xanamem largely prevented clinical progression over 12 weeks, displaying a clinically significant benefit (*d*=0.41) on the CDR-SB compared to placebo in the H group but not in the L group. In both L and H groups improvements were seen favoring Xanamem in tests of executive function (d = 0.34 and 0.26) and the MMSE (d = 0.32 and 0.16).
Conclusions: Together, these data suggest elevated plasma pTau181 may have utility for patient enrichment in future AD trials of patients with mild AD. Enrichment in this way may reduce sample size, cost, and duration of clinical trials. Xanamem showed evidence of potentially clinically meaningful benefits in these patients that will be further explored.

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SHIFT 01-407

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

CHOROID PLEXUS AND VENTRICULAR REMODELING ARE ASSOCIATED WITH EARLY PROTEIN AGGREGATION IN THE BRAIN

Seyyed Ali Hosseini[1], Stijn Servaes[1], Nesrine Rahmouni[1], Etienne Aumont[1], Joseph Therriault[1], Yi-Ting Wang[1], Arthur Macedo[1], Brandon Hall[1], Jaime Fernandez-Arias[1], Gleb Bezgin[1], Kely Quispialaya-Socualaya[1], Tevy Chan[1], Lydia Trudel[1], Yansheng Zheng[1], Serge Gauthier[1], Tharick Pascoal[2], Pedro Rosa-Neto[1]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]University of Pittsburgh, Pittsburgh, United States of America

Aims: The brain's cerebrospinal fluid (CSF) regulation system, including the choroid plexus and ventricular structures, plays a critical role in clearing metabolites from the brain parenchyma. However, the potential contribution of a debris clearance impairment to disease-associated protein aggregation, such as found in Alzheimer's disease (AD), remains underexplored. This study investigates the relationship between choroid plexus and ventricular volumes with amyloid-beta and tau aggregates—key biomarkers of AD. We also assess ventricular radioactivity as a proxy for choroid plexus function.
Methods: We analyzed data from 883 time points in 500 individuals enrolled in the Translational Biomarkers in Aging and Dementia (TRIAD) cohort at McGill University. These data included Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) brain images using [18F]AZD4694 for amyloid and [18F]MK6240 for tau. Ventricular and choroid plexus volumes were segmented via Freesurfer and adjusted for intracranial volume, together with ventricular radioactivity were evaluated using both region-of-interest (ROI) and voxel-wise analyses to assess their association with amyloid and tau accumulation.
Results: Our analysis revealed significant enlargement of the ventricular compartments, including the choroid plexus, which was strongly associated with increased amyloid and tau accumulation in the brain (Fig.1). Voxel-wise analysis demonstrated that higher ventricular radioactivity (Fig.2A) and enlarged choroid plexus volume were linked to early amyloid-β deposition. Ventricular enlargement was associated with amyloid aggregation throughout the brain, spanning both early- and late-stages. Additionally, both choroid plexus and ventricular enlargement associated with early-tau deposition (Fig.3).

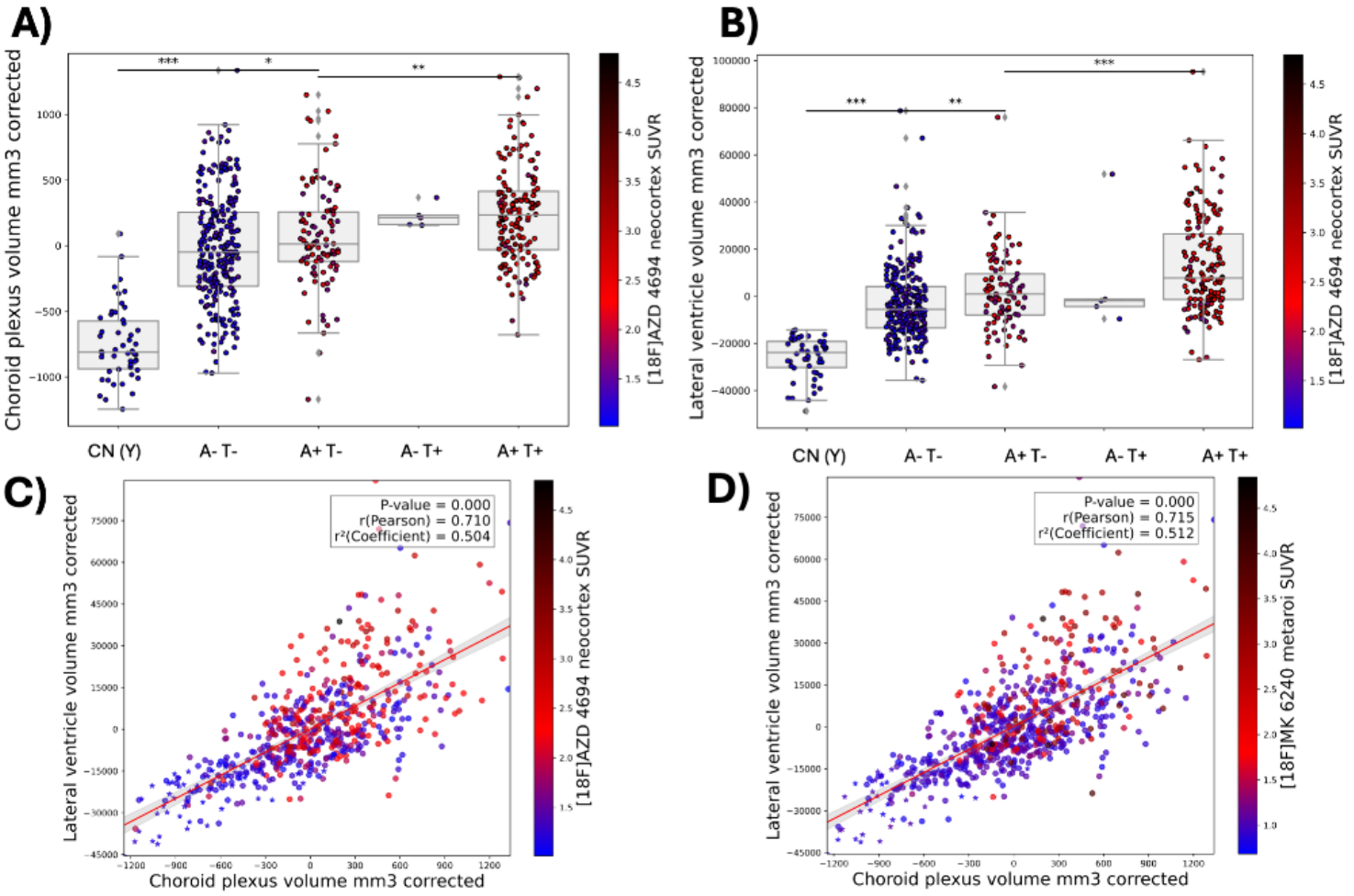

Fig1. Choroid plexus and ventricular remodeling in AD spectrum.

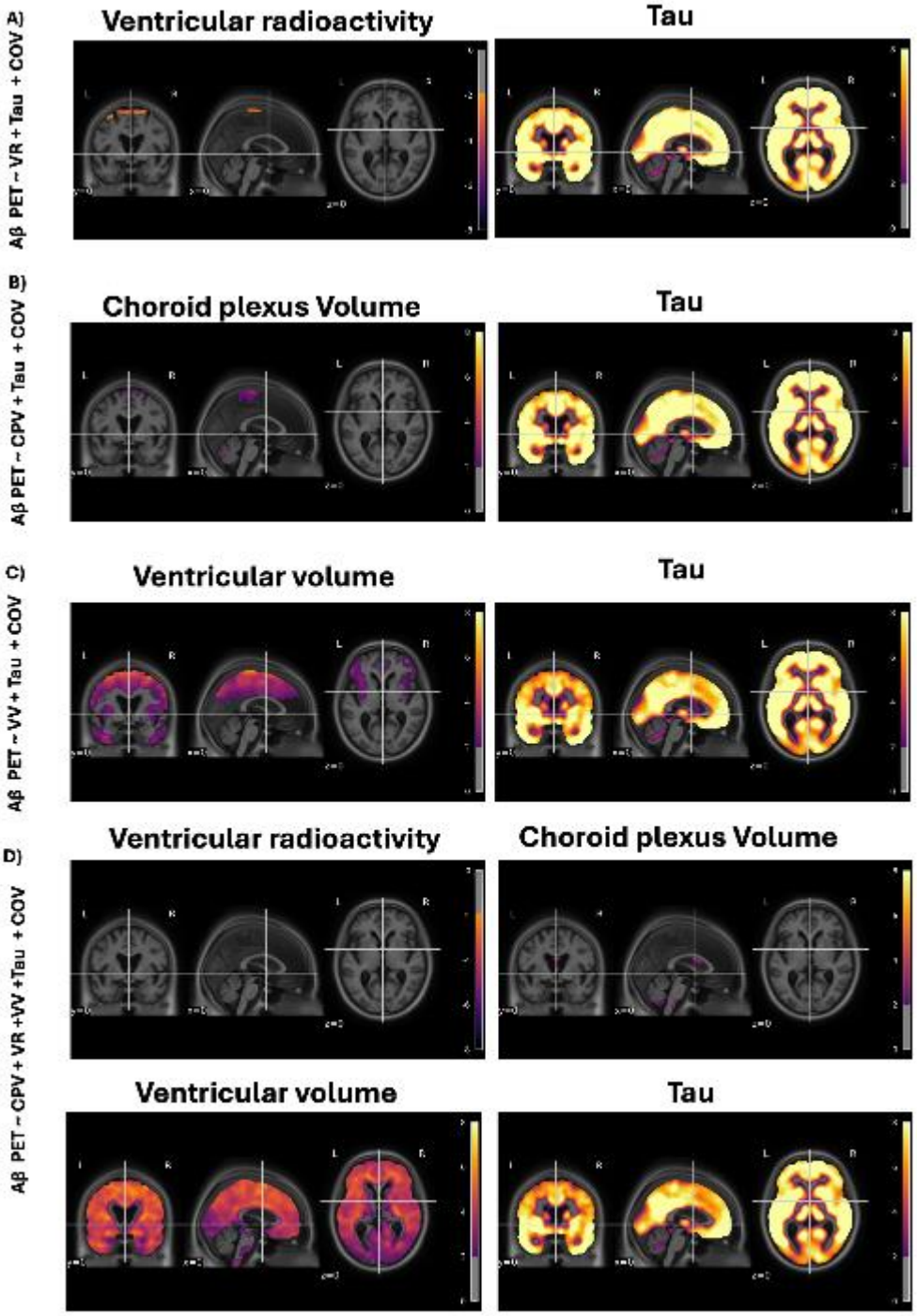

Fig2. Voxel wise analysis of Aβ PET as a function of ventricular compartments that are involved in CSF circulation.
COV = Age, Sex, Apoe, Intracranial volume.

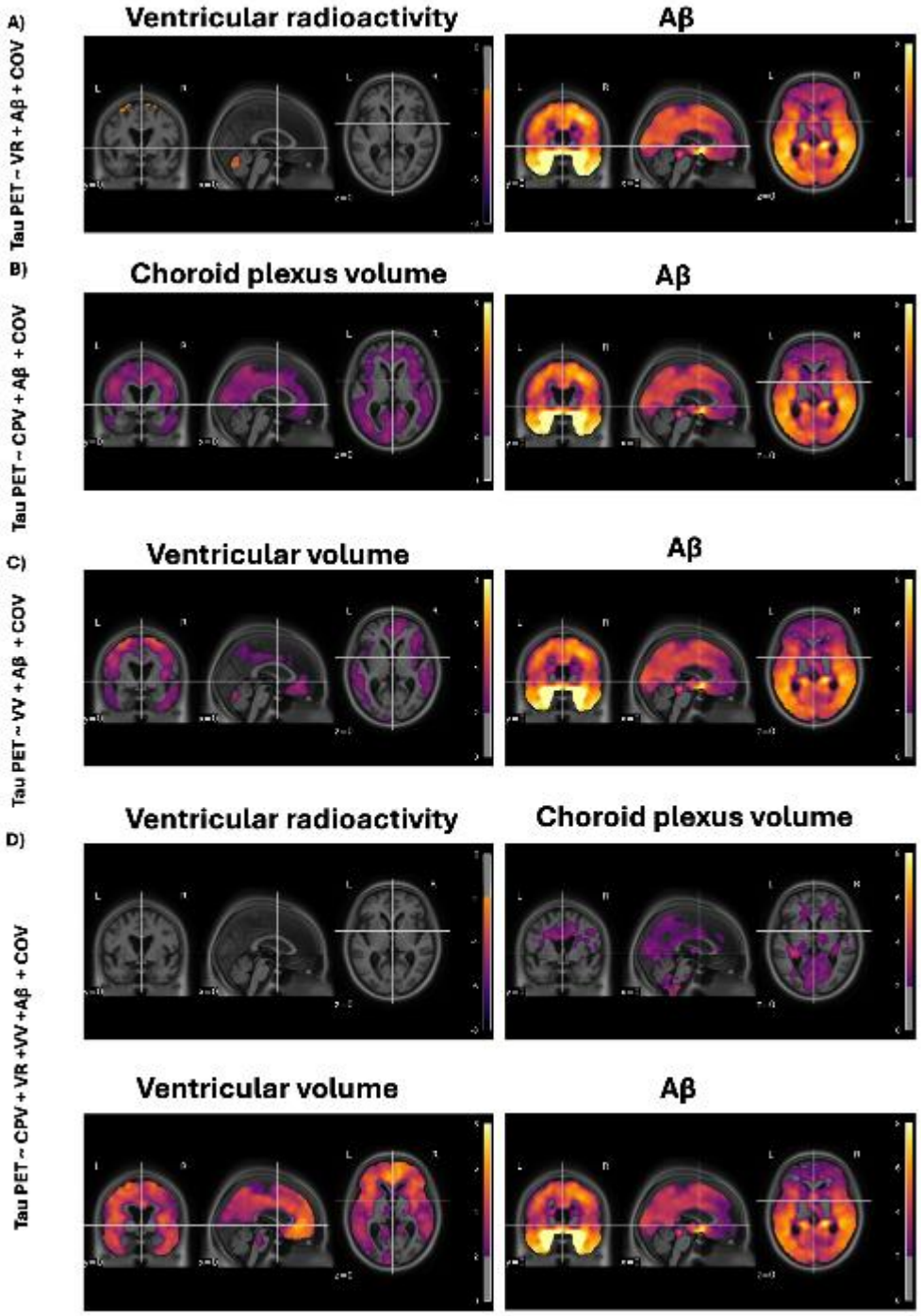

Fig3. Voxel wise analysis of Tau PET as a function of ventricular compartments that are involved in CSF circulation.
COV = Age, Sex, Apoe, Intracranial volume.

Conclusions: The results indicate that ventricular remodeling, encompassing both choroid plexus and ventricular volume enlargement, is closely associated with early amyloid and tau aggregation in the brain. These findings suggest that impaired CSF clearance through these ventricular compartments may play a role in the early-stages of AD pathology.

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SHIFT 01-408

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

ADDITIVE EFFECTS OF VENTRICULAR REMODELING AND ASTROCYTE ACTIVATION ARE ASSOCIATED WITH EARLY AMYLOID AND TAU AGGREGATION IN ALZHEIMER'S DISEASE

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Aims: Astrocyte activation, marked by elevated levels of glial fibrillary acidic protein (GFAP), is a prominent feature of neuroinflammation in Alzheimer's disease (AD). In conjunction with choroid plexus alterations and ventricular enlargement, these processes may impair cerebrospinal fluid (CSF) clearance, contributing to amyloid-β and tau protein aggregation. This study investigates the combined effects of ventricular remodeling and astrocyte activation on protein aggregation.
Methods: We analyzed data from 500 individuals in the Translational Biomarkers in Aging and Dementia (TRIAD) cohort at McGill University, incorporating 883 imaging sessions over a 4-year follow-up. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) with tracers [18F]AZD4694 (amyloid-β) and [18F]MK6240 (tau) were employed. Choroid plexus and ventricular volumes were segmented using Freesurfer and adjusted for intracranial volume. Ventricular radioactivity was used as a surrogate marker for choroid plexus function. GFAP levels were quantified in the plasma. We assessed associations between ventricular remodeling and GFAP levels with amyloid-β and tau loads using both region-of-interest and voxel-wise analyses.
Results: Significant reductions in ventricular radioactivity and enlargement of the choroid plexus and ventricular volumes were observed across amyloid-β and tau categories (Fig. 1). Amyloid-β and tau aggregation in early AD regions were significantly associated with ventricular remodeling and elevated GFAP in voxel-wise analyses (Figs. 2–3). The additive effects (no evidence of interaction or mediation) of astrocyte activation and ventricular enlargement on amyloid-β and tau persisted after adjusting for tau and amyloid-β loads. (Fig. 3).

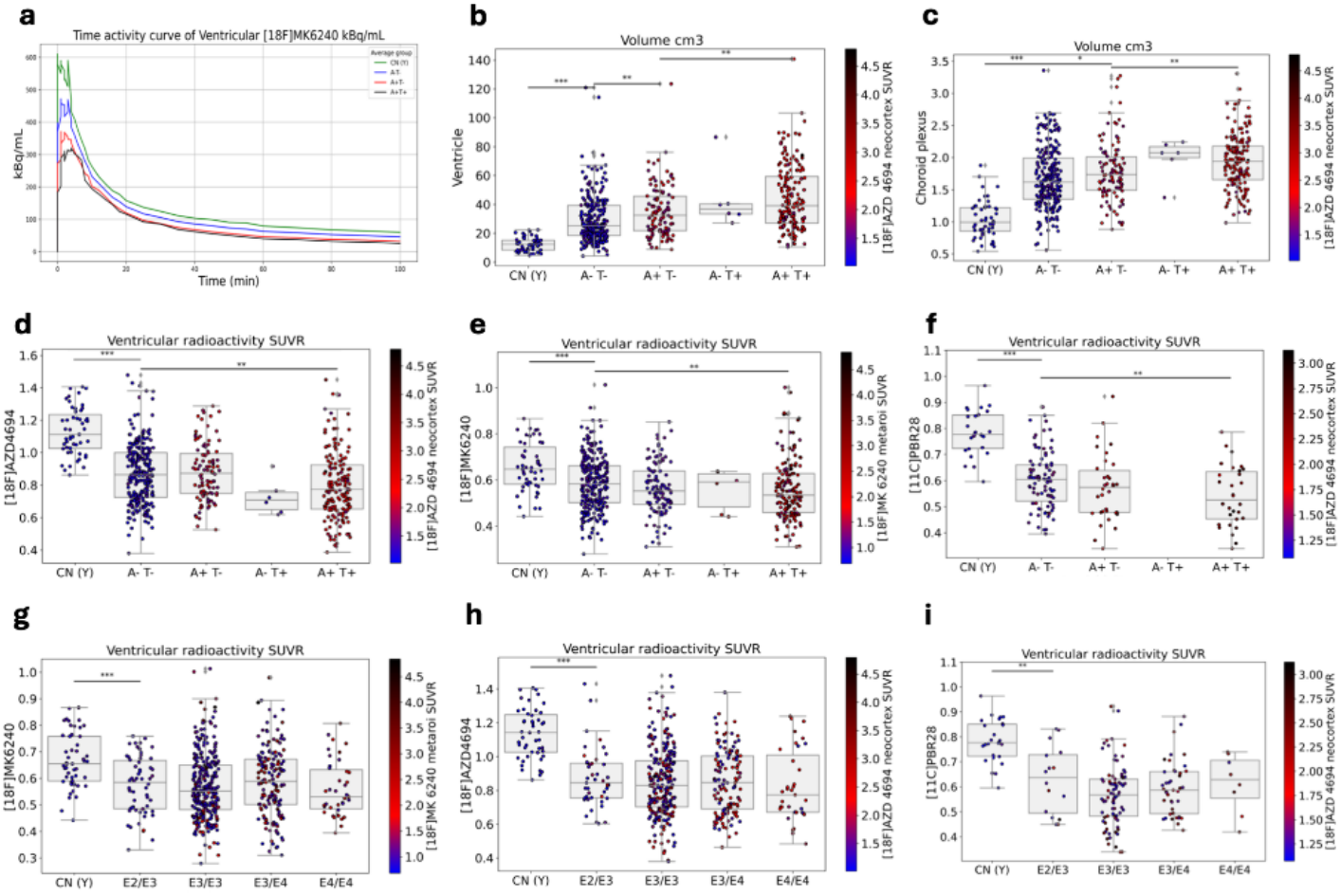

Fig1. Chorido ventricular remodeling in AD spectrum

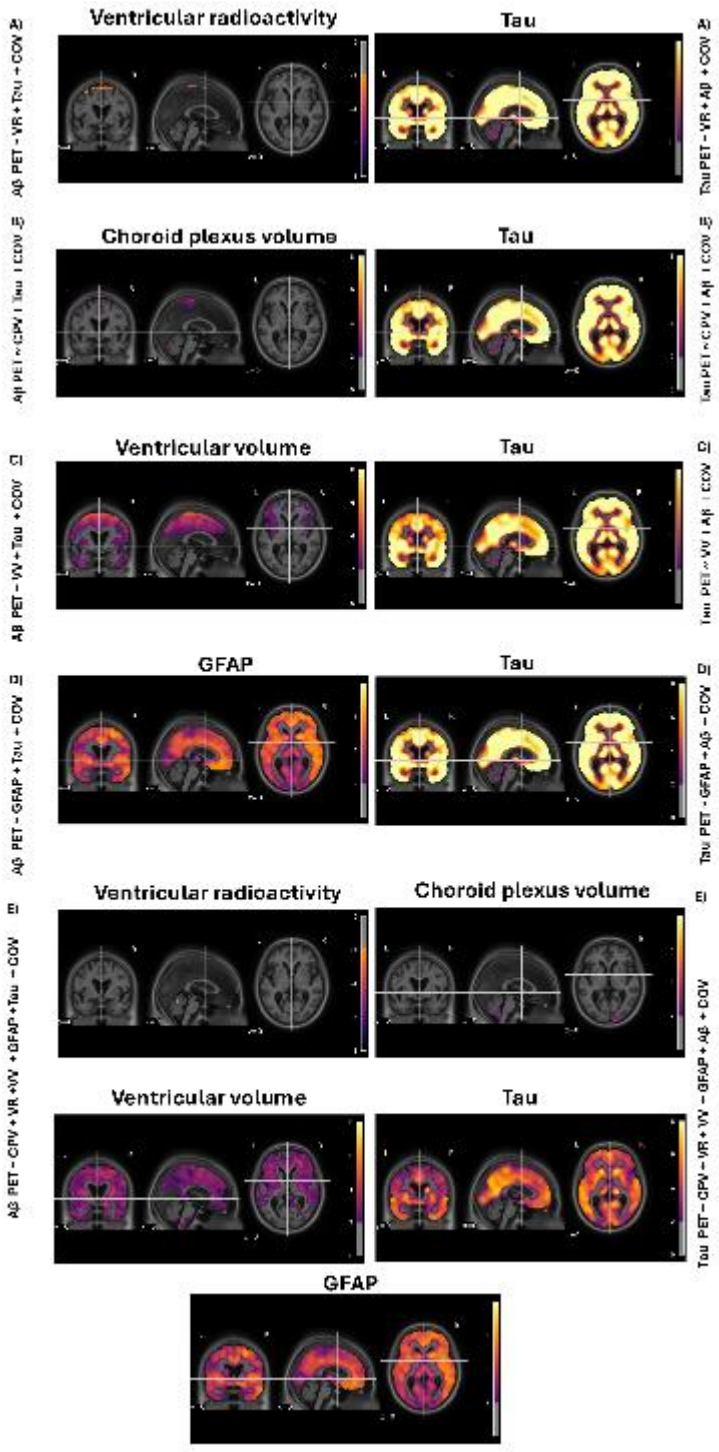

Fig2. Voxel wise analysis of Aβ PET as a function of ventricular remodeling and GFAP
COV = Age, Sex, Apoe, Intracranial volume

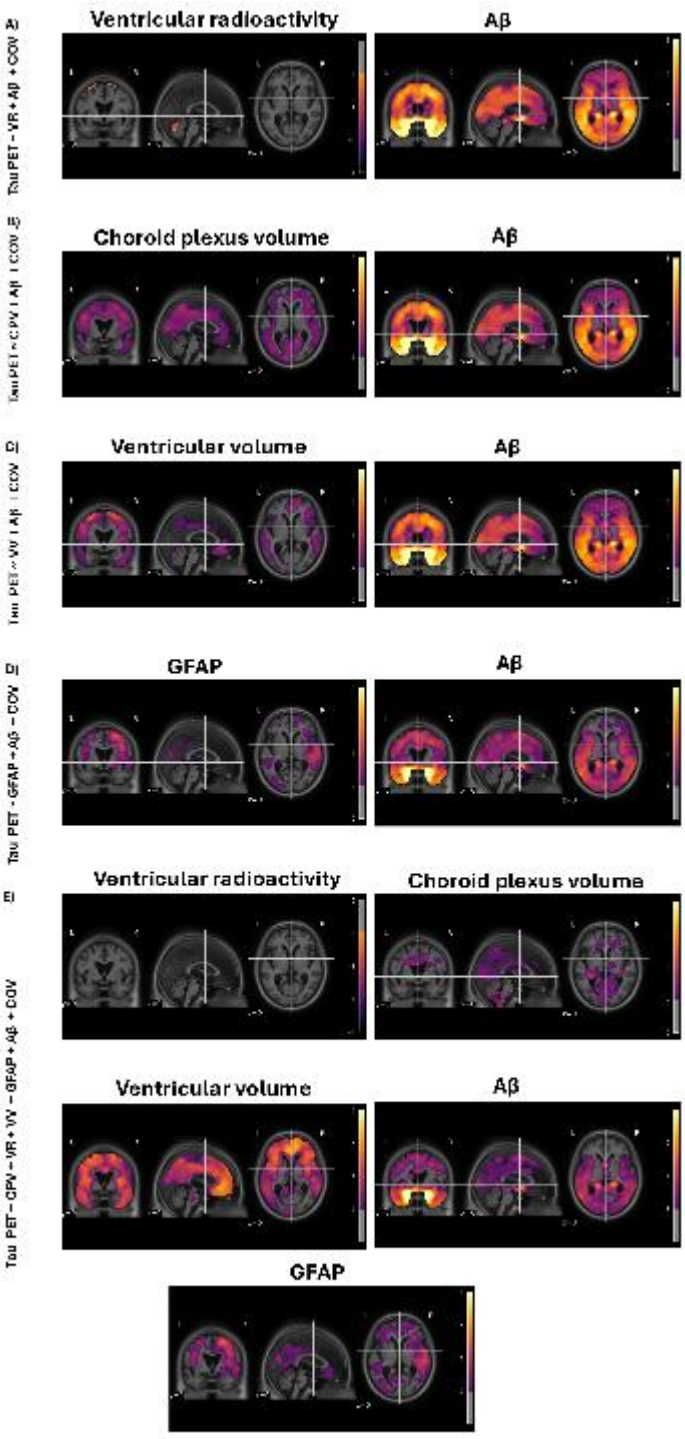

Fig3. Voxel wise analysis of Tau PET as a function of ventricular remodeling and GFAP.
COV = Age, Sex, Apoe, Intracranial volume.

Conclusions: This study highlights the additive influence of ventricular remodeling and astrocyte activation in promoting amyloid-β and tau aggregation in AD. Elevated GFAP levels, in combination with ventricular enlargement, may serve as early biomarkers for identifying individuals at heightened risk of AD progression.

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SHIFT 01-409

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

DEVELOPMENT OF BLOOD BIOMARKER FOR ALZHEIMER DISEASE USING NEURON-DERIVED EXTRACELLULAR VESICLES

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Aims: We have developed a technology to isolate extracellular vesicles (EVs) released from the central nervous system that are present in plasma.
Methods: Initially, we differentiated induced pluripotent stem cells into neurons to examine the membrane surface molecules of neuron-derived Evs (NDE) in culture media. Our analysis revealed a specific interest in neuron-specific APLP1. Subsequently, when we fractionated plasma using an iodixanol density gradient, we identified CD63, CD9, and Syntenin1 in the fraction containing APLP1, confirming the presence of APLP1-positive EVs in plasma. Our protocol for isolating NDE involves first separating total EVs from plasma using size exclusion chromatography, followed by isolating NDE through immunoprecipitation with an anti-APLP1 antibody. Using this method, we successfully isolated NDE from plasma obtained from Alzheimer's disease patients and analyzed their protein content using digital ELISA.
Results: Tau in NDE measured by digital ELISA was significantly correlated with Alzheimer's disease biomarkers in cerebrospinal fluid.
Conclusions: NDE obtained through our developed method could serve as potential biomarkers for Alzheimer's disease.

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SHIFT 01-421

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / FUNCTIONAL MRI
2 - 3 April 2025

INCREASED INTRINSIC FUNCTIONAL CONNECTIVITY ASSOCIATED WITH MEMORY RETRIEVAL IMPAIRMENT IN CLINICALLY UNIMPAIRED OLDER ADULTS

Stefano Caneva[1], Luigi Lorenzini[2], Leonard Pieperhoff[2], Federico Masserini[3], Mario Tranfa[2], Lisa Quenon[4], Daniele Altomare[5], Chris Buckley[6], Lyduine Collij[7], Gill Farrar[6], Giovanni Frisoni[8], Rossella Gismondi[9], Andrew Stephens[9], David Vállez García[10], Pieter Visser[11], Betty Tijms[12], Raffaele Cacciaglia[10], Juan Domingo Gispert[10], Luca Roccatagliata[13], Alle Meije Wink[2], Matteo Pardini[1], Frederik Barkhof[2]
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Aims: To understand the functional connectivity correlates of preserved and impaired episodic memory in clinically unimpaired older individuals
Methods: We included 186 participants from the AMYPAD Prognostic & Natural History study (PNHS; v202306, doi:10.5281/zenodo.8017084) with amyloid-PET, a Clinical Dementia Rating scale (CDR) score equal to 0 and that were assessed with Free and Cued Selective Reminding Test (FCSRT). From this test, the five Stages of Objective Memory Impairment (SOMI) were computed: SOMI 0 showing preserved memory, SOMI 1 and 2 showing retrieval difficulties, and SOMI 3 and 4 showing storage impairment. Resting-state functional magnetic resonance imaging (rs-fMRI) scans were retrieved for participants from the PNHS dataset and preprocessed with the fMRIPrep v23.0.1 pipeline. Independent component analysis was used to identify 20 components (resting-state networks) in the whole group. A dual regression was performed to compare subject-level intrinsic resting-state network connectivity between the three groups of participants with no impairment (SOMI 0), retrieval impairment (SOMI 1-2) and storage impairment (SOMI 3-4). Models were corrected for age and sex of participants.
Results: Cohort characteristics are shown in *Table 1*: a one-way ANOVA showed significant differences between groups concerning the educational level ($p = .03$) and MMSE score ($p = .04$), but post hoc comparisons revealed no significant differences. We observed significant increases in intrinsic connectivity in the retrieval impairment group (SOMI 1-2) compared to the other two groups in 3 resting-state networks, including the lateral visual, the ventral attention, and a temporo-parietal network (*Figure 1*). No differences were observed when comparing unimpaired participants to those with storage impairment.

Table 1: sample characteristics stratified by SOMI group

	Overall (N=186)	No impairment (N=39)	Retrieval imparment (N=34)	Storage impairment (N=113)
Age (years)				
Mean (SD)	60.18 (4.68)	59.41 (4.52)	59.44 (4.38)	60.67 (4.79)
Sex				
Female	116 (62.4%)	26 (66.7%)	21 (61.8%)	69 (61.1%)
Male	70 (37.6%)	13 (33.3%)	13 (38.2%)	44 (38.9%)
Education (years)				
Mean (SD)	13.63 (3.44)	14.38 (3.35)	14.56 (3.23)	13.10 (3.45)
CDR				
0 - Normal	186 (100%)	39 (100%)	34 (100%)	113 (100%)
PET Centiloids				
Mean (SD)	10.83 (16.24)	11.40 (19.91)	10.58 (15.78)	10.69 (15.00)
PET Amyloid status				
Negative	137 (73.7%)	30 (76.9%)	23 (67.6%)	84 (74.3%)
Positive	25 (13.4%)	6 (15.4%)	5 (14.7%)	14 (12.4%)
MMSE score				
Mean (SD)	29.23 (0.98)	29.41 (0.94)	29.50 (0.75)	29.09 (1.04)

No impairment = SOMI 0, Retrieval impairment = SOMI 1 and 2, Storage impairment = SOMI 3 and 4. Categorical variables are expressed as N (%). Cut-off for Amyloid positivity = 24 Centiloids.

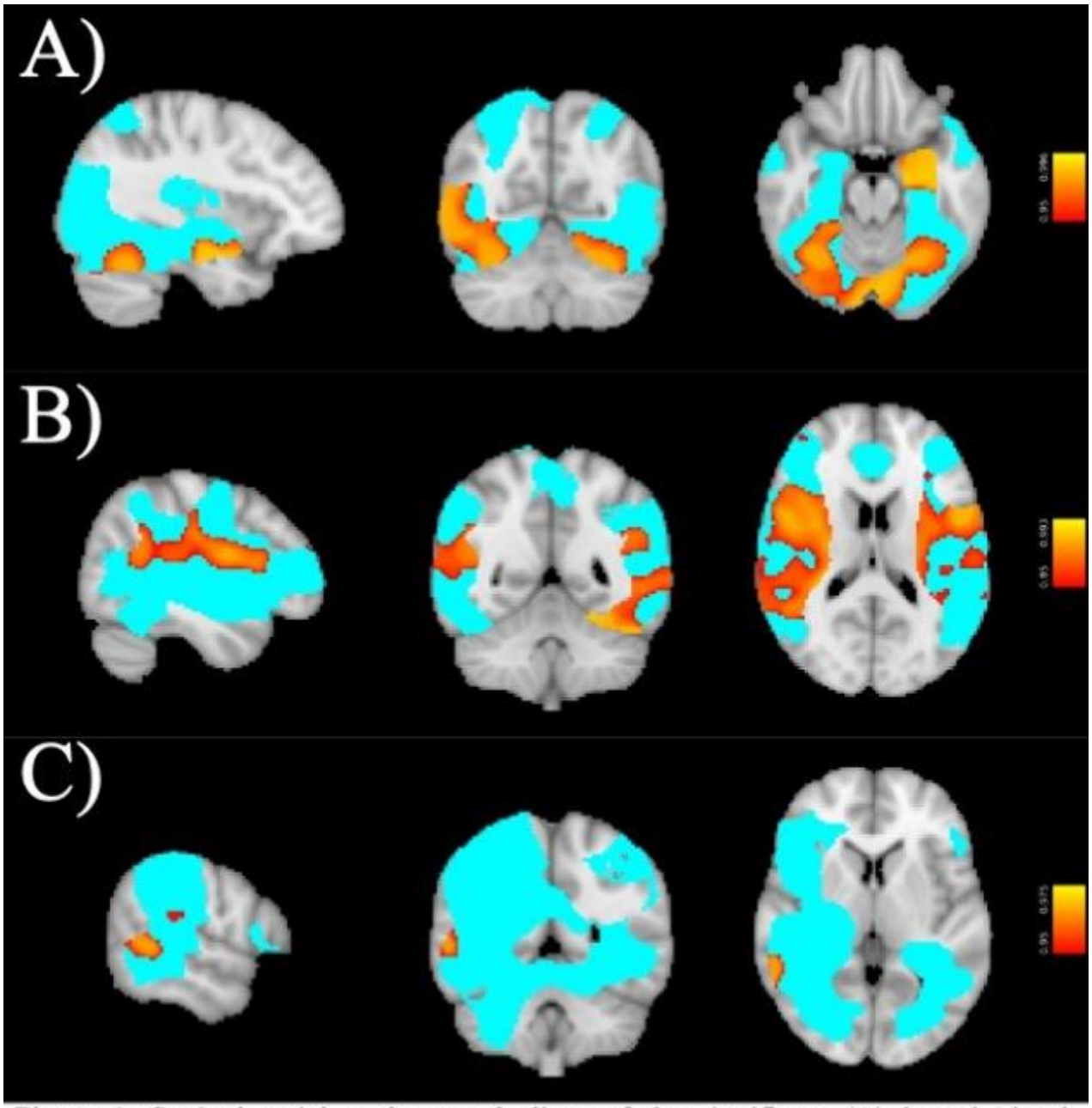

Figure 1: Sagittal, axial, and coronal slices of the significant (A) lateral visual, (B) ventral attention and (C) temporo-parietal network, respectively. Light blue areas show the entire component derived from group independent component analysis; yellow-red regions show where the retrieval impairment group had significant (1 - p value) higher intrinsic functional connectivity compared to the storage impairment group.

Conclusions: In a cohort of clinically unimpaired elderly individuals, we showed that impairment in memory retrieval is related to underlying hyperconnectivity within primary sensory and attentional networks.

SHIFT 01-423

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2 - 3 April 2025

SUBCLINICAL EPILEPTIFORM ACTIVTIY IS A MARKER OF PATHOLOGIC AGING IN ALZHEIMER'S DISEASE SPECTRUM

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Aims: Growing evidence suggests that the imbalance between excitability and inhibitory neural activity is a key aspect of cognitive decline. Subclinical epileptiform activity (SEA) has been indicated as a marker of prominent imbalance associating with accelerated progression of Alzheimer's disease (AD). The aim of our study was to investigate the incidence of SEA and the associating phenotype of SEA in the clinical spectrum of AD.
Methods: We studied 54 healthy elderly subjects, 82 AD patients, 17 patients with MCI due to AD and 42 patients with subjective cognitive decline. The study protocol included neuropsychology, structural and functional neuroimaging, laboratory testing and neurological examination. All subjects underwent 24-h Holter electroencephalography (EEG), visual analysis was conducted by two independent raters. Subjects were classified into EEG positive (SEA+) and negative (SEA-) groups based on detecting epileptiform activity on their EEG. Neuropsychology battery, structural MRI and functional MRI results were compared between the groups.
Results: Epileptiform activity was presented in 20% of healthy subjects, in 62% of MCI patients and 45% of AD patients ($p<0.001$). EEG positivity associated with significantly lower global cognitive performance ($p=0,01$). SEA+ group also performed worse on both Trail Making Test A and B ($p =0,02$ and 0,003 respectively). EEG+ patients had larger hippocampal volumes bilaterally ($p<0,001$) and reduced medial parietal volume ($p=0,001$). Furthermore, patients were characterized with hyperactive hippocampal resting state fMRI signal ($p<0.001$).
Conclusions: Presence of SEA increases in the prodromal stage of AD compare to healthy inviduals and show gradual reduction in the dementia stage, probably indicating the course of hyperexcitability. SEA associates with lower cognitive performance, special structural imaging phenotype and with pathological hyperactivation of the hippocampal regions. Therefore, SEA might be an indicator of pathologic aging.

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SHIFT 01-424

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2 - 3 April 2025

REGIONAL VARIATION IN WHITE MATTER AND OLIGODENDROCYTE DENSITY IN WHITE MATTER HYPERINTENSITIES IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's Disease (AD) is a relentless progressive neurodegenerative disease leading to severe cognitive decline and affects approximately 26.6 million people worldwide. White matter hyperintensities (WMH) are radiologically defined regions of myelin rarefaction which precede cognitive symptoms in AD by as early as 20 years and are predictive of disease onset, severity, and progression. Little is known about the composition of WMH due to the difficulty locating these lesions postmortem. We have overcome that challenge by aligning postmortem 7T MRI with gross tissue slabs. We developed novel tools to map MRI-derived WMH lesion annotations onto digital whole slide images for comparative histological analysis of WMH vs. normally appearing white matter (NAWM) regions.
Methods: We developed a quantitative digital image analysis pipeline to identify histopathologic signatures associated with clinical outcomes. We stained for myelin through Luxol Fast Blue H&E staining, identified oligodendrocyte (PLP1+) and pericyte (PDGFRB+) distribution by in situ hybridization (ISH), and stained for myelin associated glycoprotein (MAG) and proteolipid protein (PLP) by immunohistochemistry (IHC).
Results: We investigated oligodendrocyte and myelin density by white matter depth, periventricular distance, and WMH lesion depth. White matter depth and perivascular distance were identified and mapped onto whole slide images using automated white vs. gray matter classification through artificial neural network (ANN) pixel classifiers trained in the QuPath software and subsequent annotation-manipulation algorithms using the Shapely package. We performed semi-supervised machine learning to identify tissue regions most significant to WMH vs. NAWM prediction.
Conclusions: This methodology allows us to further interrogate regions of myelin rarefaction in Alzheimer's Disease. Understanding cellular neighborhoods in these regions are critical to understanding AD disease pathogenesis.

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SHIFT 01-430

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

CHALLENGES AND ACHIEVEMENTS OF A REMOTE PRECLINICAL ALZHEIMER'S DISEASE SCREENING STUDY: INSIGHTS FROM THE REAL AD STUDY

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Aims: The REAL AD study aims to validate the diagnostic and prognostic performance of the combined use of blood-based biomarkers and remote cognitive testing as a screening approach for early Alzheimer's disease employing an existing healthcare infrastructure in West-Sweden. Here, we evaluate the process of setting up and conducting a fully remote screening study, focusing on both challenges and key strategies.
Methods: A targeted recruitment campaign was launched in April 2024, simulating a realistic population screening scenario, with the goal of recruiting between 3,000 and 10,000 participants. Through a central study information and communication hub, participants are asked to answer various questionnaires, perform remotely administered cognitive tests (using NeotivTrials or Cognitron), as well as to leave a blood sample at one of the regional primary care units (Figure 1).

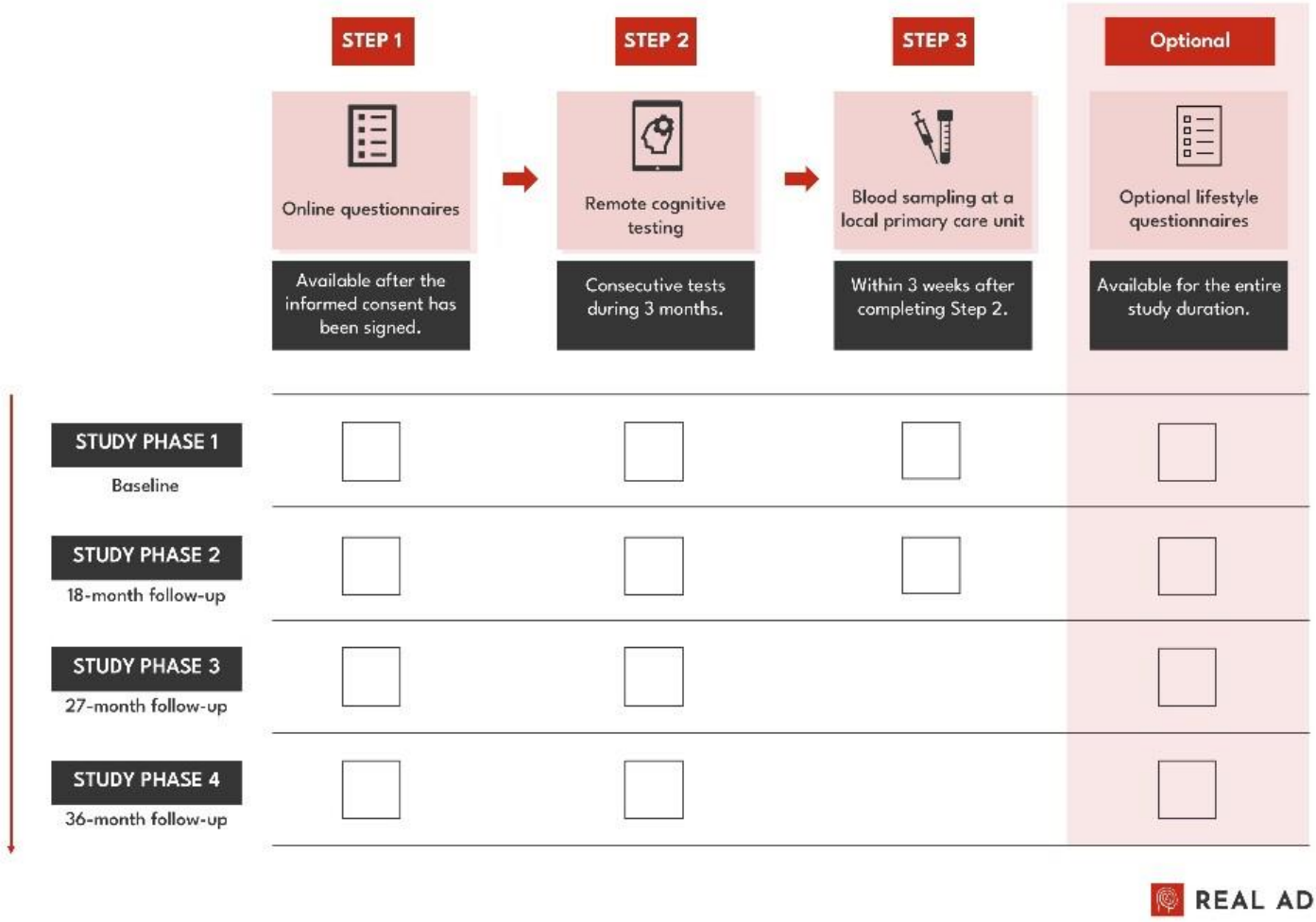

Figure 1. Each of the four steps in the screening study encompasses multiple data collection points: baseline, 18- 27- and 36-month follow-up for steps 1 (questionnaires about basic health, demographic, and lifestyle information) and 2 (remote cognitive testing), as well as the optional questionnaires on lifestyle factors; baseline and 18-months for step 3 (blood sampling).

Results: At abstract submission, 4,953 participants (mean age = 63.7 years, N_{female} = 3,420) have been recruited over a five-month period, with recruitment ongoing. We evaluate the initial phase of the study, focusing on: (1) collaborating with a wide range of actors, including the primary health care system, (2) the practicalities of conducting a fully remote screening study (in participants aged 50 to 80 years), (3) best practices for maintaining high engagement in a remote setting, and (4) participant feedback reports.
Conclusions: By mapping both the challenges and achievements of the initial phase of a remote screening study, we hope to help move the field one step closer towards the implementation of biomarkers in Alzheimer's disease diagnostic workup at all care levels, as well as inform and support future scientific studies.

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SHIFT 01-431

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

ATTITUDES OF THE OLDER POPULATION REGARDING EARLY ALZHEIMER DIAGNOSIS AND DIAGNOSTIC DISCLOSURE: A NATIONWIDE STUDY

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Aims: This study aimed to understand the attitude in the general population towards early diagnosis of Alzheimer's disease and use of Artificial Intelligence (AI) in the diagnostic process. Moreover, to investigate preferences regarding pre-biomarker counselling and diagnostic disclosure.
Methods: Between April and June 2024, we conducted a cross sectional nationwide online survey in the Danish population. An online questionnaire was sent out through a national electronic mailbox to 30,000 participants, who were randomly selected from the national Danish civil registry based on the following criteria: 1) 55-85 years, 2) 50% men and women, 3) nationwide distribution, 4) no registered dementia diagnosis, 5) not living in a nursing home, and 6) no prescribed dementia medication.
Results: A total of 13,047 individuals participated in the survey, providing a response rate of 43.3%. In the cohort, 76.4% showed interest in knowing if there were signs of Alzheimer's disease in their brain, whereas 7.9% did not want to know. Use of AI as a part of the diagnostic process was considered a good idea by 56.4%. The difference between trust in the diagnostic evaluation performed by a physician alone (56.2%) compared to AI alone (17.2%) was 39%, whereas the difference between a physician alone compared to a physician with AI (60.3%) was 4.1%. For biomarker counselling the most important issues were information about possible treatment and opportunity to ask questions. For diagnostic disclosure information regarding pharmaceutical treatments, a written summary and a follow-up consultation had the highest ratings.
Conclusions: A large proportion of the general population wants to know if they have signs of early Alzheimer's disease, and they have preferences regarding diagnostic communication. The majority trust use of AI in diagnostics if it does not stand alone

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SHIFT 01-432

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

HOW TO OBJECTIVELY MONITOR DISEASE PROGRESSION IN PARKINSON'S DISEASE?

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Aims: Dopamine transporter (DaT) imaging is a well-established diagnostic biomarker, but its potential role in objectively monitoring disease progression in Parkinson's disease (PD) has been underexplored. Previous studies so far failed to establish a longitudinal relationship between DaT signal decline and motor symptom progression, potentially due to unaddressed factors like specific brain region contribution, disease laterality, and symptom subtypes.
Methods: In this cohort study, we analyzed longitudinal imaging and clinical data from the Parkinson's Progression Markers Initiative Database, focusing on participants meeting the Movement Disorder Society (MDS) criteria for PD. Linear mixed model analyses were employed to assess the relationship between DaT signal decline and motor symptom severity increase over time. All mixed models included a random intercept and slope for each patient to account for individual disease trajectories. We hypothesized that a decline in putaminal DaT availability in the less affected hemisphere would correlate with increasing contralateral motor symptoms, as measured by the Unified Parkinson's Disease Rating Scale motor score (UPDRS-III). Additional analyses examined the effects of different brain regions (caudate, putamen), symptom categories (MDS-UPDRS-III score with and without tremor items), and disease laterality (left or right hemisphere).
Results: Among 558 participants (346 males, 212 females; mean age 62.1±9.6 years) with 1581 data points, we found a significant association between the decline in the less affected putaminal DaT signal and the increase in contralateral motor symptoms, regardless of tremor score inclusion (ß=-0.05, CI=-0.09:-0.01).
Conclusions: Our findings support the use of repetitive DaT imaging for objectively monitoring PD progression. This could facilitate personalized disease tracking, progression-based disease subtyping, and the testing of novel interventional therapies in the future.

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SHIFT 01-433

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

UPDATING DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE: RECOMMENDATIONS OF THE INTERNATIONAL WORKING GROUP (IWG)

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Aims: The movement to define Alzheimer's disease (AD) biologically, based on evolving biomarkers, has gained momentum, as reflected in the Alzheimer's Association (AA) 2024 criteria[1]. However, questions about the framework's readiness, clinical applicability, and adoption persist. The International Working Group (IWG) presents an alternative view of AD as a clinical-biological construct, focusing on "at-risk" states like "asymptomatic at risk" and "presymptomatic."
Methods: A review of literature from PubMed (July 1, 2020-September 1, 2024) using terms biomarker or amyloid or tau or neurodegeneration or preclinical or CSF or PET or Plasma and Alzheimer's disease. Collaborative writing involved 41 IWG contributors.
Results: The IWG contextualizes AA biomarkers (Core 1 and Core 2) as risk factors for clinical AD rather than standalone diagnostic tools. For asymptomatic or cognitively normal individuals, the IWG suggests interpreting these biomarkers as indicators of risk rather than confirming AD. Specifically, we propose using "asymptomatic at risk" for Core 1 biomarkers, indicating increased risk without certainty of symptom onset, and "presymptomatic" for cases where predictive data suggest a high likelihood of progressing to dementia, akin to autosomal dominant mutation carriers. These nuanced distinctions are crucial, as AD remains a heavily stigmatized diagnosis, and premature disclosure of biomarker results can have serious psychological consequences.
Conclusions: The IWG's alternative framework could offer practical guidance for clinicians navigating the widespread availability of biomarkers, especially blood-based ones. Although the differences between AA and IWG frameworks may seem semantic, they have significant implications for patient care, particularly for those at risk. Further research is needed to validate these models.

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1. Jack CR et al Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alz & Dementia 2024 DOI: 10.1002/alz.13859

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SHIFT 01-434

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

ALTERATIONS IN SLEEP MACRO- AND MICROSTRUCTURE IN ALZHEIMER'S DISEASE: NEUROPSYCHOLOGICAL, NEUROPHYSIOLOGICAL, AND NEUROIMAGING PERSPECTIVES

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Aims: Alzheimer's disease (AD) is the leading cause of dementia, often associated with impaired sleep quality and disorganized sleep structure, even at early stages. Our aim is to identify changes in sleep macrostructure and K-complex (KC) density as microstructure in AD, with regard to neuropsychological and brain structural changes.
Methods: We involved 30 AD and 30 healthy control individuals. For sleep recording a 24-hour long electroencephalogram (EEG) was performed. Hungarian version of the Addenbrooke Cognitive Examination (ACE) as neuropsychological exam and brain MRI were also performed.
Results: AD patients had significantly decreased total sleep time (TST), sleep efficiency, and relative durations of non-rapid eye movement (NREM) stages 2 (S2), 3 (S3), and rapid eye movement (REM) sleep ($p<0.01$). KC density during the TST and S2 ($p<0.001$) was significantly reduced in AD. We found strong correlations between global cognitive performance (ACE scores) and relative S3 ($p<0.001$; $r=0.86$) and REM durations ($p<0.001$; $r=0.87$). TST and NREM stage 1 (S1) durations showed a moderate negative correlation with volumes of the amygdala and hippocampus ($p<0.02$; $r=0.51$-0.55), while S3 and REM sleep had a moderate positive correlation with cingulate cortex volume ($p<0.02$; $r=0.45$-0.61). KC density strongly correlated with global cognitive function (ACE scores) ($p<0.001$; $r=0.66$) and the thickness of the anterior cingulate cortex ($p<0.05$; $r=0.45$-0.47).
Conclusions: Our results showed significant sleep structural changes in AD, alongside with cognitive decline. Decreased slow wave sleep and KCs are strongly associated with cingulate cortex atrophy. Since sleep changes are prominent in early AD, they may have a great impact in the preclinical detection of AD, and may serve as prognostic markers or therapeutic targets.

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SHIFT 01-435

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

APO-EASY®: A NOVEL IVD TOOL FOR RAPID APOE GENOTYPING AIDING TOWARDS RISK STRATIFICATION FOR ALZHEIMER'S DISEASE

Çetin Kocaefe[1,2], Miguel Casanova[3], Lucas Pham-Van[3], Joanna Michel[1], Rodwell Mkhwananzi[1], Stéphanie Boutillier[3], Hüseyin Firat[1]
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Aims: Among three variant alleles of the ApoE gene, ε4 allele is determined as a major risk factor for AD. Individuals with one ε4 allele have an increased risk for AD and the risk is further increased for those who are at a homozygous state. The ε4 allele is also linked to earlier manifestation of AD symptoms as well as the disease. Since novel modes of therapy for AD are rapidly emerging, the ApoE genetic status is gaining importance in order to select the best therapy option as well as adopting lifestyle changes that may delay the symptoms and onset of AD.
Methods: A real-time quantitative PCR assay has been developed based on the hydrolysis-probe technology aiming to discriminate rs429358 or rs7412 SNP alleles separately with the acquisition of FAM and VIC fluorophores. The IVD certified tool is designed to be applied on ThermoFisher QS5-Dx instrument complying IVD standards and standard operating guidelines are designated and certified.
Results: The assay is validated in several cohorts to provide absolute allelic discrimination in patient samples. Application standards are designated to comply both CE marking and IVD certification.
Conclusions: The rapidly developing knowledge base on the primary concepts of ApoE genetics imposes a paradigm shift towards a single-gene depicted susceptibility to AD. Two new therapeutics targeting amyloid plaques are newly introduced and considered as a hope to slow down the disease progression. Antibody based therapeutics require testing for the ApoE genetic status since ε4 allele expose patients to risk for developing Amyloid-Related Imaging Abnormalities secondary to edema or hemosiderin deposition. We believe that APO-Easy® is the tool to fulfill the precision medicine needs at the bedside.

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SHIFT 01-436

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2 - 3 April 2025

REALISE: PREPAREDNESS OF GERMAN SPECIALISTS AND MEMORY CLINICS TO DELIVER EARLY AND ACCURATE DIAGNOSIS OF AD FOR DISEASE-MODIFYING TREATMENT

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Aims: Medical experts have identified the involvement of biomarkers in dementia diagnostics as being of significant value (Frederiksen, K. et al., 2021, Int J Geriatr Psychiatry). However, there is a notable lack of implementation of PET scans and CSF diagnostics. Despite the recent decision from the Committee for Medicinal Products for Human Use of the EMA to limit the approval of disease-modifying treatments, the necessity for early, biomarker-based diagnostics has increased due to the demographic shift towards an ageing population, which demands early interventions to slow disease progression and timely access to care. The study aims to evaluate the current procedure for the early detection of Alzheimer's disease.
Methods: An online survey will be conducted with German medical experts in the diagnosis and treatment of cognitive impairment. The survey will be distributed stepwise and via email: firstly, to the directors of the 210 memory clinics in Germany. Secondly, neurologists and psychiatrists in private practice will be invited to participate in a shortened version (SV). The survey contains of three categories: socio-demographic data (eight questions per version), biomarker-based diagnostics of memory impairment (20, SV: 13 questions) and attitude and prerequisites for potential antibody treatment (eight, SV: six questions). The data collection process is scheduled for completion by December 2024.
Results: We will analyse the results from January 2025. It is anticipated that medical experts will emphasise the importance of early detection of Alzheimer's dementia. However, it is also assumed that there will be a lack of biomarker-based diagnostics, particularly in relation to lumbar puncture and MRI scans.
Conclusions: The survey will identify gaps and additional resources in Alzheimer's diagnostic and clarify how Germany's healthcare infrastructure is prepared for an increasing need for diagnostic.

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SHIFT 01-448

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

THE CLINICAL UTILITY OF LONGITUDINAL BRAIN MRI IN EARLY STAGES OF NEURODEGENERATIVE DEMENTIA

Chiara Carbone[1], Chiara Gallingani[1], Erica Balboni[2], Ludovico Luchetti[3], Giordano Gentile[3], Manuela Tondelli[1], Luca Nocetti[2], Alessandro Marti[4], Annalisa Chiari[5], Giovanna Zamboni[1]
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Aims: Diagnosing early-stage neurodegenerative disorders can be challenging, especially if baseline assessments [i.e., magnetic resonance imaging (MRI) and neuropsychology] are not conclusive. A follow-up MRI can be performed to assess for any changes, and registration-based techniques such as SIENA/FSL could enhance its interpretation. We evaluated whether SIENA/FSL, and the comparison with published normative data, can aid in identifying people with cognitive complaints with non-physiological progressive atrophy over a short period.
Methods: People with subjective cognitive decline/mild cognitive impairment/mild behavioural impairment underwent neurological examination, neuropsychological assessment, MRI, FDG-PET and/or amyloid-PET/lumbar puncture. After 18 months, neurological examination and MRI were repeated. Percentage of brain volume change/year (PBVC/y) for every subject was calculated with SIENA/FSL. At follow-up, subjects were classified as: (I) *Converters/Non-converters* based on clinical conversion to dementia, (II) *Non-converters+/Non-converters-* if clinically stable but with positive/negative biomarkers for a neurodegenerative dementia, and (III) *Non-converters-/Alzheimer's disease* (AD)/*Frontotemporal dementia* (FTD)/*dementia with Lewy bodies* (DLB) based on both clinical and biomarkers. Logistic regressions with subjects' classification as dependent variable and PBVC/y (and then also subjects' PBVC/y classification under/over the 80th/95th percentiles of normative data), basal brain volume, and ΔMMSE as regressors were performed.
Results: 110 subjects were recruited; analyses were performed on 87. Higher PBVC/y and exceeding both 80th/95th percentiles increased the probability of being classified *Converters* vs *Non-Converters* and *AD* or *FTD* vs *Non-Converters-.* Instead, only exceeding the 80th percentile increased the likelihood of being classified *Non-Converters+* vs *Non-Converters-.*
Conclusions: Our findings suggest that the application of SIENA/FSL's PBVC/y and normative data can differentiate physiological from pathological conditions. Is particularly useful applying the 80th percentile cut-off derived from normative values to subjects with a neurodegenerative disease but without clinical conversion in 18-months. This approach may improve diagnostic accuracy.

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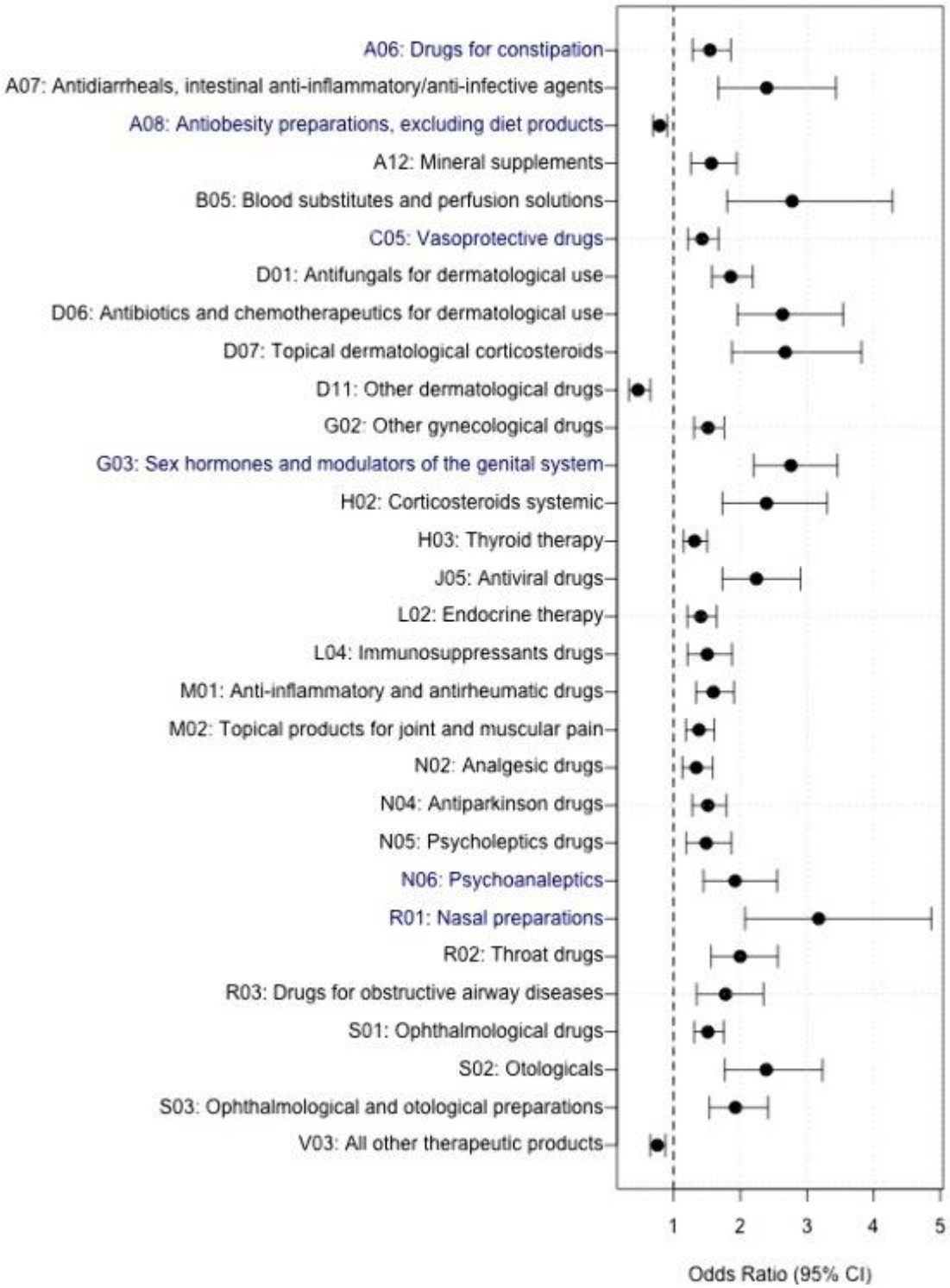
SHIFT 01-449

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

REGULAR MEDICATION USE IS ASSOCIATED WITH GREY MATTER STRUCTURE IN BRAIN REGIONS LINKED TO ALZHEIMER'S DISEASE

Baptiste Couvy-Duchesne[1], Lydie Tran[2], Evans Cheruiyot[1], Octave Guinebretiere[3], Dang Wei[4], Fen Yang[4], Stanley Durrleman[3], Thomas Nedelec[3], Fang Fang[4], Allan Mcrae[1]
[1]Institute for Molecular Bioscience, the University of Queensland, Brisbane, Australia, [2]Mater Research Institute, The University of Queensland, Translational Research Institute, Brisbane, Australia, [3]Paris Brain Institute, Icm, Paris, France, [4]Institute of Environmental Medicine, Stockholm, Sweden

Aims: We sought to investigate how grey matter mediates the reported associations between medication use and the onset of neurodegenerative disorders several years later. Our consortium identified 7 medication classes associated with Alzheimer's disease (AD) diagnosis 5 to 10 years post-prescription.
Methods: We used the self-reported records of medication use in UK Biobank and structural brain MRI measuring fine grained grey-matter structure. We trained brain predictors (Best Linear Unbiased Predictors) of medication classes (Anatomical Therapeutic Chemical [ATC] codes). Participants were 45-82 years old at the time of brain imaging (N=36,104), and we excluded participants reporting taking antiparkinsonian (N04) or anti-Alzheimer's drugs (N06D) to avoid biasing brain scores. We tested if brain-based predictors of medications could predict AD status in several older cohorts (ADNI, AIBL, ARWIBO, OASIS3).
Results: We found that 30 (out of 62, **Fig.1**) medication brain scores were associated with AD status after multiple testing corrections. Several associations: A06 (Constipation), A08 (anti-obesity), C05 (Vasoprotective), G03 (Sex hormones), N06 (Psychoanaleptics), R01 (Nasal preparations) confirmed the epidemiological results we obtained from registries (highlighted in blue, **Fig.1**). We identified 54 specific brain regions that contributed to the associations between medication and AD, which aligned with regions of known grey matter atrophy in AD (e.g., hippocampus, amygdala, medial temporal lobe). However, our results also pointed towards the peri-calcarine gyrus, mediating the association between AD and G03, or the cuneus mediating that with R01.



Conclusions: Some medication uses are associated with differences in grey matter structure, and the implicated brain structures align with those impacted in neurodegenerative disorders. Our results suggest that grey matter structure plays a role in the reported link between medication use and the later onset of Alzheimer's disease.

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SHIFT 01-450

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

PREDICTING AMYLOID BURDEN WITHOUT PET SCANS: A MULTIMODAL ATTENTION-BASED DEEP LEARNING APPROACH

Seungjun Lee[1], Wooseok Jung[2]
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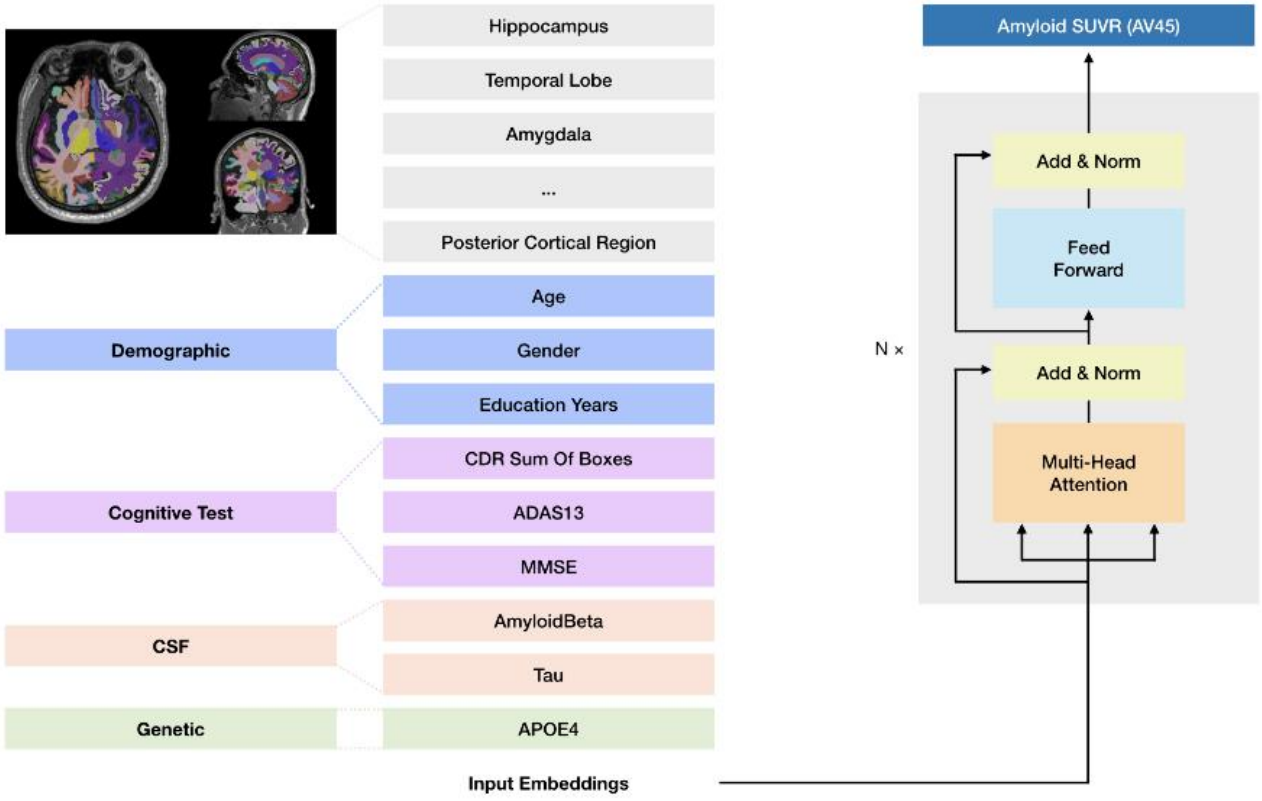
Aims: To develop a cost-effective screening tool using a multimodal attention-based deep neural network to predict amyloid standardized uptake value ratio (SUVR) without PET scans, aiming to identify patients who would benefit from PET scans, thereby optimizing resource allocation and reducing healthcare costs.
Methods:



Data were collected from 372 participants in the ADNI study, including 3D T1-weighted MRI scans, demographic information (age, sex, education years), cerebrospinal fluid (CSF) biomarkers (amyloid beta, tau), genetic information (APOE4 status), and cognitive test scores (CDR-SB, ADAS13, MMSE). MRI features were extracted using VUNO Med-DeepBrain, segmenting MRI into 104 distinct regions. A multimodal attention-based model was developed to predict average AV-45 SUVR values, utilizing separate feature embeddings for each modality.
Results: The model achieved a mean absolute error (MAE) of 0.12 (95% CI: 0.10-0.14) in predicting SUVR, outperforming traditional machine learning methods such as random forests (MAE: 0.16, 95% CI:

0.14-0.18) and support vector regression (MAE: 0.17, 95% CI: 0.15-0.19). Feature importance analysis revealed that MRI-derived features, particularly the volumes of hippocampus, temporal lobe, and posterior cortical region, as well as CSF biomarkers and genetic information as the strongest predictors. Age showed moderate importance, while sex had relatively lower importance.
Conclusions: This attention-based multimodal model offers a novel and cost-effective approach for predicting amyloid burden using diverse data sources. It highlights key biomarkers relevant for the early detection of Alzheimer's disease. By streamlining the use of PET scans, the model has the potential to reduce unnecessary procedures and healthcare costs. Future work could explore additional modalities, such as blood-based biomarkers and other MRI sequences (e.g., FLAIR and SWI), to further enhance the model's predictive power and clinical utility.

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SHIFT 01-454

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
2 - 3 April 2025

NOVEL STRATEGY TO PREVENT BDNF RECEPTOR CLEAVAGE AND TO RESTORE SYNAPTIC PHYSIOLOGY IN ALZHEIMER'S DISEASE

Maria José Diógenes[1], João Fonseca-Gomes[2], Tiago Costa-Coelho[2], Mafalda Manso[2], Sara Oliveira[2], Sandra Vaz[2], Nuno Aleman[2], Henrique Barbacena[2], Leonor Rodrigus[2], Tiago Mendonça[2], Tiago Rodrigues[2]
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Aims: To explore the therapeutic potential of new therapeutic target, the cleavage of TAT-TrkB.
Methods: The methods included: analysis of human samples, brain tissue, and cerebrospinal fluid; electrophysiological recordings in mice hippocampal slices and cultured neurons; transcriptomic studies; ELISA, Western blot and immunocytochemistry; Lentiviral transduction of neurons; toxicity and behavioral assays in the 5XFAD animal model.
Results: We found that TrkB-FL cleavage is a hallmark of AD-related pathology progression in humans, and it correlates with the levels of $A\beta_{1-42}$. One of the cleavage products of TrkB-FL, the TrkB-ICD, causes loss of dendritic spines, alters synaptic transmission, and impacts the expression levels of synapse-related genes. We designed small TAT-fused peptides and screened their ability to prevent TrkB-FL receptor cleavage. Among these, a TAT-TrkB peptide with a lysine-lysine linker prevented TrkB-FL cleavage both in vitro and in vivo. The TAT-TrkB demonstrated to be able to cross de blood brain barrier and to enter neurons without affecting membrane integrity. TAT-TrkB prevents $A\beta_{1-42}$-induced synaptotoxicity and loss of synaptic BDNF signaling. *In vivo* administration of TAT-TrkB improves synaptic deficits and cognitive performance of 5xFAD mice. Moreover, TAT-TrkB reduces the amount of p-Tau and the size of Aβ plaques. No evidence of liver or kidney toxicity was found.
Conclusions: TAT-TrkB specifically blocks a disease mechanism of AD whose therapeutic potential has not been addressed before. The *ex vivo* and *in vivo* studies conducted herein establish proof-of-concept evidence for the efficacy and safety of this therapeutic strategy. We anticipate that by preserving BDNF signaling, preventing TrkB-ICD accumulation, and decreasing Tau hyperphosphorylation, this peptide has the potential to be a disease-modifying drug that can prevent and/or reverse cognitive deficits in patients with AD.

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SHIFT 01-470

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2 - 3 April 2025

A MULTI-MODAL IMMUNOTHERAPEUTIC TARGETING AMYLOID FORMATION AND ENHANCING CLEARANCE OF AMYLOID AGGREGATES IN NEURODEGENERATIVE DISORDERS

Aditya Iyer, Julie Goemaere, Karine Goraj, Damien Toulorge
Amyl Therapeutics, R&d, Liege, Belgium

Aims: Our pan-amyloid immunotherapeutic protein has been generated by fusing a human IgG Fc with a conformational binder. Results from *in vitro and ex vivo* studies demonstrate the ability of our immunotherapeutic protein to inhibit the amyloid formation of $A\beta_{1-42}$, Tau, and α-synuclein and promote clearance by phagocytosis of their corresponding aggregates.
Methods: Using fluorescence spectroscopy, we evaluate the inhibition of amyloid formation of $A\beta_{1-42}$, Tau, and α-synuclein. We employ a combinatorial approach with surface plasmon resonance (SPR), ELISA, and immunogold labeling to assess *in vitro* binding to several amyloid aggregate morphologies. We use immunofluorescence microscopy studies to evaluate *ex vivo* binding to amyloid aggregates in relevant mouse, Alzheimer's disease (AD), and Parkinson's disease (PD) brain tissues and fluorescence microscopy studies to assess phagocytic clearance of amyloid aggregates.
Results: We demonstrate that our immunotherapeutic has a nanomolar binding affinity to, and promotes the disassembly of, amyloid aggregates of $A\beta_{1-42}$, Tau, and α-synuclein. Additionally, we show pan-amyloid aggregation inhibition and clearance of amyloid aggregates by THP-1 differentiated macrophages and human iPSC-derived microglia. Importantly, our immunotherapeutic inhibits seeded aggregation of Tau in mouse primary neurons using Tau seeds isolated from AD patients. Furthermore, we present data confirming *ex vivo* binding to amyloid deposits in tissues from AD/PD mouse models and human patients.
Conclusions: Our immunotherapeutic inhibits aggregation, binds existing amyloid aggregates with high affinity, and promotes the clearance of amyloid aggregates of $A\beta_{1-42}$, Tau, and α-synuclein. These results strengthen our platform technology as a potential therapeutic solution in amyloid-related neurodegenerative diseases like AD and PD.

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SHIFT 01-485

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2 - 3 April 2025

WITHANIA SOMNIFERA (ASHWAGANDHA) IMPROVES SPATIAL MEMORY, ANXIETY AND DEPRESSIVE-LIKE BEHAVIOR IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

Nora Gray[1], Noah Gladen-Kolarsky[1], Olivia Monestime[1], Melissa Bollen[1], Jae-Woo Choi[2], Liping Yang[2], Armando Alcazar Magana[3], Claudia Maier[2], Amala Soumyanath[1]
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Aims: *Withania somnifera* (WS), also known as ashwagandha, is a popular botanical supplement used to treat various conditions including memory loss, anxiety and depression. Previous studies from our group showed an aqueous extract of WS root (WSAq) enhances cognition and alleviates markers for depression in *Drosophila*. Here, we sought to confirm these effects in the 5xFAD mouse model of β-amyloid (Aβ) accumulation.
Methods: Six- to seven-month-old male and female 5xFAD mice were treated with WSAq in their drinking water at 0 mg/mL, 0.5 mg/mL or 2.5 mg/mL for four weeks. In the fourth week of treatment, spatial memory, anxiety and depressive-like symptoms were evaluated. At the conclusion of behavioral testing, brain tissue was harvested, immunohistochemistry was performed, and the cortical expression of antioxidant response genes was evaluated.
Results: Both concentrations of WSAq improved spatial memory and reduced depressive and anxiety-related behavior. These improvements were accompanied by a reduction in Aβ plaque burden in the hippocampus and cortex and an attenuation of neuroinflammatory markers. Antioxidant response genes were upregulated in the cortex of WSAq treated mice.
Conclusions: Oral WSAq treatment could be beneficial as a therapeutic option in AD for improving disease pathology and behavioral symptoms. Future studies focused on dose optimization of WSAq administration and further assessment of the mechanisms by which WSAq elicits its beneficial effects will help inform the clinical potential of this promising botanical therapy.

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SHIFT 01-499

On-Demand Oral Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
2 - 3 April 2025

INHIBITION OF IFITM3 IN CEREBROVASCULAR ENDOTHELIUM ALLEVIATES ALZHEIMER-RELATED PHENOTYPES

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Aims: Interferon-induced transmembrane protein 3 (IFITM3) modulates γ-secretase in Alzheimer's disease (AD). While IFITM3 knockout reduces amyloid β protein (Aβ) production, its cell-specific effect on AD remains unclear. This study aims to investigate the role of IFITM3 of the cerebrovascular endothelial cells in AD.
Methods: snRNA-seq was used to assess IFITM3 expression. AAV-BI30 was injected to reduce IFITM3 expression in the cerebrovascular endothelial cells (CVECs). The effects on AD phenotypes in cells and AD mice were examined through behavioral tests, two-photon imaging, Western blot, immunohistochemistry, and qPCR.
Results: IFITM3 expression was increased in CVECs of AD patients. Overexpression of IFITM3 in primary endothelial cells enhanced Aβ generation through regulating BACE1 and γ-secretase. Aβ further increased IFITM3 expression, creating a vicious cycle. Knockdown of IFITM3 in CVECs decreased Aβ accumulation within cerebrovascular walls, reduced Alzheimer-related pathology, and improved cognitive performance in AD transgenic mice.
Conclusions: Knockdown of IFITM3 in CVECs alleviates AD pathology and cognitive impairments. Targeting cerebrovascular endothelial IFITM3 holds promise for AD treatment.

SHIFT 01-503

On-Demand Oral Poster on Board - Shift 01
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / COMORBIDITY OF NEURODEGENERATION WITH COVID-19
2 - 3 April 2025

THE ASSOCIATION BETWEEN EARLY ADVERSITY AND DEPRESSION BEFORE AND DURING THE COVID-19 PANDEMIC

Morgane Kuenzi[1], Delia Gheorghe[2], Abhaya Adlakha[1], Sarah Bauermeister[1]
[1]University of Oxford, Psychiatry, Oxford, United Kingdom, [2]Transylvanian Institute of Neuroscience, Cluj-Napoca, Romania

Aims: Dementia is one of the leading causes of death and at least 55 million people worldwide currently have dementia (WHO). For prevention and the development of interventions, it is essential to identify the factors increasing the risk of developing dementia. Early adversity has long-lasting effects over the life course and numerous studies show that early adversity is associated with a higher risk of depression, a risk factor for developing dementia.
Methods: Given the important links between early adversity, depression, and dementia risk, and in light of the Covid-19 pandemic, which provides a fertile ground for the experience of adversity, this study aims to examine the associations between early adversity and depression at different time points, including before and during the Covid-19 pandemic. Data from the English Longitudinal Study of Ageing (ELSA) (waves 3, 6, and 9) and data from the ELSA Covid-19 substudy (wave 2) were used in a path analysis.
Results: Preliminary results show a significant effect of early adversity only on the first two waves of depression (3 and 6). Interestingly, a carry-over effect of depression was found, with depression significantly impacting depression in the subsequent wave in all waves. Significant mediations of early adversity via different waves of depression were also found.
Conclusions: The preliminary results show the lasting direct and indirect effects of the experience of early adversity on later depressive symptoms - a risk factor for the development of dementia. It is therefore important to address the lasting effects of early adversity on depression through effective interventions.

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SHIFT 01-508

On-Demand Oral Poster on Board - Shift 01
DEMYELINATING DISEASES / ANIMAL MODELS
2 - 3 April 2025

UNRAVELLING THE POTENTIAL ROLE OF THE APELIN RECEPTOR IN NG2 CELL-MEDIATED REMYELINATION IN A CUPRIZONE MODEL OF MULTIPLE SCLEROSIS

Lyubomir Gaydarski[1], Nikola Stamenov[1], Aleksandar Iliev[1], Stancho Stanchev[1], Georgi Kotov[2], Ivanka Kostadinova[3], Ivalina Valchinkova[3], Boycho Landzhov[1]
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Aims: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammation, demyelination, gliosis, and neurodegeneration. The cuprizone model, an established animal model, inducing demyelination, followed by microglial and astrocytic proliferation and axonal damage. Acute exposure for 5 weeks allows for complete demyelination and substantial remyelination if the cuprizone administration is discontinued. Neurons and macroglia primarily develop within the subventricular zone (SVZ), where NG2+ glial progenitor cells play crucial roles in remyelination. The apelinergic system, consisting of the apelin receptor (APLNR) and its ligands apelin and elabela, is involved in neurogenesis and potentially plays a key role in neurodegeneration. This study investigates the relationship between APLNR and NG2+ cells during de- and remyelination in a cuprizone-induced model of MS.
Methods: Thirty 8-week-old C57BL/6 mice were divided into three groups (control, demyelination, and remyelination). Cuprizone administration followed established protocols for 5 weeks. Immunofluorescence and confocal microscopy of the SVZ region were employed to assess APLNR and NG2+ expression.
Results: We report significant changes in NG2+ and APLNR cell populations in the SVZ. The highest number of NG2+ cells was observed in the remyelination group, while the lowest was in the demyelination group. APLNR-positive cells were most abundant in the demyelination group, with fewer in the control and remyelination groups. Co-localization analysis showed variable APLNR expression in NG2+ cells, highlighting the potential involvement of the APLNR in NG2+ cell-mediated remyelination.
Conclusions: Our study provides valuable insights into the complex pathomorphological processes in MS and suggests a key role for the apelinergic system in modulating NG2+ cell activity during demyelination and remyelination. Further investigation is required to fully understand the therapeutic potential of modulating the APLNR in a future treatement for MS.

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SHIFT 01-511

On-Demand Oral Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
2 - 3 April 2025

ROLE OF FIBROUS ASTROCYTES IN COGNITIVE DYSFUNCTION AND NEUROPSYCHIATRIC SYMPTOMS IN HUNTINGTON'S DISEASE

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Aims: Huntington's disease (HD) is a neurodegenerative disorder affecting the striatum, leading to motor, cognitive, and neuropsychiatric symptoms, with apathy being notably prevalent and linked to cognitive decline and increased suicide risk. However, the etiology or pathophysiology of cognitive decline in HD is still unknown. This study aims to uncover the cellular mechanisms behind cognitive decline in HD.
Methods: We used WT and HD (zQ175 model) mice, employing methods such as immunofluorescence, AAVs expressing diphtheria toxin (dTA) in astrocytes, spatial transcriptomics, and behavioral analyses.
Results: Increased inflammation and white matter (WM) atrophy, risk factors for cognitive decline, are found in the striatum of patients and mouse models of HD and dysfunction of striatal astrocytes in HD plays a critical role in these processes. We found that WM traversing the dorsomedial striatum (DMS) of HD mice is specifically and strongly associated with reactive 'fibrous' astrocytes, a phenomenon that increased with disease severity. Fibrous astrocytes are intimately associated with neuronal axons present in the WM regulating synaptic transmission and myelination. We discovered that the abnormal accumulation of fibrous astrocytes in HD is associated with the atrophy of WM in the DMS. HD fibrous astrocytes specifically associate with axons derived from the secondary motor cortex, which regulate motivation-related behaviors such as apathy. We conducted spatial transcriptomics in WT and HD mice and identified key transcriptional alterations in DMS fibrous astrocytes. Removal of fibrous astrocytes in the DMS of HD mice using AAVs expressing dTA in astrocytes resulted in improved apathetic and cognitive behaviors.
Conclusions: In conclusion, this research uncovers a novel cellular mechanism involving fibrous astrocytes in HD, offering new insights into cognitive decline and suggesting potential therapeutic strategies for mitigating cognitive and neuropsychiatric symptoms in HD.

SHIFT 01-520

On-Demand Oral Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

BIOLOGICAL BRAIN AGE AS A PREDICTOR OF PARKINSON'S DISEASE PROGRESSION

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder with diverse motor and non-motor symptoms, including cognitive decline. Ageing can affect PD heterogeneity, as individuals of the same chronological age may present with different biological brain ages. The role of biological brain age in PD progression remains unclear. We investigated whether biological brain age predicts disease progression in prodromal and de novo PD.
Methods: We included data from 716 de novo PD patients, 609 individuals with prodromal PD, and 181 healthy controls from the PPMI cohort. Biological brain age was estimated using a minimally preprocessed T1-weighted structural MRI-based method (Dartora et al., 2024, Front Aging Neurosci). We calculated the brain age gap at baseline – the difference between biological brain age and chronological age – and analysed its association with clinical progression over time using linear mixed models. Models were adjusted for chronological age, with additional adjustment for education in the case of cognitive variables.
Results: In the prodromal stage, a higher brain age gap – indicating a higher biological brain age than chronological age, and consequently an older-looking brain – predicted worse olfaction over time (UPSIT estimate=-17.78, $p<0.001$). In de novo PD, a higher brain age gap correlated with greater global cognitive decline (MoCA estimate=-3.18, $p<0.01$), as well as worsening motor experiences of daily living (UPDRS part II estimate= 6.71, $p<0.01$). No significant associations were observed in healthy controls.
Conclusions: An older-looking brain in prodromal stages is associated with greater olfactory decline, a symptom well-known to precede PD onset. In de novo PD, an older-looking brain predicts worse symptom progression, including faster cognitive decline. These results highlight the potential of biological brain age as a biomarker for predicting disease progression.

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SHIFT 01-522

On-Demand Oral Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2 - 3 April 2025

REPURPOSING AN ANTICANCER AGENT FOR THE TREATMENT OF HUNTINGTON'S DISEASE

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Aims: Huntington's disease (HD) is neurodegenerative disease caused by a CAG triple repeat expansion in the huntingtin gene (*HTT*), resulting in cognitive, psychological and motor impairments. Pathological hallmarks include aggregation of mutant HTT protein (mHTT) and selective degeneration of striatal medium-spiny neurons and striatal astrogliosis, resulting in the robust striatal degeneration characteristic of human HD. To date, effective therapeutic treatments for HD have not been identified. Previous work in our lab has found Protein kinase CK2, a serine/ threonine kinase involved in a large variety of cellular functions, as a potential therapeutic target in HD. Here we explore the therapeutic potential of a CK2 pharamcological inhibitor as a treatment for the amelioration of HD.
Methods: We conducted pharmacological treatments using gavage administration of the FDA designated orphan drug Silmitasertib (CX4945) in WT and zQ175 (HD) mice at early- and late-symptomatic stages. Motor behavior and neuropathology were assessed.
Results: We previously found that the alpha prime catalytic subunit of CK2 (CK2α') is pathologically induced in the striatum of HD patients and mouse models and CK2α' haploinsufficiency reduced mHTT aggregation, restored RNA signatures associated with neuronal and astrocytic functions, and ameliorated motor deficits in a knock-in mouse model of HD (zQ175). To determine the therapeutic potential of CK2α' in the treatment of HD we utilized CX4945, currently in clinical trials for treatment of various cancers. We found that zQ175 HD mice treated with CX4945 showed ameliorated motor deficits compared to vehicle treated mice and decreased mHTT aggregation and neuropathology. Importantly, CX4945 also increased astrocytic uptake of mHTT aggregates, and modified their spatial and subtype distribution and physiological characteristics.
Conclusions: These results establish CX4945 as a promising therapeutic agent for HD and reveal novel regulatory mechanisms of astrocytes in HD.

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SHIFT 01-528

On-Demand Oral Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
2 - 3 April 2025

TOOL FOR PREDICTING SURVIVAL TO GUIDE CARE PLANNING IN NURSING HOME RESIDENTS WITH DEMENTIA

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Aims: To develop survival prediction tables to inform physicians and individuals with dementia about survival probabilities after admission to nursing home, and to determine whether survival after admission can be predicted with good accuracy.
Methods: We conducted a nationwide registry-linkage study involving data from 2.649 individuals with dementia from the nursing home population in the Swedish registry for cognitive/dementia disorders (SveDem). The data was collected between 2012 and 2022, and included sociodemographic factors, comorbidities, assessment of function, Body Mass Index (BMI), and dates of death obtained from several Swedish records. Cox's proportional hazards regression models were used to create tables illustrating 3-year survival probabilities for different risk factor profiles.
Results: By May 2022, 1.473 (55.6%) patients in our cohort had died, and the median survival time from nursing home admission was 1.8 years (interquartile range: 1.03 to 3.04) for women and 1.6 years (interquartile range: 0.96 to 2.54) for men. Older age, male sex, lower BMI, higher dependency in ADL, and higher comorbidity burden were predictors of mortality. The prediction model achieved a c-index of 0.66 (95%-CI: 0.65 to 0.67) and demonstrated good calibration.
Conclusions: Three-year survival after nursing home admission can be predicted with moderate accuracy. The survival prediction tables developed from this study can be used by staff and persons with dementia in nursing homes to make more informed decisions and improve care planning.

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SHIFT 01-529

On-Demand Oral Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
2 - 3 April 2025

LUMEN: A LARGE LANGUAGE MODEL COLLATERAL INFORMATION GATHERING TOOL FOR DEMENTIA ASSESSMENT

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Aims: Dementia diagnostic assessments are often time-consuming, complex, and distressing for both patients and their caregivers. The increasing prevalence of dementia, combined with the need for accurate and efficient assessments to facilitate potential disease-modifying treatments, highlight the need for innovative tools. This study aimed to develop and test a prototype conversational AI, LUMEN (Large Language Model for Understanding and Monitoring Elderly Neurocognition). Designed to collect collateral information from caregivers prior to diagnostic appointments, aiming to improve diagnostic accuracy, enhance patient/caregiver experiences and reduce clinician workload.
Methods: Development was informed by a Patient and Public Involvement meeting, followed by a clinician workshop and a modified Delphi process involving 130 clinicians. This led to the scripting and annotation of conversations tailored to dementia subtypes and safety concerns. Open-source Large Language Models were assessed for adaptability (contextual response tailoring) and medical vocabulary richness (breadth and depth in dementia-related scenarios): Mistral 7B was selected. Advanced prompt engineering, including "chain-of-thought" and "flipped classroom" techniques, was employed to enhance LUMEN's contextual understanding and empathy. Testing involved clinical case vignettes with clinicians simulating caregivers, allowing comparison of LUMEN's diagnostic outputs to case diagnoses using AUROC and agreement in categorisation (LLM vs. clinician) using Cohen's kappa.
Results: LUMEN demonstrated promising diagnostic accuracy with an AUC of 0.75 (across all common dementia sub-types) and substantial agreement with clinicians' categorisations (Cohen's kappa 0.66). Additionally, the System Usability Scale (SUS) showed high levels of clinician satisfaction. Feedback from PPI and clinician workshops further supported LUMEN's clinical utility and acceptability.
Conclusions: LUMEN has significant potential to improve dementia diagnostic workflows by reducing clinician burden and enhancing diagnostic precision. Future work will focus on further validation in clinical settings and optimisation of the system for wider healthcare use.

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SHIFT 01-531

On-Demand Oral Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / SUPPORT DEVICES & MONITORING
2 - 3 April 2025

ARTIFICIAL INTELLIGENCE FOR UNDERSTANDING ALZHEIMER'S DISEASE PROGRESSION

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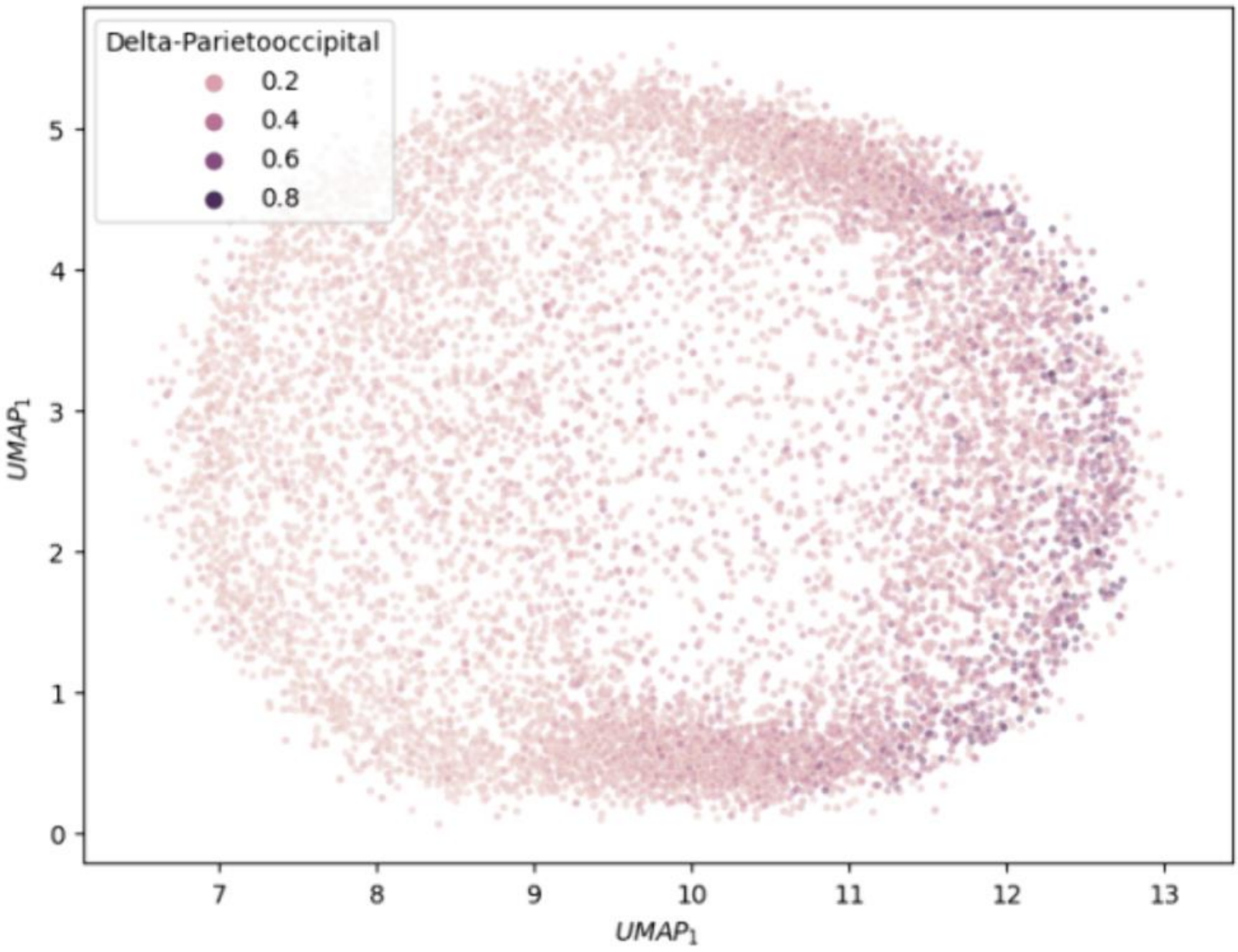
Aims: Dementia and cognitive decline are multi-faceted conditions with significant inter-individual variability. Traditional diagnostic methods, such as questionnaires and clinician-based evaluations, are time consuming and rely heavily on subjective measures. Neuroimaging techniques can offer objective measures in a short amount of time, but how to best leverage the recorded data for early dementia diagnostics is still an ongoing problem. We implement a deep learning algorithm capable of unsupervisedly extracting neurophysiological features from electroencephalography (EEG) signals to better characterize Alzheimer's Diseases (AD) progression.
Methods: We developed an LSTM-based Autoencoder designed to extract low-dimensional features from EEG signal segments. Autoencoders are unsupervised neural networks trained to produce outputs that closely resemble their inputs by first encoding input data into a low-dimensional feature space and then reconstructing it from these features. The LSTM layers allow the model to capture the time-dependent properties of multi-channel EEG data. An EEG dataset of N=223 individuals over 60 years, at different disease stages from healthy to AD, is used to train the models. The distribution of the learned features can be used as knowledge generation machine to better understand the neurophysiology of pathological ageing.
Results: The autoencoder successfully learns to encode meaningful EEG information in an unsupervised manner. This information is structured within the feature space, enabling interpretability. Both alpha and delta band powers are smoothly encoded, demonstrating the model's ability to capture physiological features.


Delta-Parietooccipital
0.2
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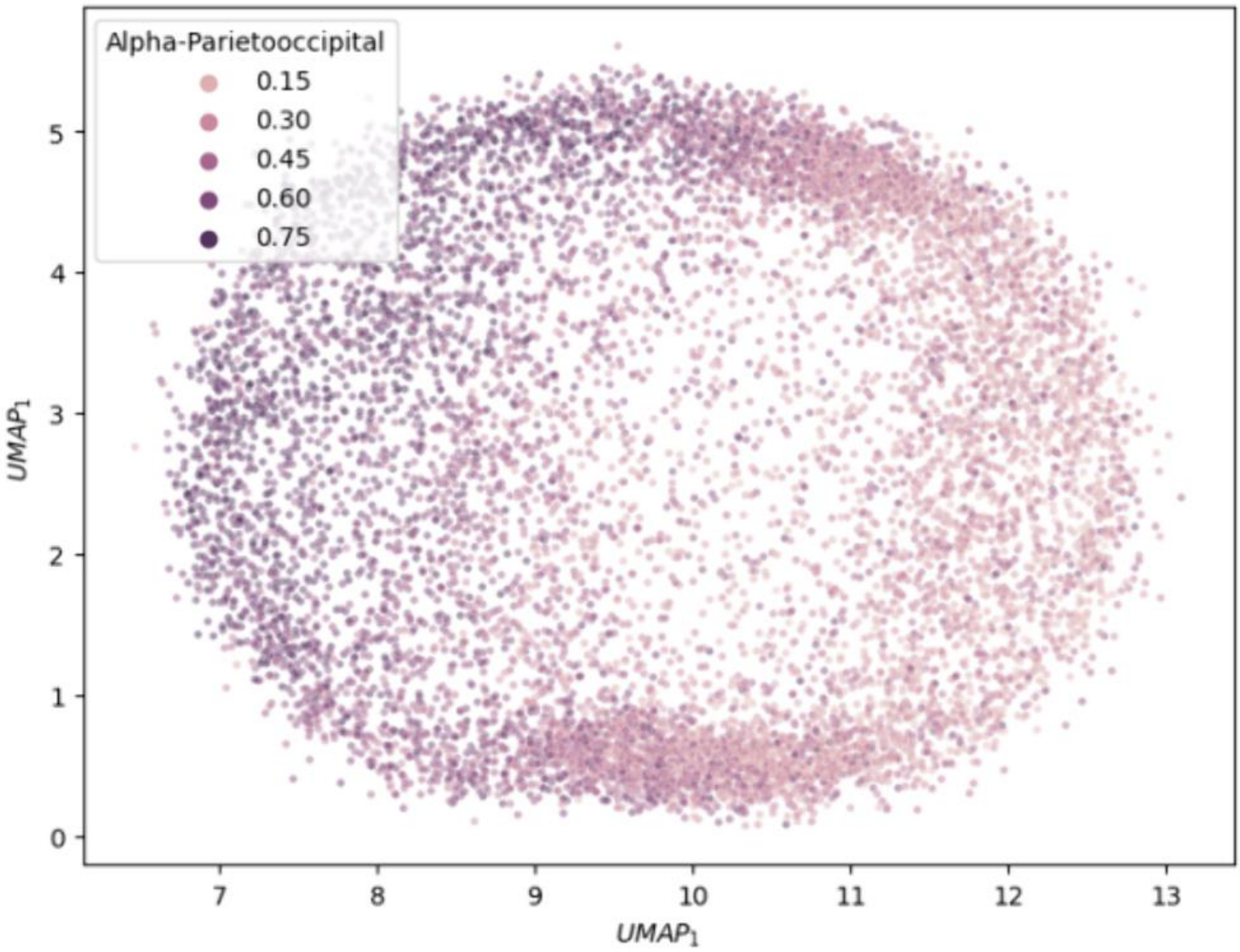

Conclusions: Our data-driven approach effectively captures inherent information, typically considered expert knowledge, without requiring human input. Although alpha slowing is well-known to be linked to neurodegenerative diseases, lower frequency bands are still underexplored. This methodology holds significant potential for further unsupervised biomarker discovery for cognitive decline stratification and early detection.

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SHIFT 01-558

On-Demand Oral Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
2 - 3 April 2025

CHRONIC PAIN AND PERSONALITY IN PARKINSON'S DISEASE, FIBROMYALGIA AND CHRONIC MIGRAINE

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Aims: To compare personality between Parkinson's disease (PD) patients with and without chronic pain and patients with other chronic pain etiologies (fibromyalgia (FM) and chronic migraine (CM)).
Methods: One hundred patients were included: n=25 in each group (PD patients with chronic pain, PD patients without pain, FM and CM patients). Chronicity of pain was validated by a Visual Analog Scale ≥ 4 for at least three months, and supplementary pain questionnaires were also evaluated (Brief Pain Inventory (BPI), Chronic Pain Acceptance Questionnaire-8 (CPAQ-8) and Pain Catastrophism Scale (PCS)). Personality was assessed with the Temperament and Character Inventory (TCI), and anxio-depressive state with the Hospital Anxiety Depression scale (HAD). Anovas and post-hocs tests were used to compare groups.
Results: TCI Harm Avoidance scores were higher in the FM group compared to both PD groups, and TCI Self-Directedness scores were lower in the FM group compared to PD without chronic pain group. Total HAD was superior in the FM group. PD patients with chronic pain also had lower BPI and PCS scores and higher CPAQ-8 scores compared to both other chronic pain groups (FM and CM).
Conclusions: In accordance with the literature, FM patients presented a specific personality of pain with higher Harm Avoidance and lower Self-Directedness scores (Naylor, Boag and Gustin 2017). Nonetheless, this type of personality was not observed in our PD patients with chronic pain. Hence, it seems that chronic pain in PD may be different from other chronic pain etiologies and that PD patients may have another perception of their chronic pain with less feeling of discomfort (BPI) and a better acceptance of it (CPAQ-8).

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SHIFT 01-559

On-Demand Oral Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
2 - 3 April 2025

SUPPLEMENTAL AMBIENT LIGHTING INTERVENTION TO IMPROVE SLEEP IN PARKINSON'S DISEASE: A PILOT TRIAL

Mariana Figueiro[1], Rachel Saunders-Pullman[2], Andrea Yoo[2], Adina Wise[2], Roberto Ortega[3], Deborah Raymond[2], Barbara Plitnick[1], Jennifer Brons[1], Judy Liang[2], Susan Bressman[2], Mengxi Yang[2], David Pedler[1]
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Aims: Sleep disturbances in Parkinson's disease (PD) are common and often adversely affect quality of life. Light therapy has benefited sleep quality and mood outcomes in various populations but results to date with conventional light therapy boxes in PD patients have been mixed. The present study sought to determine whether a supplemental lighting intervention (SALI) would improve objective (actigraphy) and subjective (questionnaires) measures of sleep and sleepiness (primary outcomes) as well as subjective (questionnaires) measures of mood (secondary outcomes) in PD. We hypothesized that the SALI, applied in the morning and designed to maximally affect the circadian system, would improve measures of sleep and mood in PD patients.
Methods: In this single-arm, within-subjects intervention study, baseline objective sleep (actigraphy), subjective sleep quality (questionnaires), and subjective mood (questionnaires) data were collected for 1 week. Lighting was then administered to participants via table/floor lamps installed in the home or via personal light therapy glasses for 2 hours in the morning, 7 days per week, over the following 4-week period. Post-intervention data for the same outcomes were collected during the final week of the intervention period.
Results: Among 20 participants (12 women, 8 men; mean [SD] age 72.1 [9.5] years, disease duration 9.0 [5.2] years), objective sleep time increased significantly by 19.9 minutes from 381 to 400 minutes (p = 0.026).
Conclusions: Our study demonstrated that the supplemental lighting intervention led to significantly (p = 0.026) increased sleep time as measured by actigraphy. We therefore concluded that passive and easily administered lighting interventions for improving sleep in PD patients hold promise as a treatment for mitigating symptoms and improving quality of life in PD patients.

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SHIFT 01-567

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / ANIMAL MODELS
2 - 3 April 2025

MECHANISMS UNDERLYING BEHAVIORAL ABNORMALITIES IN PRODROMAL ALZHEIMER'S DISEASE

Anuradha Korukonda, Margaret Tish, Jake Atallah, Eugene Guo, Brittany Pate, David Weinshenker
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Aims: During early stages of Alzheimer's disease (AD), patients often suffer from prodromal symptoms such as anxiety, depression, agitation, and sleep disturbances prior to the onset of cognitive impairment. Incidentally, the brainstem noradrenergic locus coeruleus (LC) is the first structure to develop hyperphosphorylated 'pretangle' tau pathology in the brain and norepinephrine (NE) influences several of these physiological processes. It is critical to evaluate if early tau accumulation in the LC and the manifestations of prodromal behaviors are causally linked. We thus developed a translationally-relevant tau mouse model that recapitulates the 'LC first' phenomena commonly observed in humans.
Methods: Adult male and female tyrosine hydroxylase (TH)-Cre mice (2-3 months) underwent intra-LC infusions with a Cre-dependent adeno-associated virus expressing EYFP or P301S mutant human tau (n=8-12/group). Mice underwent behavioral tests to assess sleep latency, locomotor activity, compulsivity, anxiety-like behavior, and association memory deficits at 3, 6, 9 months post-infusion. Following behavioral tests, brain sections were immunostained with TH to assess for LC integrity, AT8 to detect pretangle tau, NE transporter (NET) to evaluate NE fiber intensity in projection regions, and GFAP and IBA1 as neuroinflammatory markers. Immunoreactivity (IR) was calculated as a measure of fluorescence via ImageJ.
Results: Hyperphosphorylated tau was detected in cell bodies and somatodendritic compartments of LC neurons. At 3-months, mice expressing pathogenic tau showed hypersomnia or decreased latency to fall asleep and anxiety-like behavior. However, at 6 and 9 months, tau mice exhibited anxiolytic phenotype with intact cognition. In tandem, tau accumulation in the LC provoked robust astrocyte inflammatory responses in the LC and projection regions.
Conclusions: Tau pathology in the LC contributes to manifestations of prodromal symptoms. Further studies will address molecular mechanisms underlying tau-mediated LC dysfunction in early AD.

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SHIFT 01-570

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2 - 3 April 2025

THE EFFECT OF EARLY ADVERSE EXPERIENCES ON COPING STRATEGIES, MENTAL HEALTH, BRAIN, AND COGNITION

Morgane Kuenzi[1], Delia Gheorghe[2], Sarah Bauermeister[3]
[1]University of Oxford, Psychiatry, Oxford, United Kingdom, [2]Transylvanian Institute of Neuroscience, Cluj-Napoca, Romania, [3]University of Oxford, Oxford, United Kingdom

Aims: Literature has shown the detrimental effects of the experience of early adversity on later-life mental health, brain, and cognition. However, these associations are complex, and the underlying mechanisms are not yet understood. Consequently, identifying how early adverse experiences impact mental health, brain, and cognition tackles the difficult question of the mechanisms. The mechanistic pathway needs to be investigated to promote healthy brain and cognitive aging by identifying and intervening on the risk and protective factors.
Methods: This study aims to investigate the effect of early adversities and the role of coping strategies and neuroticism on mental health, brain, and cognition. The UK Biobank dataset (N = 502,363, M_{age} = 58, SD_{age} = 8.09) including behavioral and imaging data was used and combined in a structural equation model (SEM).
Results: The results highlight different effects according to the early adversity experienced. Only physical neglect was associated with cognition and none of the early adversities have a direct effect on brain volume. However, significant mediations through some coping strategies were found between early adversity and cognition and between early adversity and brain volume.
Conclusions: The results found are in line with the literature findings showing associations between early adversity and mental health, brain, and cognition. Importantly, this study highlights the importance of personality traits and coping strategies used in these associations, showing that actively working on these coping strategies may buffer the negative impact of early adversity on mental health, brain, and cognition and promote healthy aging.

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SHIFT 01-573

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2 - 3 April 2025

DELIRIUM PREVALENCE ON WORLD DELIRIUM AWARENESS DAY IN AUSTRALIA

Gideon Caplan
Prince of Wales Hospital, Geriatric Medicine, Sydney, Australia

Aims: Objectives Delirium manifests with psychiatric symptoms during acute illness, causes increased mortality, dementia and costs, yet there are no licensed treatments for delirium. Delirium is frequently missed, particularly when not tested for. Australia has a unique system of Delirium Clinical Care Standards introduced in 2016 mandatory in all hospitals. The Standards mandate screening and testing for delirium, as well as policies for treatment and communication to patients and families about the implications of delirium. We examined whether these standards impact delirium detection rates.
Methods: Recent participation on 15th March 2023, in the World Delirium Awareness Day (WDAD) survey, the largest delirium survey to date, allows us to compare delirium incidence with other countries. The study was conducted as a single-day point prevalence study measuring delirium prevalence in the morning and evening across multiple hospitals in Australia. There was no funding for this survey.
Results: There were 204 participating wards from 30 hospitals across Australia. Written delirium policies were reported in 90.4% of Australian respondents compared to 66.8% internationally. Delirium policies were associated with higher rates of multiple non-pharmacological interventions, less pharmacological interventions, and more frequent delirium assessments. Delirium prevalence was detected in 15.8% of patients surveyed on WDAD in Australia. The most frequently used delirium assessment tool in Australia was the 4AT in 58% whereas internationally the CAM-ICU (20.1%) was used most frequently. In comparison, delirium was overall recorded internationally in 17.4% of patients but analysis by income showed the rate was 22.9% of patients in the non-high-income countries and 15.7% in the high-income group ($p<0.01$).
Conclusions: Delirium policies do not change detection rates but do affect treatment programs for patients with delirium.

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SHIFT 01-574

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2 - 3 April 2025

OPIOID USE AND RISK OF HOSPITALIZATION IN OLDER PEOPLE WITH DEMENTIA

Christina Jensen-Dahm[1], Janet Janbek[1], Thomas Laursen[2], Christane Gasse[3], Gunhild Waldemar[1]
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Aims: Older people with dementia are frequently prescribed opioids, but little is known about adverse events associated with opioids in this population. Thus, the aim was to investigate whether uses of opioids is associated with an increased risk of hospitalization in older people with dementia.
Methods: Matched cohort study using Danish nationwide registries. All Danish residents (≥65 years) diagnosed with dementia between 2008-2018 were included. Individuals with no opioid use in the year prior to dementia diagnosis (washout period) were included. Exposure was first redeemed opioid prescription after dementia diagnosis. Persons exposed to opioids were matched with up to two unexposed persons on age and gender. Outcome was all-cause 180-days hospitalization. Cox proportional hazards models compared rates of hospitalization within 180 days after the initiation of opioid treatment and adjusted for potential confounders.
Results: Forty-two percent (31,619/75,471) of older people with dementia redeemed an opioid prescription after diagnosis. Among exposed, 7,356 (23.3%) were hospitalized within 180 days, compared with 7,618 (12.1%) of unexposed, and opioid use was associated with a 4-fold risk of hospitalization (fully adjusted hazard ratio: 3.86 (95% CI, 3.72-4.01)), but 8-fold within the first 14 days ((7.77 (7.15-8.45)). Exposed were more often admitted due to fractures, infections, and cardiovascular events.
Conclusions: Our findings suggest that opioids are associated with an increased risk of hospitalization, but whether this is due to the opioid, the indication, or both needs to be clarified. Future studies should aim at identifying patients or treatment patterns associated with a particularly high risk of adverse events to support a risk–benefit assessment at an individual level.

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SHIFT 01-575

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2 - 3 April 2025

GENETIC COVARIANCE ANALYSIS IDENTIFIES TMEM106B AND ACE AS GENETIC LOCI SHARED BETWEEN ALZHEIMER'S DISEASE AND PRIMARY PSYCHIATRIC DISORDERS

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Aims: Objectives: Neuropsychiatric Symptoms (NPS) (e.g., aggression, psychosis, anxiety, apathy, depression, agitation, sleep disturbances, repetitive behaviors) occur in 85% of Alzheimer's Disease (AD) patients, and are associated with accelerated decline and greatly increased suffering of patients and their caregivers. Our understanding of the etiology of NPS in AD is inadequate, with treatments for NPS often being ineffective and associated with serious adverse effects.
Methods: Methods: To better characterize the genetic overlap between AD and major psychiatric disorders and identify potentially shared biological processes we conducted local genetic covariance analyses between AD and depression, and AD and schizophrenia using LAVA, capitalizing on the largest most recent GWAS summary statistics for these traits (AD: n=487,511; bipolar disorder: n=413,466; depression: n=1,154,267; schizophrenia: n=130,644). Identified overlapping genomic loci were followed up with finemapping and *in silico* functional analyses.
Results: Results: Local genetic covariance analyses identified four loci shared between AD and depression and five loci shared between AD and schizophrenia. Finemapping and *in silico* functional analyses at these loci pinpoint a missense variant in *TMEM106B* as a causative variant shared with depression, and a regulatory region variant in *ACE* as a causative variant shared with schizophrenia.*TMEM106B* is a lysosomal protein critical for clearance of misfolded proteins and *ACE* is the main component of the renin-angiotensin system (RAS) critical for blood pressure regulation and homeostasis, is located on the cellular membrane of neurons.
Conclusions: Conclusions: These findings support the notion of pleiotropic overlap between AD and depression and schizophrenia, respectively, and pinpoint *TMEM106B* and *ACE* as shared genetic drivers. Further functional characterization of these loci and molecular pathways will be critical to characterize the specific underlying biological processes.

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SHIFT 01-578

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

FUNCTIONAL ALTERATIONS IN PD-MCI AND PD-NC: CLINICAL CORRELATES WITH ZFALFF IN RESTING-STATE FMRI

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Aims: This study investigates functional brain alterations in Parkinson's disease patients with mild cognitive impairment (PD-MCI) and without mild cognitive impairment (PD-NC) using the fractional amplitude of low-frequency fluctuations (zfALFF) in resting-state fMRI. The aim is to explore how these functional changes correlate with disease severity, medication use, and cognitive performance.
Methods: A total of 30 participants were included: 18 with PD-MCI and 12 with PD-NC. Resting-state fMRI data were processed to compute zfALFF values across various brain regions. Clinical variables, including disease duration (DDX), Levodopa Equivalent Daily Dose (LEDD), and UPDRS ON scores, were statistically correlated with zfALFF values. Neuropsychological assessments were conducted to examine the relationship between zfALFF and cognitive performance in domains such as attention, executive functioning, memory, and language.
Results: Significant differences in zfALFF were observed between PD-MCI and PD-NC groups. In the PD-MCI group, zfALFF was positively correlated with LEDD, suggesting that higher medication dosages were associated with increased functional activity in specific brain regions. UPDRS ON scores showed distinct correlation patterns in PD-MCI and PD-NC, indicating varying functional alterations. Additionally, neuropsychological variables revealed different correlations with zfALFF, particularly in cognitive domains like attention and executive functioning, reflecting the neural basis of cognitive impairment in Parkinson's disease.
Conclusions: This study demonstrates that zfALFF, as a measure of resting-state functional activity, shows distinct patterns of correlation with clinical and neuropsychological variables in PD-MCI and PD-NC. These findings emphasize the role of functional connectivity alterations in cognitive decline in Parkinson's disease and suggest the potential of zfALFF as a biomarker for disease progression.

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SHIFT 01-579

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

PREDICTING COGNITIVE AND PSYCHIATRIC SYMPTOMS FROM BLOOD-BASED BIOMARKERS IN A HETEROGENEOUS COHORT OF NEURODEGENERATIVE AND PSYCHIATRIC DISORDERS

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Aims: To examine the predictive capacity of blood-based biomarkers—neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and phosphorylated tau (p-tau217)—for cognitive and psychiatric symptoms in a well-characterised cohort with neurodegenerative and psychiatric disorders.
Methods: Participants (n=480) from the Markers in Neuropsychiatric Disorders (MiND) Study were categorised into three diagnostic groups: neurodegenerative disease (ND, n=90), primary psychiatric disorder (PPD, n=146), and controls (n=93). The presence of cognitive and/or psychiatric symptoms was coded for participants in the ND and PPD groups. Plasma levels of NfL, GFAP, and p-tau217 were analysed for all participants, and log-transformed values were used in analyses. Logistic regression models controlled for age and sex.
Results: NfL levels significantly predicted cognitive symptoms (OR=2.32, p=0.03), and GFAP levels predicted psychiatric symptoms (OR=3.87, p=0.01) across the entire sample. In the PPD group, GFAP predicted both cognitive (OR=13.40, p=0.03) and psychiatric symptoms (OR=236.99, p<0.001). In the ND group, GFAP predicted psychiatric symptoms only (OR=8.38, p=0.03). There were significant differences between diagnostic groups in the presence of cognitive symptoms (χ^2=101.18, p<.001) and psychiatric symptoms (χ^2=67.46, p<.001). NfL, GFAP and p-tau217 levels significantly differed between participants with and without cognitive symptoms (p=0.002, p=0.002, p<0.001), but no significant differences were observed for psychiatric symptoms (all p>0.05).
Conclusions: Blood-based biomarkers, particularly NfL and GFAP, can predict the presence of cognitive and psychiatric symptoms in both ND and PPD, and meaningful differences in symptom profiles were observed across the PPD, ND, and control groups. The strong association between GFAP and psychiatric symptoms highlights its potential role in clinical assessment and underscores the need for further investigation into these biomarkers as tools for early diagnosis, intervention, and prognosis.

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SHIFT 01-581

On-Demand Oral Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2 - 3 April 2025

DIETARY SUPPLEMENTATION WITH PANAX QUINQUEFOLIUS ENHANCES SYNAPTIC RESILIENCE AND MODULATES PROTEOSTASIS IN AGE-RELATED COGNITIVE DECLINE

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Aims: Age-related synaptic decline and lysosomal dysfunction contribute to cognitive impairments. This study aimed to test the hypothesis that dietary agents, such as Panax quinquefolius (Cereboost), enhance synaptic resilience and offset age-related cognitive decline by activating the autophagy-lysosomal pathway, specifically targeting the lysosomal enzyme cathepsin B (CatB).
Methods: Hippocampal explants from rodent brains were treated with Cereboost to assess its effects on CatB activation and synaptic integrity. Synaptic integrity was measured by pre- and post-synaptic markers, and lysosomal function was evaluated by monitoring CatB activity. Proteostasis stress was induced using the lysosomal inhibitor chloroquine, allowing for assessment of synaptic resilience. In a preclinical model, aged rodents were supplemented with Cereboost for 6 weeks, followed by cognitive performance tests. Post-testing, brain samples were submitted for unbiased LC-MS proteomics to assess global protein expression changes.
Results: Cereboost treatment significantly enhanced active CatB isoform levels in hippocampal explants and improved pre- and post-synaptic markers in a correlative manner. This activation of the CatB autophagy-lysosomal pathway protected synaptic integrity during lysosomal stress induced by chloroquine. Additionally, 6 weeks of Cereboost supplementation in aged rodents prevented age-related cognitive decline. Unbiased LC-MS proteomics revealed significant modulation of proteins involved in synaptic function and autophagy pathways, further supporting Cereboost's neuroprotective effects.
Conclusions: Cereboost promotes synaptic resilience and cognitive function by modulating the autophagy-lysosomal pathway and enhancing CatB activity. Proteomic analysis suggests a broad impact on age-related pathways. These findings highlight dietary agents like Cereboost as potential therapeutic strategies for age-related cognitive decline and neurodegenerative disorders.

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SHIFT 01-584

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

PROVEN TREATMENT SUSCEPTIBLE TAU-P301S MOUSE MODEL FOR PRECLINICAL PROOF OF CONCEPT STUDIES

Sofie Carmans, Wannes Dejonckheere, Tom Cornelissen
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Aims: Tauopathies, including Alzheimer's disease (AD) and frontotemporal dementia (FTD), are driven by the accumulation of hyperphosphorylated tau, which leads to neurodegeneration. Here we aimed to comprehensively characterize the Tau[P301S] mouse model. The objective was to evaluate the model's potential in reflecting tau-driven pathology and its suitability for preclinical therapeutic testing.
Methods: In the Tau[P301S] mouse model, tau hyperphosphorylation, neuronal dysfunction, and motor impairments were assessed. Key biomarkers, including NF-L, were monitored. Tau pathology was examined histologically in the cortex, spinal cord, hippocampus and brainstem. Behavioral phenotyping included long-term potentiation (LTP) and motor testing (rotarod and clasping assays). The impact of therapeutic interventions, including anti-tau antibodies and small molecule inhibitors, was evaluated to assess the model's responsiveness.
Results: Hyperphosphorylated tau was first detected in the cortex and spinal cord at 3–4 months of age, later appearing in the hippocampus and brainstem. LTP deficits were observed at 3.5 months, with motor impairments developing between 3.5 to 6 months. Clasping behavior emerged at 3.5 months and worsened progressively. In accordance, rotarod performance declined gradually from 4 months onwards, leading to almost complete motor failure by 5.5 months. Neuronal loss was prominent in the spinal cord, accompanied by increased astrocytosis and microgliosis. Treatment with anti-tau antibodies and small molecule inhibitors showed significant therapeutic effects.
Conclusions: The Tau[P301S] mouse model exhibits a strong correlation between tau hyperphosphorylation, motor impairments and neuroinflammation, making it a robust platform for preclinical studies. The consistent phenotype, along with measurable in vivo biomarkers, supports its use in testing potential disease-modifying therapies for tauopathies. The model effectively reflects human tau pathology and provides a reliable framework for evaluating therapeutic efficacy.

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SHIFT 01-585

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

MUTATION-DEPENDENT PHENOTYPE IN NOVEL HUMAN TAU KI MOUSE MODELS

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Aims: Several studies focusing on understanding the pathological mechanism of tauopathies employ overexpressing tau mouse models to enhance pathological aspects of disease. However, despite their utility, these lines come with several limitations, making it hard to distinguish between disease-related phenotypes from overexpression-associated artefacts.
Methods: Here, we propose the generation of novel human tau knock-in (MAPT KI) non-overexpressing physiologically relevant mouse models. Through base-editing, FTD-causing splice-shifting and exonic mutations were inserted
Results: These lines show an extremely interesting allele-specific pathological phenotype. Mouse lines with mutations that cause a shift in splicing show behavioural deficits which are associated with hyperphosphorylation of tau but modest higher order structure formation (monomers/small oligomers). In contrast, in a mouse line with an exonic mutation, tau is not hyperphosphorylated, but it is seed-competent and aggregated in fibrils. These differences are also detectable in plasma. Proteomic analysis has shown different functional pathways associated with the specific mutation-phenotypes of tau in these mice, one involved in synaptic loss and cytoskeletal remodelling, the other in autophagy and RNA metabolism. Crossing the MAPT KI mouse lines with APP-mutant NLGF line, induces an acceleration in the exonic-aggregation-prone mutation but not in the splice-shifting MAPT KI.
Conclusions: It would therefore appear that there are significant genotype:phenotype differences, linked to specific functional pathways, that diverge in the earliest stages of pathogenesis, leading to two different diseases, and that APP has an effect on specific forms of tau.

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SHIFT 01-586

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

A NOVEL, CONSTITUTIVE, MONOGENIC MOUSE MODEL OF TAUOPATHY OVEREXPRESSING P301L HUMAN TAU IN THE BRAIN

Matthew Hamm[1], Kevin Mcnaught Jr[2], Jessica Shubin[1], Emely Gazarov[1], Zachary Strickland[1], John Howard[1], Susan Fromholt[1], Guilian Xu[1], David Borchelt[1], Jada Lewis[1]
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Aims: Characterization of a novel model of tauopathy that constitutively overexpresses P301L human tau in the brain
Methods: Transgenic founders were generated via DNA pronuclear microinjection of a CamK2-tauP301L construct into murine zygotes. Brain tissue from the lead line, "cTau^{P301L}", was assessed biochemically and immunohistochemically for expression and biodistribution of tau. Brains were detergent-fractionated and immunoblotted with a tau antibody panel or sagittally sectioned and stained with 3,3'-diaminobenzidine-based immunohistochemistry and Gallyas silver staining.
Results: Immunoblotting tris-soluble fractions of cTau^{P301L} brains ranging 2-12 months of age revealed a steady level of total human tau expression across ages. Immunoblots with antibodies targeting disease-associated phospho-tau epitopes, including serine 396/404, revealed a significant increase in specific phospho-tau species in 12-month animals compared to 2-month animals. We performed similar immunoblots of detergent-insoluble cTau^{P301L} brain fractions with both total and phospho-tau antibodies. These revealed a paucity of insoluble tau in 2 and 4-month brains but a marked presence of insoluble tau in both 8 and 12-month cTau^{P301L} animals.
Immunohistochemical staining of cTau^{P301L} brain sections revealed an age-related accumulation of total-human and phospho-tau protein in the hippocampus, frontal cortex, and olfactory bulb. At 12 months of age, Gallyas silver staining revealed silver-positive neurofibrillary tangles in the same neuronal populations.
Conclusions: Our data indicate the constitutive "cTau^{P301L}" mouse stably expresses P301L human tau in the hippocampus and forebrain, resulting in age-dependent accumulation of tau in these brain regions. This data further indicates that the cTau^{P301L} model possesses a similar distribution of tau pathology as the commonly used, bigenic, rTg4510 mouse model of tauopathy. As a monogenic, constitutively-expressing model, the cTau^{P301L} represents a straightforward and potentially cheaper alternative for studying tau pathology *in vivo* than the bigenic rTg4510 line.

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SHIFT 01-587

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2 - 3 April 2025

MODELING STRUCTURAL AND FUNCTIONAL CONNECTOMICS WITH SPATIAL TRANSCRIPTOMICS IN A MOUSE MODEL OF TAUOPATHY

Elizabeth Hipskind[1], Lindsay Fadel[1], Steen Pedersen[2], Caitlyn Ortiz[2], Jonathan Romero[2], Md. Abul Hassan Samee[2], Robia Pautler[1,2]
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Aims: Functional connectivity is a measure of communication between brain regions. We investigated how tau pathology impacts structural and functional connectivity in the brain and cognitive decline over the course of tau accumulation. Furthermore, we link these to spatial transcriptomic changes to understand the underlying mechanisms of tauopathy.
Methods: We used the rTg4510 mouse model of tauopathy at 3-months (before tau tangles), 6-months (beginning of tangle deposition), and 10-months (tangles, some neurodegeneration). First, we assessed spatial learning and memory using Morris Water Maze. Next, we defined structural and functional connectivity using diffusion tensor imaging and resting-state functional MRI, respectively. We then conducted high resolution spatial transcriptomics. We will use a machine learning (ML) model to assess how tau-mediated structural and functional changes relate to learning and memory performance and gene expression.
Results: As reported, deficits in spatial learning and memory appeared in 3-month rTg4510 mice, even before tau tangle formation, and worsened in the 6- and 10-month groups. We observed increased FC (hyperconnectivity) at 3-months, while the 10-month group exhibits a mix of hypo(decreased)- and hyper-connectivity. At 10-months, we observed decreased white matter in the tau mice. We are currently identifying changes in spatial transcriptomics at different disease stages. We will use ML to define the relationships between learning and memory, transcriptomic data and structural and functional and structural connectivity to identify key contributors to tau-mediated cognitive decline.
Conclusions: This novel approach bridges the gap between brain function and structure and behavioral performance with a focus on functional brain connections that support memory across disease progression. Linking these changes with spatial transcriptomics will identify regional patterns of susceptibility and enhance our understanding of the neurobiological underpinnings of AD.

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SHIFT 01-590

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2 - 3 April 2025

BRAIN LIPID METABOLISM IS ALTERED IN TAUOPATHY MICE AND RESCUED BY APOE DEFICIENCY

Art Janssen[1], Sarah Vanherle[1], Manuel Gutiérrez De Ravé[1], Kirstin Boonen[1], Siebe Vlekken[1], Jana Hardy[1], Yanyan Wang[1], Ilie-Cosmin Stancu[1], Jeroen Bogie[2], Jerome Hendriks[2], Ilse Dewachter[1]
[1]Hasselt University, Biomed, Neuroscience, Diepenbeek, Belgium, [2]Hasselt University, Biomed, Immunology, Diepenbeek, Belgium

Aims: The most important risk factor for the development of late onset AD is ApoE, the major lipid transporter in the CNS. Recent reports of putative protective mutations within the ApoE gene suggest that delay of tau pathology and symptom onset by modulating ApoE function. Furthermore, putative protective mutant ApoE and ApoE isoforms are associated with alterations in lipid metabolism. Finally, as lipids exert vital (intra)cellular functions, in cellular membrane composition and signalling pathways crucial for dealing with pathological insult, we here study the relation between lipid metabolism and tau pathology and tau-induced neurodegeneration.
Methods: TauP301S (T+) mice were used in combination with ApoE KO mice. Immunohistochemical stainings and biochemical analyses were used to investigate AD pathology in these mouse models. Furthermore, lipidomic analysis was performed.
Results: T+ mice with ApoE deficiency (KO) show markedly reduced tau pathology, neurodegeneration and activated microglia, compared to T+ ApoE WT mice. Furthermore, changes in lipid metabolism between T+ ApoE KO and WT mice are observed. Further detailed lipidomic analysis showed vastly altered lipid profiles between WT and T+ ApoE WT but not between WT and T+ ApoE KO mice, showing a rescue-like effect. Phospholipids were among the most significantly altered lipid species, with phosphatidylinositides (PIs) being the most significant. The functional association between tau and PIs, including their pathways, has been further explored *in vitro* and *in vivo*.
Conclusions: ApoE deficiency rescues tau pathology within a tauopathy mouse model and induces a shift in lipid metabolism. Signalling phospholipids were among the most significantly altered species. These lipids play crucial roles in cellular signalling and thereby normal cell functioning, including tau phosphorylation. Here we explored the potential of this novel link and pathway for therapeutic intervention in tauopathies.

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SHIFT 01-596

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2 - 3 April 2025

AI-DRIVEN BRAIN CELL TYPE TRANSCRIPTOME UNVEILS MOLECULAR SIGNATURE OF ALZHEIMER'S RESILIENCE AND RESISTANCE

Eloïse Berson, Amalia Perna, Nima Aghaeepour, Thomas Montine
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Aims: Cell type-specific dissection of neurological disorders' molecular signatures is critical to decipher their complex underlying mechanisms and efficiently derive therapeutic targets. Single-cell technologies have led to key findings in mechanisms of brain diseases; however the partial transcriptional coverage coupled with the high cost and technical skills required have hindered its broad applicability and potential to unveil robust cell type-specific candidates.
Methods: Here we develop and validate an AI-based framework that enables low cost and large-scale cell type-specific investigation of comprehensive transcriptional program investigation of Alzheimer's disease (AD) subtypes. Our approach leverages the ability of the transformer model to digest a large volume data and learn a generalizable mapping, thereby restoring cell type-specific RNA profile from bulk expression. Notably, it allows the investigation of cell type-specific transcriptomic programs in complex and heterogeneous phenotypes such as resilience and resistance to AD.
Results: We identify astrocytes as the major cell mediator of cognitive resilience and excitatory neurons and oligodendrocyte progenitor cells as major cell types of brain resistance, with putative molecular candidates. Applied to optimally preserved mouse brain, we show the potential of our approach to restore whole tissue cell-type specific transcriptome offering a framework for unbiased investigation of whole brain cell transcriptional programs.
Conclusions: Emerging evidence highlights significant heterogeneity in aging and AD trajectories, highlighting the need to scale biological studies to reflect more accurately population diversity. Through Cellformer, we showcase the potential of AI to amplify diversity in population-level, high-density molecular research, making such needed studies more accessible and cost-effective.

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SHIFT 01-597

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2 - 3 April 2025

HIPPOCAMPAL ASTROCYTE MORPHOLOGY FOLLOWS AN UNEXPECTED TRAJECTORY WITH AGE IN A TRANSGENIC RODENT MODEL OF TAUOPATHY

Karine Cambon[1], Emma Augustin[1], Tatiana Vinasco-Sandoval[2], Miriam Riquelme-Perez[1], Mylène Gaudin[1], Gwenaëlle Aurégan[1], Julien Mitja[1], Sueva Bernier[1], Charlène Joséphine[1], Fanny Petit[1], Caroline Jan[1], Anne-Sophie Hérard[1], Marie-Claude Gaillard[1], Agathe Launay[3], Emilie Faivre[3], Luc Buee[3], David Blum[3], Alexis-Pierre Bemelmans[1], Gilles Bonvento[1]
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Aims: Individual protoplasmic astrocytes have very complex and diverse spongiform shapes. The morphological diversity of astrocytes is determined by the structural and functional interactions of the astrocyte with its microenvironment. When faced with pathological conditions, astrocytes reorganize their morphology. Yet, little is known about the astrocytic response in pure tauopathies and its evolution over time. Here, we aimed to investigate the consequences of a primary neuronal tau pathology on astrocytes fine morphology and at three stages of the disease using the transgenic Thy-Tau22 mouse model.
Methods: We developed a pipeline of analyses including 3D reconstruction of hippocampal tdTomato-labeled astrocytes via a PHP.eB adeno-associated virus, confocal microscopy, Imaris software morphometric analysis and an advanced statistical analysis.
Results: We first showed that hippocampal astrocytes in Thy-Tau22 mice progressively accumulate hyperphosphorylated tau with age.During normal ageing, the complexity of astrocytes morphology peaked at adulthood then declined. In contrast in Thy-Tau22 mice, tauopathy was associated with a simpler initial morphology followed by the appearance of a cluster of complex cells at the most advanced stage. Using principal components analysis and hierarchical clustering based on 10 morphological features, we were able to identify different astrocyte morphotypes whose relative proportion varies differently with age between WT and Thy-Tau22 mice. Interestingly, we revealed that a fraction of astrocytes with a complex morphology reemerges late in tauopathy-affected animals.
Conclusions: Our data highlight the concept of significant and reversible structural plasticity of astrocytes when faced with chronic pathological conditions.

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SHIFT 01-598

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2 - 3 April 2025

DECODING THE INTERCELLULAR SIGNALS DRIVING THE EMERGENCE OF AN ALZHEIMER-ASSOCIATED ASTROCYTE STATE

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Aims: Using a dataset of 1.65 M single-nucleus transcriptomes from the prefrontal cortex of 437 individuals, we previously identified specific microglial and astrocytic states that are enriched in concert along the trajectory to Alzheimer's Disease (AD). Causal modeling suggested that the frequency of a lipid-associated microglial state (Mic.13) mediates the transition from amyloid to tau pathologies, while a stress-response astrocyte state (Ast.10) mediates the effect of tau on cognitive decline via synaptic loss. The coordinated enrichment of these glial states suggests possible cell-cell communications underlying the AD cascade. Here, we aim to identify cell-cell signals that engender the Ast.10 state. Disrupting this cell-cell crosstalk to block astrocyte differentiation into Ast.10 may help prevent AD-associated cognitive impairment.
Methods: Using NicheNet, we inferred ligands that regulate the Ast.10 signature. We used partial least-squares regression to predict Ast.10 frequency across donors based on their prioritized ligands expression. To validate these ligands, we performed neighborhood analysis on Visium spatial transcriptomic profiles of human cortical tissues and an analysis of mouse data.
Results: We identified 13 ligands that are highly predictive of Ast.10 frequency in the cortex and replicated the results in an additional 183 brains. Spatial transcriptomic data revealed that the prioritized ligands in the immediate neighborhood (but not random locations) significantly correlate with Ast.10 signature, to a much higher degree than with other astrocyte states. Genetic ablation of top receptor PLXNB1 in mice reduces Ast.10 signature *in vivo*. Single-cell spatial validation using MERSCOPE, and *in vitro* perturbation are ongoing.
Conclusions: Our system-wide approach revealed cell-cell signals driving the pathologic Ast.10 state. We have validated one of these, PLXNB1, and highlight a new approach to evaluate our other prioritized ligand-receptor pairs as potential therapeutic targets against AD.

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SHIFT 01-599

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2 - 3 April 2025

TAU-RELATED ATYPICAL PARKINSONISMS ARE DISTINGUISHED BY IRON DYSREGULATION IN DISTINCT CELL POPULATIONS

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Aims: Atypical Parkinsonisms include 4-repeat tauopathies such as Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD). These diseases neuropathologically differ by the structure and deposition patterns of tau filaments but are also vastly heterogenous, including cases with atypical distribution of tau pathology that altogether lack an etiological understanding. We explore cell type-specific dysregulation of iron homeostasis as a possible pathological feature distinguishing these tauopathies.
Methods: Using a unique histology method which combines DAB-enhanced Perl's iron staining with immunohistochemistry, we evaluated pathological iron deposition in tau (anti-AT8) -affected and -unaffected cell types (MAPT+neurons, GFAP+astrocytes, HLA-DR+microglia, TPPP/P25+oligodendrocytes) in early-affected subcortical and cortex regions of 13 PSP and 5 CBD post-mortem human brains. Gene expression profiles of iron-loading cell population are evaluated using spatial transcriptomics.
Results: Iron accumulation was not observed in the early-affected frontal cortex of CBD cases. In vulnerable subcortical nuclei, iron accumulated in microglia and did not co-localize with tau. PSP cases showed two distinct patterns of pathological iron accumulation in early subcortical regions: astrocytic-predominant deposition with and without neuronal involvement. 7 cases without neuronal deposition showed classical neuropathological presentation of PSP tau pathology. Some PSP cases with occasional or equivocal tau-positive tufted astrocytes in the basal ganglia – including those presenting with pallido-nigro-luysial atrophy (PNLA) - showed greater microglial iron burden and unusual neuronal deposition. In PSP frontal cortex, iron deposition was found in concomitant aging-related tau astrogliopathy (ARTAG)-tau-positive astrocytes. Transcriptomic analysis of strategic astrocytes corroborate our disease-related observations.
Conclusions: We reveal distinct cellular iron dysregulation profiles associated with disease-specific deposition of tau, regardless of overlapping involvement of anatomical regions. Our findings suggest a novel pathological variant that distinguish different phenotypes of tau-related atypical Parkinsonisms and provide insight into differing underlying pathomechanisms.

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SHIFT 01-608

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

HYPOCHLOROUS ACID MODIFICATION OF EX VIVO TAU SEEDS SUBSTANTIALLY REDUCES SEEDING CAPACITY

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Aims: Despite evidence suggesting near ubiquitous presence of tau assemblies capable of self-propagation (tau seeds) in aged populations (Manca & Standke, 2023), specific processes leading to neuroinflammation/neurotoxicity remain unresolved. Recently, neutrophils have been examined as an example of cells which may infiltrate the brain parenchyma during neuroinflammatory events and produce significant amounts of reactive oxygen species (ROS). Utilizing Alzheimer's disease neuropathologic changes (ADNC) and primary age-related tauopathy (PART) cases, we investigated how hypochlorous acid (HOCl), the primary ROS generated by activated neutrophils, production relates to tau exposure, and how it affects pathologically relevant tau posttranslational modifications and seeding activities.
Methods: We utilized an ultrasensitive 3R/4R tau selective real-time quaking-induced conversion (RT-QuIC) assay coupled with primary human tissue and cells, longitudinal clinical assessments, immunoblotting, negative stain EM, flow cytometry, and ROS detection assays to compare the effects of early and late-stage ADNC and PART derived-tau on neutrophils and identify modifications by HOCl.
Results: Tau seeding activity is significantly reduced or ablated by incubation with HOCl solutions, yet some seeding activity in ADNC cases persisted even after 60-minute incubations (though reduced by 100-1000-fold). All cases exhibit modification of highly ordered insoluble tau species. Additionally, ex vivo tau seeds increased normal human neutrophil ROS production by 3-7-fold during co-stimulation with opsonized zymosan (initiator of phagocytosis and ROS) compared to stimulation with opsonized zymosan alone.
Conclusions: Our findings suggest biochemically distinct neocortical tau seeds marking differential pathological processes instigate, and are affected by, increased neutrophil ROS production, with evidence of divergent outcomes of HOCl exposure between PART and ADNC cases.

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SHIFT 01-609

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2 - 3 April 2025

A SINGLE-CELL ATLAS OF A HIBERNATING BRAIN REVEALS SIGNATURES OF ALZHEIMER'S DISEASE IN GLIA

Pablo Largo-Barrientos[1], Roman Praschberger[2], Gonzalo León-Espinosa[3], Suresh Poovathingal[1], Kristofer Davie[1], Patrik Verstreken[1]
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Aims: Hibernation demands rapid brain adaptations, involving cycles of reduced metabolic rate during torpor, followed by brief periods of arousal. Previous studies link hibernation to Tau hyperphosphorylation and synapse loss, but a mechanistic connection to Alzheimer's disease (AD) remains unclear. We aimed to determine whether there are common gene expression patterns across the different cell types in the hippocampus of hibernating animals (golden hamsters) and AD patients.
Methods: We induced hibernation in golden hamsters by placing them in a hibernaculum, a controlled environment that progressively reduced the temperature (from 20 to 4°C) and light hours (from 12 to 0). We euthanized animals in the three stages of the hibernation cycle (euthermic=control, torpor and arousal) and dissected the hippocampus. We performed single-nucleus RNA sequencing to reveal the transcriptome of around 100,000 cells and generated the first single-cell resolution atlas of a hibernating animal. We used different bioinformatic strategies to compare our dataset with previously published single-cell datasets from AD patients and animal models.
Results: We unveiled large transcriptional shifts across the hibernation cycle in all cell types, especially glia. Common transcriptional changes in vesicle trafficking, mitochondrial and ribosomal genes are observed in all different cell types. In addition, hibernation triggers an inflammatory-like response in astrocytes and microglia that resembles cell states observed in AD, despite the absence of Aβ-accumulation and neurodegeneration.
Conclusions: Our findings reveal complex brain transformations that help preserve vital functions under extreme conditions and they suggest that early cellular changes in AD may be a natural adaptive protective process.

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SHIFT 01-612

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS
2 - 3 April 2025

RECONSTITUTING THE UBIQUITINATION OF TAU FIBRILS FROM ALZHEIMER'S DISEASE BRAIN TISSUE

Luca Ferrari, Max Schmid, Sascha Martens
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Aims: Tau fibrils found in Alzheimer's Disease are modified post-translationally with ubiquitin, a key regulator of the proteostasis network. This network plays a crucial role in removing protein aggregates and is therefore of great therapeutic interest. We set out to discover how the ubiquitination machinery targets Tau fibrils, and how this targeting impacts proteostasis processing.
Methods: We leverage a reconstitution approach to understand how ubiquitin can be covalently attached to Tau fibrils. We first obtain Tau tangles from *postmortem* human brains diagnosed with Alzheimer's. Our approach allows us to circumvent limitations associated with *in vitro* generated Tau fibrils, lacking disease-specific molecular folds and post-translational modifications. We then dissect the interaction of Tau aggregates with the ubiquitination machinery, to understand the set of biochemical reactions that lead to Tau ubiquitination.
Results: We identified Tau fibril-specific E3 ligases, key enzymes of the ubiquitination machinery responsible for target recognition during ubiquitination. We proceeded with a detailed mapping of the interaction between E3 ligases and Tau tangles, highlighting a role of ubiquitin in further recruiting the ubiquitination machinery. We are currently dissecting whether the interaction of E3 ligases is productive (thus resulting in the ubiquitination of Tau tangles) or unproductive. Finally, we are connecting our reconstituted systems with the autophagy machinery and other components of the proteostasis network, to understand how E3 ligases impact Tau fibrils recognition by these systems.
Conclusions: We previously showed that Tau fibrils ubiquitin load is not sufficient to recruit a functional autophagy machinery (Ferrari et al 2024, Science Advances). Our findings pave the way to therapeutically enhance Tau fibrils ubiquitination and consequent removal by the proteostasis network, including autophagy, the proteasome and disaggregases.

SHIFT 01-613

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS
2 - 3 April 2025

STRUCTURES OF LRP2 REVEAL A MOLECULAR MACHINE FOR ENDOCYTOSIS

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Aims: The low-density lipoprotein (LDL) receptor-related protein 2 (LRP2 or megalin) is representative of the phylogenetically conserved subfamily of giant LDL receptor-related proteins, which function in endocytosis and are implicated in diseases of the kidney and brain.
Methods: Here, we report high-resolution cryoelectron microscopy structures of LRP2 isolated from mouse kidney, at extracellular and endosomal pH.
Results: The structures reveal LRP2 to be a molecular machine that adopts a conformation for ligand binding at the cell surface and for ligand shedding in the endosome. LRP2 forms a homodimer, the conformational transformation of which is governed by pH-sensitive sites at both homodimer and intra-protomer interfaces. A subset of LRP2 deleterious missense variants in humans appears to impair homodimer assembly.
Conclusions: These observations lay the foundation for further understanding the function and mechanism of LDL receptors and implicate homodimerization as a conserved feature of the LRP receptor subfamily.

SHIFT 01-614

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
2 - 3 April 2025

LIVER DERIVED FGF21 CONTRIBUTES TO PROTECTION AGAINST ALZHEIMER'S DISEASE PATHOGENESIS

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Aims: Fibroblast growth factor 21 (FGF21), a hepatokine involved in metabolic regulation, is reported to confer neuroprotection in animal and cellular models of Alzheimer's disease (AD). We have shown that toxicant activation of the aryl hydrocarbon receptor (AhR), a well-studied sensor of environmental toxicants, results in suppression of FGF21 expression. These observations suggest the existence of a mechanistic link between exposures to toxicants, the liver AhR, FGF21, and AD pathology, and provide a rationale for how environmental toxicants might contribute to the onset of AD and related cognitive deficits. Our **main research goal** is to characterize the involvement of AhR-FGF21 axis towards AD pathogenesis and to establish that liver-derived FGF21 can be neuroprotective of AD pathology, as well as evaluate the sensitivity of the AhR-FGF21-AD axis to prevalent and persistent environmental toxicants.
Methods: 7-8 months old AhRiCKO mice were used for bilateral ICV injection of tau aggregates. Cognitive function was assessed 1 month post-injection. Neuroprotection against spread of tau pathology was assessed by Immunohistochemical analysis using AT8 and other tau antibodies, as well as biochemical analysis. Synaptic function was analyzed by electrophysiology.
Results: Our behavioral data show significant improvement in cognitive function of AhRiCKO mice exposed to ICV injection of tau aggregates compared to control mice. This improvement in cognitive functions coincided with reduction of tau pathology in the brains of these mice.
Conclusions: Our findings provide a novel mechanistic link between liver AhR biology, FGF21 expression, and AD pathology and show how FGF21 can be neuroprotective against AD and related neurodegeneration, improve cognitive functions and halt the progression of the disease. Our data are critical for future mechanistic investigations designed to advance the AD field and potentially point to promising new therapeutic strategies.

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SHIFT 01-617

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS & PLASTICITY
2 - 3 April 2025

ISOFORM-SPECIFIC TAU DRIVES DISTINCT NEURAL DISRUPTIONS AND BEHAVIORS IN BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

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Aims: This study aimed to investigate the underlying pathophysiology of behavioral variant frontotemporal dementia (bvFTD), focusing on the role of 4R and 3R tau accumulation in neuronal dysfunction and their correlation with bvFTD-like clinical phenotypes.
Methods: A previously validated lentiviral tool was used to express human wild-type 4R and 3R tau in the medial ventral prefrontal cortex (mvPFC) of 8-week-old male wild-type C57BL/6 mice via stereotaxic injection. Three months post-injection, we evaluated the effects of tau accumulation on behavior, brain histology, brain morphometry (T1 MRI), and connectivity (DTI).
Results: Three months after stereotaxic injection, hyperphosphorylated 3R and 4R tau were significantly expressed in the medial ventral prefrontal cortex (mvPFC) of C57BL/6 mice. Both isoforms induced a significant reduction in parvalbumin (PV) expression, reflecting altered inhibitory transmission, with no effect on GAD synthesis. However, 4R tau selectively impaired mvPFC projections to the amygdala and CA1, with significant impact on synaptic density. Behaviorally, these changes induced distinct bvFTD-like phenotypes, with 4R tau specifically leading to significant spatial memory impairments and increased disinhibition. Both isoforms, however, similarly affected goal-achievement behavior.
Conclusions: These results show that while 4R and 3R tau isoforms both affect inhibitory transmission, 4R tau uniquely disrupts neural connectivity and synaptic density mainly in mvPFC projections to the amygdala and CA1. This differential tau pathology induces distinct bvFTD-like behaviors, with 4R tau having a significant impact on spatial memory and disinhibition. These findings provide important insights into how tau isoforms drive bvFTD pathology and highlight the role of the medial prefrontal cortex and its projections in the core underlying neuropathology of the bvFTD phenotype.

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SHIFT 01-619

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
2 - 3 April 2025

QUANTITATIVE AUTORADIOGRAPHY OF ALZHEIMER'S DISEASE-RELATED TAU DEPOSITION IN PARIETAL CORTEX OF MEN AND WOMEN

Anat Biegon[1], Vanessa Carter[1], Jasbeer Dhawan[1], Sarah Murphy[2], Aviram Nessim[2], Thomas Beach[3], Geidy Serrano[3], Erin Sundermann[4], Maricedes Acosta-Martinez[2]
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Aims: Measure the density of tau deposits in parietal cortex sections obtained from men and women who died with Alzheimer's disease (AD), mild cognitive impairment (MCI) and cognitively normal controls (CN).
Methods: Frozen postmortem samples of parietal cortex were obtained from 104 men and women who died with AD, MCI or CN (n=16-18/sex/diagnosis, matched for age). Cryostat sections of the samples were processed for quantitative autoradiography with the tau-specific radiotracer [^{18}F]T807, using published methodology. Labeled sections and accompanying standards were exposed to radiation sensitive film for one hour and images analyzed with FIJI software. Results were analyzed by 2 way ANOVA (sex x diagnosis) using SPSS.
Results: High density of tau deposits (>3SD relative to CN) was evident in 75% of women and 43% of men with AD. Statistical analysis of image data revealed a highly significant main effect of diagnosis ($p=0.001$) as well as a significant sex X diagnosis interaction ($p=0.016$). Tau density was significantly higher in the parietal cortical grey matter of the AD group relative to the CN ($p=0.001$) and MCI ($p=0.002$) groups, which did not differ from each other. Subsequent one-way ANOVA stratified by sex showed a highly significant ($p=0.005$) effect of diagnosis in women, driven by a large (>50 fold) increase in tau density in AD relative to both MCI and CN ($p=0.004$), which did not differ from each other. In men, the effect of diagnosis was more modest and did not reach statistical significance ($p=0.2$).
Conclusions: Women with an antemortem diagnosis of AD demonstrate higher levels and frequency of tau deposition in the parietal cortex relative to men with the same diagnosis.

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SHIFT 01-620

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
2 - 3 April 2025

AD-RELATED CHANGES IN AMYLOID, TAU, NEUROINFLAMMATION AND NMDA RECEPTOR MARKERS FOLLOW DISTINCT PATTERNS IN HIPPOCAMPAL AND CORTICAL REGIONS

Anat Biegon[1], Vanessa Carter[1], Jasbeer Dhawan[1], Sarah Murphy[2], Aviram Nessim[2], Thomas Beach[3], Geidy Serrano[3], Erin Sundermann[4], Maricedes Acosta-Martinez[2]
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Aims: Measure the density of amyloid, tau, neuroinflammation and NMDA receptors in specific hippocampal and cortical regions among men and women who died with Alzheimer's disease (AD) or mild cognitive impairment (MCI) relative to cognitively normal controls (CN).
Methods: Frozen postmortem samples of hippocampus, entorhinal cortex and parietal cortex were obtained from 104 men and women who died with a clinical diagnosis of AD, MCI or CN (n=16-18/sex/diagnosis, matched for age). Cryostat sections were processed for quantitative autoradiography of amyloid, Tau, TSPO (neuroinflammation marker) and NMDA receptors using [^{3}H]PiB, [^{18}F]T807, [^{3}H]PK11195 and [^{3}H]MK801, respectively. All tracers were used at concentrations around Kd, utilizing published methodology. Images were analyzed with FIJI software. Absolute specific density was measured and ratios of AD and MCI groups over mean CN were calculated in the hippocampal CA1 field, dentate gyrus and subiculum, as well as in entorhinal and parietal cortex and compared by sex and diagnostic group.
Results: The rank order of AD-related increases in amyloid was parietal cortex > entorhinal cortex>>all regions of the hippocampus. Tau increases followed the order entorhinal cortex>parietal cortex>subiculum>CA1>dentate. TSPO increased in subiculum>CA1≥dentate≥entorhinal cortex>parietal cortex. Yet another pattern was observed with the NMDA receptor, which decreased in density in AD in CA1>subiculum≥entorhinal cortex>parietal cortex and dentate gyrus. Effect sizes were generally larger in women but the regional distribution pattern was largely conserved in both sexes.
Conclusions: Different biomarkers associated with AD diagnosis and progression demonstrate anatomically distinct patterns of change in the hippocampus and cortex, suggesting differential regional vulnerability to different aspects of the disease onset and progression. The dentate gyrus was relatively resistant to changes in all four markers utilized in this study.

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SHIFT 01-621

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
2 - 3 April 2025

UNEXPECTEDLY HIGH FREQUENCY OF CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE) NEUROPATHOLOGICAL CHANGE IN A HOMELESS POPULATION

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Aims: The aim of our current study was to determine the prevalence of various tau pathologies in a specific population of 34 homeless individuals. Our previous research in this population had already demonstrated the presence of Lewy body type alpha-synucleinopathy, occurring at a frequency higher than the average reported in the literature.
Methods: We systematically evaluated various neocortical areas, the, hippocampus, amygdala, basal ganglia, thalamus, cerebellum, brainstem, as well as the cervical, thoracic, and lumbar sections of the spinal using immunohistochemistry for Tau (AT8), amyloid-β, p62, TDP-43, α-synuclein, and 3R/4R tau. In each case, we also assessed the presence of vascular pathology according to the VCING (Vascular cognitive impairment neuropathology guidelines) criteria.
Results: Alzheimer's disease pathology was confirmed in a total of 9 cases. However, unexpectedly, the neuropathological changes in 4 of our cases clearly met the diagnostic criteria for CTE, with an additional 13 cases showing pathology as suspected CTE. Furthermore, argyrophilic grain disease was identified in 4 cases. According to the VCING criteria, all 34 cases were categorized as low score.
Conclusions: CTE, which has garnered increasing attention among athletes of contact sports, was detected in a homeless population. Our findings contribute to the expansion of current knowledge on CTE and offer new perspectives on understanding the aetiopathogenesis of the disease.

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SHIFT 01-622

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
2 - 3 April 2025

ELUCIDATING THE ROLE OF ACUTE STRESS ON TAU KINETICS IN AN AWAKE AND BEHAVING MOUSE

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Aims: Recently, we published data exploring the stress response and how it impacts the production of Aß. That study found that male and female animals have differing responses to acute restraint stress, with female animals exhibiting a 50% increase immediately following stress, but male animals remaining relatively unchanged. This is due to the role of ß-arrestin in trafficking CRF receptor in male mice, but not female mice, leading to a sexual dimorphic stress response. The current study aims to explore the stress response in how it relates to tau.
Methods: These studies rely on in vivo microdialysis. Using large membrane probes, we can perfuse the ISF and collect tau from within the hippocampus rapidly. Samples obtained from in vivo microdialysis are then analyzed using a tau sandwich ELISA. Additionally, blood collected from animals is measured for corticosterone to determine stress levels via ELISA.
Results: We found that tau levels increase in both male and female animals in response to acute restraint stress, which suggests a separate mechanism is at play in this response, as opposed to the beta-arrestin pathway that was previous described. While both sexes show an increase in ISF tau in response to stress, females display higher increases compared to males.
Conclusions: Stress is one of the largest modifiable risk factors for AD, contributing to about 8% of disease risk. Understanding the impact stress has on a protein level is important for determining its role in increased risk for disease. While we have explored how Aß changes in response to stress, little has been done to examine how tau changes. These studies give an understanding of how stress interacts with the proteins of AD and how we can potentially impact them to limit disease risk.

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SHIFT 01-634

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2 - 3 April 2025

TRANSCRIPTION FACTOR AND TRANSCRIPTOME ALTERATIONS ASSOCIATED WITH NEURONAL TAU PATHOLOGY IN PRIMARY TAUOPATHY

Nils Briel[1,2], Viktoria Ruf[1], Paul Feyen[1,3], Günter Höglinger[3,4,5], Felix Struebing[1,3], Jochen Herms[1,3,5]
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Aims: Previous studies on the genetic architecture of progressive supranuclear palsy (PSP) have highlighted the enrichment of glial and neuronal genetic risk loci . Furthermore, we have identified systems-level epigenetic alterations in protein degradation pathways in excitatory neurons in primary tauopathies (Briel et al. 2022). In this study, we aimed to identify potential molecular drivers of neurofibrillary tangle burden in PSP.
Methods: We generated unpaired single-nucleus ATAC-seq and RNA-seq datasets from post-mortem frontal cortex samples from a cohort of 8 PSP and 8 control cases. Over 55,000 (ATAC) and 83,000 (RNA) nuclei passed quality control. Using the *Seurat* and *chromVAR* frameworks, we conducted reference-based cell type annotation, differential gene expression (DGE) analysis, transcription factor motif enrichment (DTF) analysis, and constructed weighted gene co-expression networks using *hdWGCNA*. We associated gene networks with neuronal tau pathology using *psupertime*, which incorporates molecular features as predictors and ordinal semi-quantitative assessment of tau burden as outcomes.
Results: Pseudobulk DGE analysis revealed the most pronounced transcriptional alterations in excitatory neurons, astrocytes, and oligodendrocytes. In excitatory deep-layer neurons, the top enriched gene ontology terms were related to protein folding and RNA splicing, and were paralleled by deregulation of ROR-family TFs and STAT2. DTF analysis revealed the most dysregulated TFs in inhibitory neurons, followed by excitatory neurons and oligodendrocytes. The cross-sectional increments in neuronal tau burden were paralleled by sequences of inflammatory, protein degradation, and cellular stress responses.
Conclusions: Our analysis demonstrates a distinct divergence in the extent of DGE and DTF across cell types in PSP, and further describes a presumed pathogenic trajectory of neuronal tau deposition in this primary tauopathy. Candidate prioritization from this exploratory study can aid in focusing on disease-relevant pathways, but warrants further functional validation.

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SHIFT 01-635

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2 - 3 April 2025

PROGNOSTIC COVARIATE ADJUSTMENT USING PD COURSE MAP IN THE MOVES-PD STUDY

Nicolas Beaume[1], Stanley Durrelman[1], Graziella Mangin-Laignel[1], Adeebah Adams[2], Vincent Thuillier[3], Pascal Minini[3], Catherine Coulouvrat[3], Judith Peterschmitt[4]
[1]Qairnel, Paris, France, [2]Sanofi, Midrand, South Africa, [3]Sanofi, Gentilly, France, [4]Sanofi, Cambridge, United States of America

Aims: To evaluate the increase in statistical power achieved by prognostic covariate adjustment in a post-hoc analysis of the MOVES-PD[a] phase 2 trial, which assessed venglustat in GBA1-associated Parkinson's disease.
Methods: We employed PD Course Map[b,c], a digital twin technology, to predict the trajectory of the primary endpoint (MDS-UPDRS II+III) using screening and baseline data from MOVES-PD participants. Two prognostic covariates were derived: the predicted primary outcome (PPO, i.e. predicted change of the endpoint from baseline) and the Parkinsonian Age at baseline, an estimated time-index in the disease course. The primary outcome was analysed both with and without these scores as covariates.
Results: Using prognostic scores alongside the pre-specified covariates (primary endpoint at baseline, MoCA at baseline, LEDD at baseline, GBA mutation severity) resulted in a 0.38 point reduction in the confidence interval of the treatment effect for PPO and 0.45 for Parkinsonian Age. This adjustment results in a 10.74% (resp. 10.6%) reduction of the required sample size for a hypothetical Phase 3 trial compared to relying solely on the original covariates.
Conclusions: Regulatory agencies recognize prognostic covariate adjustment as a valid method to enhance statistical power. Our findings demonstrate that prognostic covariates derived from PD Course Map reduced the variance of the outcome in the MOVES-PD data, resulting in improved confidence intervals for the interpretation of the phase 2 data. Variance reduction would translate in lower sample size in future trials. These results support the utility of PD Course Map in optimizing the design of clinical trials in Parkinson's disease. This study was funded by Sanofi. References: [a]Giladi N et al. Lancet Neurol. 22 (2023) [b]Maheux E, et al. Nat Commun. 14 (2023) [c]Couronné R. et al. Mov. Disord. 35 (2020)

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TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2 - 3 April 2025

PREDICTION-POWERED CLINICAL TRIAL: A NEW APPROACH FOR INCREASING POWER IN TRIALS ASSESSED IN THE MOVES-PD STUDY

Stanley Durrelman[1], Pierre-Emmanuel Poulet[1], Graziella Mangin-Laignel[1], Nicolas Beaume[1], Bruno Jedynak[2], Adeebah Adams[3], Pascal Minini[4], Vincent Thuillier[4], Catherine Coulouvrat[4], Judith Peterschmitt[5]
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Aims: To apply a new method[a] using digital twins to estimate treatment effects called prediction-powered clinical trials (PPCT) a on MOVES-PD study[b] data. To assess the resulting reduction of the variance of the outcome.
Methods: We used PD Course Map[c,d], a digital twin technology to forecast the progression of the primary outcome (MDS-UPDRS Part II+III) from the baseline data of each participant in the MOVES-PD study. We used these predictions as an artificial comparative group for both the placebo and treated arms. We computed a treatment estimate derived from the prediction-power inference, which is proven to be asymptotically unbiased and with lower variance than the classical estimates. We compared the empirical results with the average treatment effect with or without the predicted outcome as a prognostic covariate as an alternative way increase power in trials with predictions.
Results: Both PPCT and prognostic covariate adjustment outperformed the classical treatment effect, with similar performance as expected from the theory. The usual approach yields a treatment effect of 2.88 with a variance of 3.89, while PPCT (resp. covariate adjustment) yielded a treatment effect of 2.89 (resp. 2.89) with a variance of 3.64 (resp. 3.59).
Conclusions: The empirical evaluation of PPCT confirmed the theoretical properties of this new estimator. Whereas it has similar performance as covariate adjustment for continuous outcomes, PPCT overcomes the risks of covariate adjustment in Cox models that were raised by the regulators. Therefore, it provides a promising approach to increase power in trials with time-to-event outcomes. This study was funded by Sanofi. References: [a]Angelopoulos AN. et al. Science 382 (2023) [b]Giladi N et al. Lancet Neurol. 22 (2023). [c]Maheux E, et al. Nat Commun. 14(2023) [d]Couronné R. et al. Mov Disord. 35 (2020)

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SHIFT 01-639

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2 - 3 April 2025

COMPARATIVE GENETIC ANALYSIS OF ALZHEIMER DISEASE IN WEST AND EAST AFRICA: INSIGHTS FROM THE READD-ADSP

Rufus Akinyemi[1], Farid Rajabli[2], Motunrayo Coker[1], Scott Kyle[2], Kazeem Akinwande[1], Larry Adams[2], Samuel Diala[1], Patrice Whitehead[2], Mayowa Ogunronbi[1], Kara Hamilton-Nelson[2], Albertino Damasceno[3], Andrew Zaman[2], Joshua Akinyemi[4], Yared Zewde[5], Gary Beecham[6], Biniyam Ayele[7], Allison Caban-Holt[8], David Ndetei[9], Anthony Griswold[2], Fred Sarfo[10], Susan Blanton[2], Albert Akpalu[11], Michael Cuccaro[2], Kolawole Wahab[12], Katalina Mcinerney[13], Reginald Obiako[14], Olusegun Baiyewu[15], Pedro Mena[2], Njideka Okubadejo[16], Izri Martinez[2], Adesola Ogunniyi[17], Brian Kunkle[2], Raj Kalaria[18], Jeffery Vance[2], Christiane Reitz[19], Giuseppe Tosto[20], Scott William[21], William Bush[22], Jonathan Haines[23], Goldie Byrd[8], Margaret Pericak-Vance[2]
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Aims: The "Recruitment and Retention for Alzheimer's Disease Diversity Genetic Cohorts in the ADSP (READD-ADSP)" is creating a resource aimed at increasing ancestral diversity in AD studies to analyze the genetic architecture of AD across various populations. READD-ADSP is a collaboration between four US sites and partners with ten countries in Africa through the Africa Dementia Consortium (AfDC). The goal is to characterize AD genetic factors in diverse populations, including African Americans (AA), Hispanic/Latinos in the US, and Africans. In this preliminary study, we explored known AD loci by whole

genome sequencing (WGS) individuals from five countries in Africa.
Methods: We performed combined and stratified (West and East Africa) association analysis on WGSed 191 AD and 208 cognitively unimpaired controls from West (Nigeria, Ghana) and East (Kenya, Ethiopia, Mozambique) Africa. We employed mixed-model regression approach (SAIGE) where we controlled for age, sex, population substructure (PC1:3), and relatedness. We investigated 86 known AD index markers from non-Hispanic White (NHW) (Bellenguez et al.2022) and AA (Ray et al.2024) GWA studies.
Results: We replicated four index markers in combined analysis: *APOEe4* (OR=2.4;CI:1.8-3.3;p=1.5x10^{-8}), ABCA7 (rs12151021;OR=1.5;CI:1.1-2.0;pv=0.01), *BCKDK* (rs889555;OR=0.7;CI:0.5-0.9;pv=0.01), and SPPL2A (rs8025980;OR=0.7;CI:0.5-1.0;pv=0.03). Stratification by West and East African samples showed regional differences in alleles risk significance, notably with *APOEe2* being significantly protective in West Africa(p=0.02), but not in East Africa(p=0.5).
Conclusions: Our findings demonstrate an initial study of generalization of known genetic risk loci for AD in African populations, highlighting genetic variations between West and East Africa. The significant association of the *APOEe4* allele confirms its role in AD risk across Africa, while larger sample sizes are needed to elucidate the role of *APOE*e2 across African populations. Data collection is ongoing across the AfDC, and updated results will be presented.

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SHIFT 01-640

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2 - 3 April 2025

SOCIAL DETERMINANTS OF HEALTH IN PEOPLE WITH ALZHEIMER´S DISEASE FROM PERU, STUDY NESTED IN THE PERUVIAN ALZHEIMER DISEASE INITIATIVE (PEADI)

Maryenela Illanes-Manrique[1,2,3], Syntia Laos-Mejia[4], Pilar Giron-Davila[1], Midiam Silva-Bullon[2], Larry Adams[5,6], Sheila Castro-Suarez[3,7], Julia Rios-Pinto[8], Pedro Mena[6], Elison Sarapura-Castro[2], Farid Rajabli[5,6], Ivan Cornejo-Herrera[9], Katalina Mcinerney[10], Michael Cuccaro[5,6], Angel Medina-Colque[11], Jeffery Vance[5,6], Koni Mejia[12,13], Edward Ochoa-Valle[14], Serggio Lanata[15], Azizi Seixas[16], Margaret Pericak-Vance[5,6], Mario Cornejo-Olivas[1,2]
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Aims: Social, behavioral, and environmental determinants of health (SDOH), such as access to and quality of education and healthcare, and socioeconomic factors, influence health outcomes, including dementia. We aim to identify the main SDOH associated with Alzheimer's disease (AD) by comparing AD cases to cognitively unimpaired (CU) individuals in the PeADI study.
Methods: The Social Determinants of Brain Health Questionnaire (SDOBH-Q) underwent expert review by local and international neurologists/psychiatrists and local linguistic adaptation. We administer the revised questionnaire to over 100 AD cases and 100 CU individuals from an ongoing genetic study of AD (PeADI) in Peru. This includes participants from three predominantly rural regions in the Andean highlands (Huancayo, Cusco, Puno) and three coastal urban regions (Lima, Callao, Tacna). The association between identified SDOH and AD status will be analyzed using multivariable regressions, adjusted for age, gender, and population substructure.
Results: The revised SDOBH-Q questionnaire consists of 15 sections and 79 questions. The pilot assessment was completed by 28 CU volunteers: 17 from Lima and 11 from Huancayo. Preliminary data from the first 60 participants have been collected across regions from both the coast and the Andean highlands of Peru.
Conclusions: Specific SDOH, such as neighborhood, education, healthcare access, economic conditions, and environmental factors, may increase the risk of AD in older Peruvian individuals. Gaining a deeper understanding of how genetic and environmental factors interact in the context

of AD and related dementias across diverse populations, including Latinos, is critical for future research.

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SHIFT 01-644

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

PLASMA P-TAU217, P-TAU181 AND P-TAU231 ARE ASSOCIATED WITH COGNITIVE DECLINE [OVER 6 YEARS] IN EARLY STAGES OF AD

Rosalie Cottez[1], Hélèna Denis[1], Cyntia Tremblay[1], Andréanne Loiselle[1], Sébastien Hébert[1,2], Nicole Leclerc[3,4], Henrik Zetterberg[5,6], Consortium For The Early Identification Of Alzheimer's Disease – Quebec (Cima-Q)[7], Frederic Calon[1,8], Alexa Pichet-Binette[9,10]
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Aims: Our study aimed to compare the associations of three plasma phosphorylated tau (p-tau) biomarkers with clinical progression and cognitive decline in preclinical stages of Alzheimer's disease (AD).
Methods: A total of 290 older adults from the CIMA-Q cohort (Québec, Canada) were followed for up to 6 years. They included cognitively healthy (n=56), subjective cognitive decline (n=115), early MCI (n=88), and early AD (n=31). Participants who were cognitively healthy or had subjective cognitive decline were grouped as cognitively unimpaired (CU, n=171). Three plasma p-tau were measured: p-tau217 (S-PLEX MesoScale), p-tau181 and p-tau231 (Simoa HD-X, University of Gothenburg). We compared p-tau levels between diagnostic groups at baseline and clinical progression (progression from CU to MCI, n=29, and MCI to AD, n=15). We investigated associations between the p-tau assays and MoCA at baseline with linear models and longitudinal scores with linear mixed effect models.
Results: Plasma p-tau levels from the three assays were higher in AD patients compared to MCI or CU participants, particularly with p-tau217 ($\beta_{AD\text{-}CU}$=8.6; $\beta_{AD\text{-}MCI}$ =7.7, all p<0.001). However, p-tau concentrations did not differentiate CU or MCI progressors. Higher levels of the three p-tau were associated with worse MoCA score at baseline, with stronger associations with p-tau217 (β=-0.44 vs -0.33 and -0.31 with other assays). Longitudinally, higher p-tau217 levels at baseline were more strongly associated with decline in MoCA over time (β_{217}=-0.054, p<0.001), particularly in the highest quartile of p-tau217 values (Q4), which declined more than all other quartiles ($\beta_{Q4\text{-}Q1}$=0.29, p<0.01), with less marked differences with p-tau181 or p-tau231.
Conclusions: Plasma p-tau217, compared to p-tau181 and 231, was most strongly associated with cognitive decline, highlighting its potential as an early biomarker for monitoring AD progression.

Table 1: Description of the CIMA-Q cohort

Characteristic	CU[1], n= 171	MCI, n= 88	AD, n= 31
Age (years)	72.8 (5.4)	76.1 (6.0)	77.5 (6.8)
Sex, W, n(%)	121 (71%)	45 (51%)	16 (52%)
BMI, (kg/m²)	26.5 (4.7)	27.0 (4.3)	25.8 (3.6)
Education, (years)[a]	14.7 (3.6)	13.9 (4.0)	16.0 (4.7)
ApoE ε4 positive, n(%)	34 (20%)	30 (34%)	15 (48%)
MoCA	27.9 (1.5)	24.2 (2.1)	19.0 (4.3)
pTau217, (pg/mL)	3.2 (2.4)	4.7 (3.2)	12.7 (9.5)
pTau181, (pg/mL)	5.1 (3.0)	6.5 (3.2)	11.0 (5.5)
pTau231, (pg/mL)	6.0 (2.7)	7.0 (2.7)	10.2 (4.6)

Values are presented as means (SD), unless otherwise specified. [1]CU: we put together participants who were cognitively healthy or had subjective cognitive decline, all recruited from the general population.
AD, Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; p-tau, phosphorylated-tau protein.
a: 31 missing values

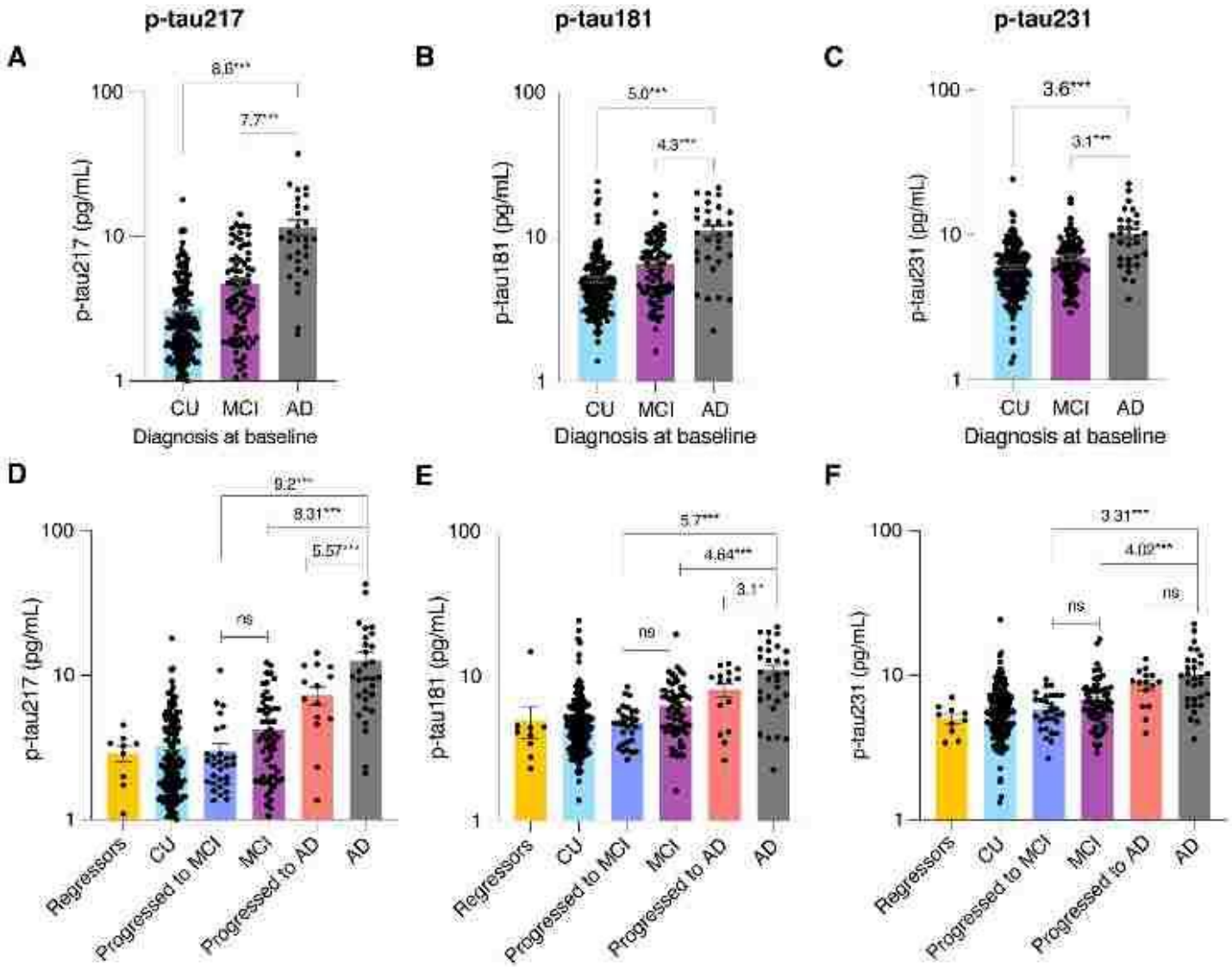

Figure 1. Plasma levels of p-tau217, p-tau181 and p-tau231 between clinical diagnosis at baseline and clinical progression over six years.

A-C: P-tau levels comparisons between diagnostic groups at baseline. **D-F:** Comparisons between diagnostic groups with a focus on progressors over a 6-year follow-up period. Regressors were patients with MCI at baseline who reverted to CU. Progressed to MCI. CU participants at baseline who progressed to MCI. Progressed to AD: MCI participants at baseline who progressed to AD dementia.***p<0.0001; ** p<0.001; * p<0.05. In all panels, p-tau levels are presented as log10-transformed means and standardized beta coefficients adjusted for age and sex are reported.

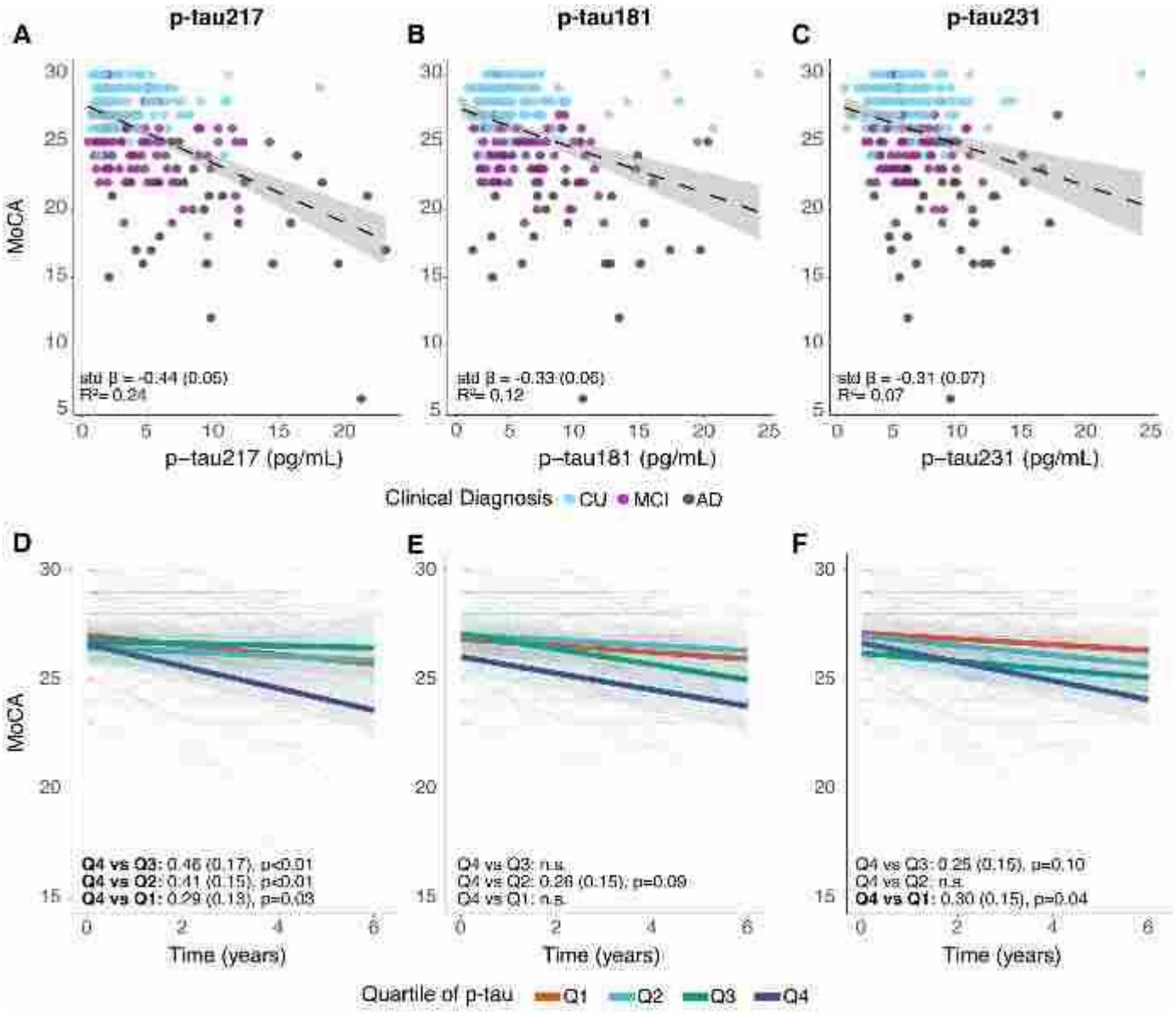

Figure 2. Cross-sectional associations and longitudinal decline of MoCA scores with plasma p-tau217, p-tau181 and p-tau231 biomarkers.

A-C: Cross sectional analysis of three plasma p-tau biomarkers and the MoCA. Linear regression analyses were controlled for age, sex and education as covariates. Standardized β coefficients (std β) for p-tau and adjusted R^2 are reported, with all p-values <0.001. **D-F:** Linear mixed effect models with random slope and intercept were fitted, with p-tau levels split into quartiles (Q) and longitudinal MoCA scores as outcome. Models included age, sex and education as covariates. Q4 was used as the reference group for statistical comparisons reported on graphs. Quartiles comparisons are presented as std β (standard error) and p-value, with all significant results in bold. Note that results were consistent when using continuous p-tau levels in linear mixed effect models.

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SHIFT 01-645

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

NEUROBIOSTAND: A EUROPEAN CONSORTIUM TO STANDARDISE P-TAU MEASUREMENTS IN PLASMA

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Aims: NEuroBioStand is an EU-funded project aiming at standardising the measurement of neurodegenerative diseases biomarkers by using new metrological strategies. One of the objectives is to harmonise P-tau plasma measurements between analytical platforms by developing a candidate reference measurement procedure (RMP) with a target uncertainty of less than 15%. Prototype reference materials will be certified by using this method.
Methods: Recombinant phosphorylated protein and synthetic phosphopeptide materials were sourced as candidate primary calibrators together with their labelled internal standards. Purity was evaluated for the protein and peptide materials by high resolution mass spectrometry coupled to liquid chromatography (LC HRMS) and mass fraction was determined by amino acid analysis. A candidate reference measurement procedure is being developed by LC HRMS for high accuracy measurement of different phosphorylated epitopes in plasma.
Results: NEuroBioStand's consortium has prioritized P-tau181, P-tau217 and P-tau231 as clinically-relevant biomarkers. P-tau calibrators have been characterised in terms of purity and mass fraction by amino acid analysis and LC-MS. In particular, the full characterisation of the phosphorylation status of the protein candidate primary calibrator has been carried out to determine the site occupancy of the most relevant phosphorylation sites by using the SI-traceable quantified phosphorylated peptide materials. The peptide and/or the protein calibration materials are under investigation for the development of an RMP in plasma, exploiting the potential of isotope dilution (ID) coupled to targeted mass spectrometry and nano liquid chromatography (nanoLC).
Conclusions: Traceability to SI units is necessary to ensure standardised measurements across analytical platforms. This will be achieved through the certification of matrix-based reference materials

through the collaboration of national metrology institutes, clinicians, academics and IVD-providers and with the final aim of standardising P-tau cut-off values and reference ranges for AD.

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SHIFT 01-646

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

DIFFERENCES BETWEEN PLASMA PHOSPHORYLATED TAU ISOFORM BIOMARKERS IN A COMMUNITY COHORT.

Lawrence Honig, Yian Gu, Min Suk Kang, Dolly Reyes-Dumeyer, Cory Weinfeld, Badri Vardarajan, Richard Mayeux
Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, Neurology Department, New York, United States of America

Aims: Plasma biomarkers are increasingly considered for assessment of biologically defined Alzheimer's disease (AA 2024 criteria), using blood draw, without requiring cerebrospinal fluid analysis or molecular PET imaging. Here we assess the relationship of three different phophorylated tau (phosphotau) biomarkers with neurodegeneration and clinical dementia diagnosis in a community-based longitudinally-studied Caribbean Hispanic cohort (EFIGA).
Methods: Plasma Aβ40, Aβ42, total tau, NfL, GFAP, and three different phosphorylated tau isoforms: P-tau181, P-tau217, and P-tau231, were analyzed in 1824 participants using Quanterix HD-X platform technology. Clinical information included demographics, neuropsychological tests, body mass index, renal function indices, APOE genotype, and cognitive status (normal, MCI, or dementia). SPSS vn29 was used to perform correlations, ROC, and regression analyses.
Results: All three P-tau measurements were robust, with low intrasample coefficient of variances of 4%-5%. Phosphotau measurements did not relate to serum creatinine levels, or body mass index. P-tau181, P-tau217, and P-tau231 were highly correlated with each other: Spearman's correlation coefficients were 0.70-0.75. Overall, P-tau 181 was more correlated with P-tau217, than either was with P-tau231. Neurodegenerative markers GFAP and NfL were better correlated with P-tau217, than with P-tau181, and that than P-231. ROC curves showed that the detection of clinical dementia was similar for NfL, GFAP, and the phosphotau measures, with P-tau217 consistently performing best. In APOE4 non-carriers, NfL and GFAP were superior to isolated phosphotau measures, perhaps reflecting a higher proportion of non-amyloid neurodegeneration in that group.
Conclusions: These results show the feasibility of measuring 8 biomarkers in plasma from an underrepresented community population. While P-tau181, P-tau217, and P-tau231 showed similar performance, subtle differences may reflect their relative detection of amyloid-induced neurodegeneration, differential assay performances, assay-interfering factors, or disease-stage specificity.

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SHIFT 01-647

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

MTBR-TAU368 IMPROVES DIAGNOSTIC ACCURACY FOR FTLD-TAU FROM FTLD-TDP.

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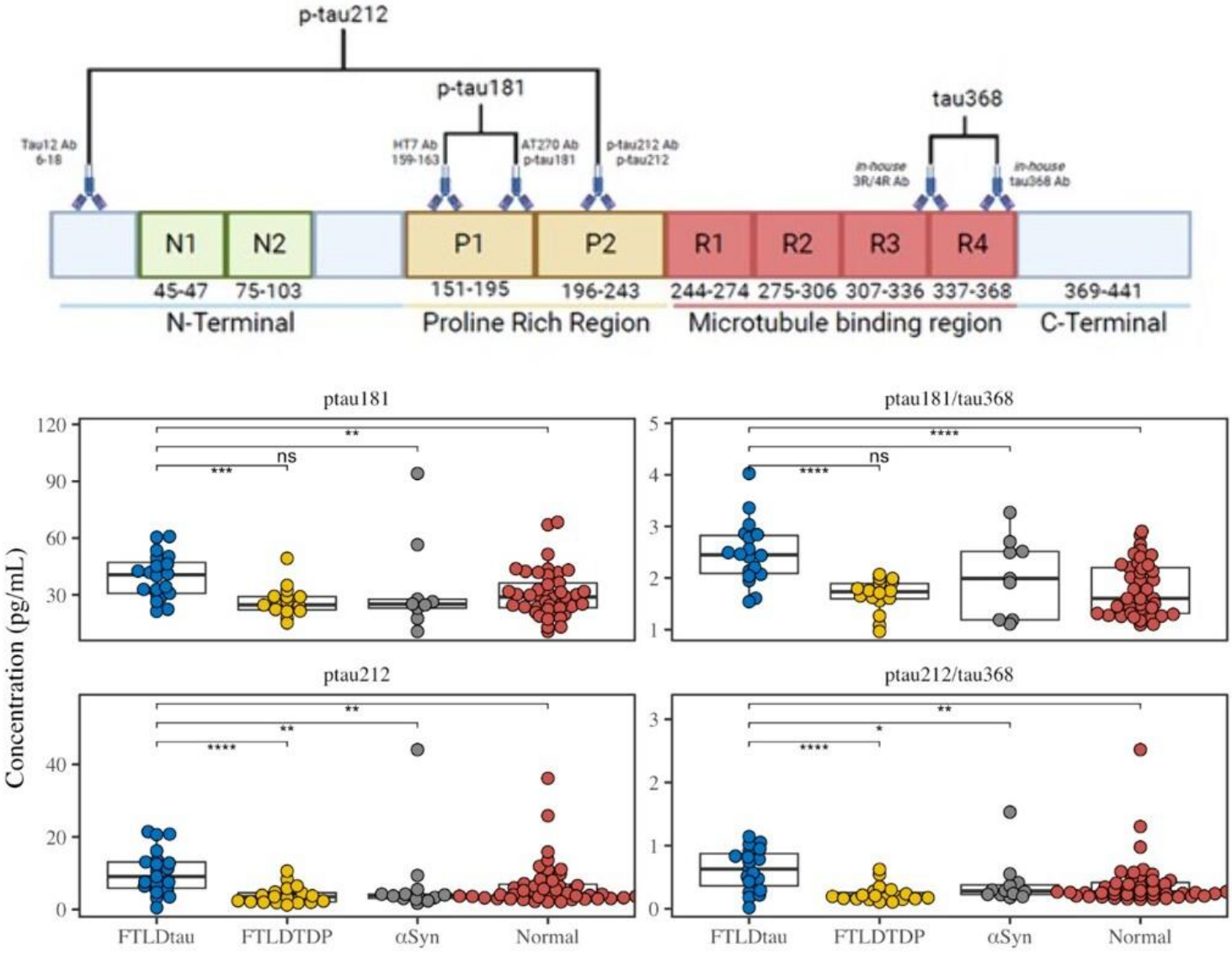
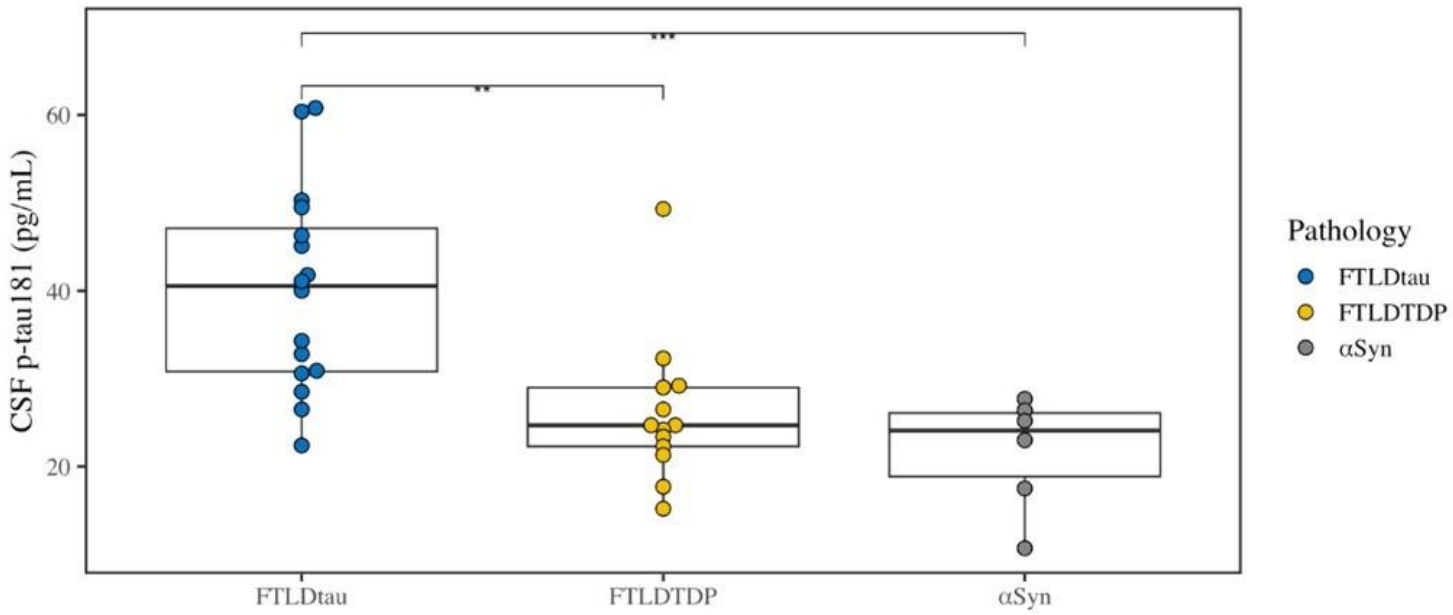
Aims: Phosphorylated-tau (p-tau) biomarkers are typically specific for Alzheimer's disease (AD) and are less elevated in the cerebrospinal fluid (CSF) of frontotemporal lobar degeneration (FTLD). FTLD is a pathologically and clinically heterogeneous neurodegenerative disorder, and we currently lack biomarkers to differentiate the two major pathological subtypes 1) FTLD-tau and 2) FTLD-TDP. In this study, we test CSF p-tau181, p-tau212, and MTBR-tau368 (Fig.1) in patients with autopsy- or mutation-confirmed FTLD-tau and FTLD-TDP without AD pathology; clinically healthy individuals without cognitive impairment and autopsy-confirmed Lewy body disease with alpha-synuclein (αSyn) were included as reference groups.
Methods: Autopsies were performed at the University of Pennsylvania in the Center for Neurodegenerative Disease Research. Definite diagnosis was based on autopsy results or determined genetically. We used Lumipulse technology to measure p-tau181 levels and Simoa to measure p-tau212 and MTBR-tau368 in 49 healthy controls, 22 FTLD-Tau, 20 FTLD-TDP and 13 αSyn. For further analysis we excluded individuals with evidence of AD pathology. Wilcoxon test was used to compare groups. AUC-ROC was used to discriminate FTLD-Tau from FTLD-TDP participants. Spearman correlations tested associations between p-tau212 and tau burden by region.
Results: Both p-tau181 and p-tau212 levels significantly increased in FTLD-Tau compared to healthy controls, people with FTLD-TDP, and people with αSyn pathology (Fig.2). Results remained significant when people with evidence of AD pathology were excluded (Fig.3&4). P-tau181 and p-tau212 ratio with

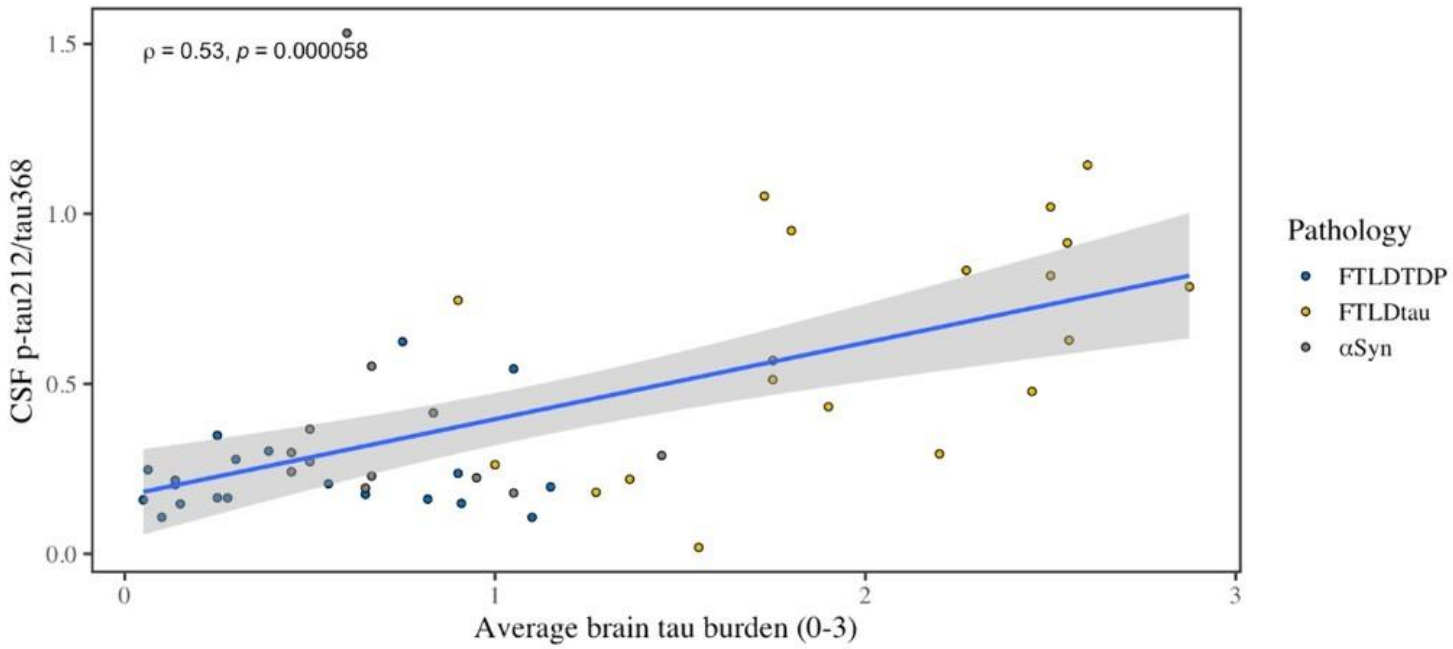
MTBR-tau368 significantly improved accuracy in discriminating FTLD-Tau from FTLD-TDP reaching AUC=0.92; 95%CI (0.80 – 0.99) (Fig. 5). Biomarkers significantly correlated with tau burden across brain regions (Fig. 6&7).

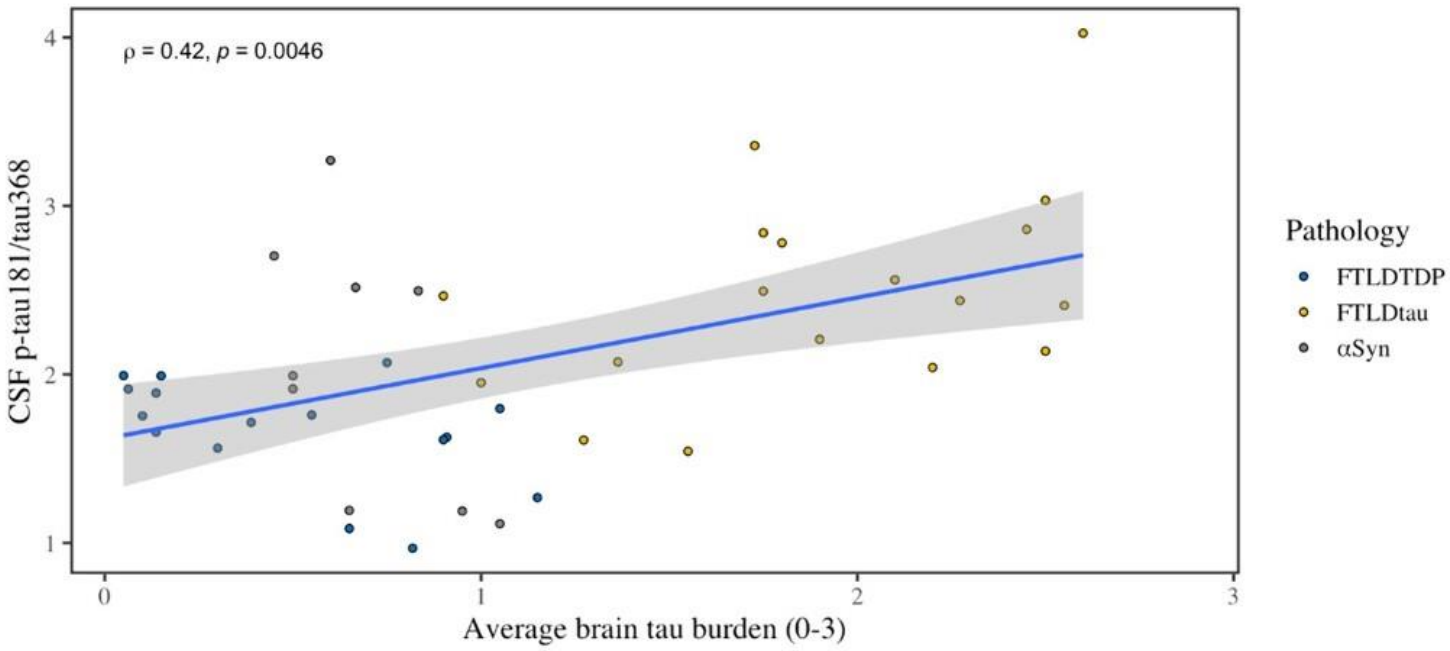
Conclusions: MTBR-tau368 significantly improves the accuracy of p-tau immunoassays to differentiate FTLD-tau from FTLD-TDP and αSyn. Those biomarkers will support the diagnosis of tauopathies and might find utility in clinical trials design.





FTLD-Tau vs. FTLD-TDP	AUC	AUC 95% CI	Threshold	Threshold 95% CI	Sensitivity	Specificity	Accuracy
p181/t368 + p212/t368	0.92	0.80 -- 0.99	0.24	0.21 -- 0.30	0.81	0.89	0.85
ptau181/tau368	0.9	0.76 -- 1.00	2.04	1.96 -- 2.14	0.82	0.96	0.89
ptau212/tau368	0.85	0.72 -- 0.95	0.35	0.25 -- 0.51	0.71	0.88	0.81
ptau212	0.83	0.69 -- 0.93	5.98	4.47 -- 8.20	0.69	0.86	0.78
ptau181	0.81	0.66 -- 0.94	32.87	28.13 -- 38.91	0.69	0.81	0.75
tau368	0.54	0.38 -- 0.70	16.47	11.60 -- 21.45	0.55	0.55	0.55
tau368/TTau	0.53	0.35 -- 0.69	0.33	0.22 -- 0.41	0.41	0.69	0.5




ρ = 0.42, p = 0.0046
CSF p-tau181/tau368
Average brain tau burden (0-3)
Pathology
FTLDTDP
FTLDtau
αSyn

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SHIFT 01-648

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2 - 3 April 2025

FLUID BIOMARKERS OF AMYLOID-B, TAU, NEURODEGENERATION, AND SYNAPTIC DYSFUNCTION IN INDIVIDUALS EXPOSED TO REPETITIVE HEAD IMPACTS – PRELIMINARY FINDINGS FROM THE NEWTON STUDY

Suzan Van Amerongen[1,2], Suzie Kamps[1,2], Kasper Schelvis[1,2], Dirk Van Paassen[1,2], Lynn Boonkamp[3], Eugeen Vanmechelen[4], Julie Goossens[4], Rik Ossenkoppele[1,2,5], Yolande Pijnenburg[1,2], Philip Scheltens[6], Charlotte Teunissen[3], Inge Verberk[3], Everard Vijverberg[1,2]
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Aims: This study aimed to examine the utility of plasma and CSF biomarkers to detect various pathophysiological processes in individuals exposed to repetitive head impacts (RHI) and to investigate associations with clinical features.
Methods: We included 79 RHI-exposed individuals and 35 asymptomatic age- and sex-matched controls with no exposure to head impacts (aged 30 – 80; **Table 1**). Plasma was measured for hyperphosphorylated tau (pTau)217, pTau181, amyloid beta (Aβ)-40, Aβ-42, neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and synaptosomal-associated protein, 25kDa (SNAP25). We compared plasma biomarkers between RHI-exposed and unexposed participants using analyses of covariance (ANCOVAs), including covariates age, sex, and body mass index. Additionally, we tested associations with traumatic encephalopathy syndrome (TES) criteria, neuropsychological test results, and estimates for RHI exposure (i.e., total years of exposure, age of first exposure) using multivariable linear regressions.

Table 1. Sample characteristics

	RHI-exposed individuals (N=79)	Unexposed controls (N=35)
Demographics		
Age, mean ± SD	53.9 ± 11.8	54.4 ± 11.2
Sex (male), N (%)	72 (91.1)	31 (88.6)
Level of education (Verhage), mean ± SD *	5.4 ± 1.1	5.9 ± 0.9
Body mass index, mean ± SD **	27.5 ± 4.7	25.1 ± 3.3
RHI history		
Primary sport		-
Self-defense/combat sports, N (%)	39 (49.4)	-
Soccer, N (%)	18 (22.8)	-
Rugby, N (%)	11 (13.9)	-
Military, N (%)	7 (8.9)	-
Other, N (%)	4 (5.1)	-
Total years of RHI exposure, mean ± SD	26.0 (11.6)	-
Age of first exposure, mean ± SD	12.3 ± 5.5	-
Biomarkers + genotype		
Plasma, N (%) available	77 (97.5)	35 (100)
Cerebrospinal fluid, N (%) available	35 (44.3)	-
Biomarkers indicating underlying AD pathology [a], N (%)	17 (21.5)	5 (14.3)
ApoE genotype, N (%) available	31 (39.2)	0 (0)
ε4 allele carrier, N (%)	*9 (11.4)*	-
Traumatic Encephalopathy Syndrome		
No TES, N (%) [b]	34 (43.0)	-
No TES, subjective decline, N (%)	*24 (21.1)*	-
No TES, no complaints, N (%)	*10 (12.7)*	-
TES – cognitive impairment, N (%)	30 (38.0)	-
TES – neurobehavioral dysregulation, N (%)	24 (30.4)	-
TES – psychiatric features, N (%)	27 (34.2)	-
TES – motor features, N (%)	6 (7.6)	-
Provisional level of certainty of CTE pathology		
Suggestive of CTE, N (%)	13 (16.5)	-
Possible CTE, N (%)	14 (17.7)	-
Probable CTE, N (%)	15 (19.0)	-
Cognition + depressive symptoms		
Mini-Mental State Examination, mean ± SD **	27.4 ± 3.1	29.5 ± 0.7
Montreal Cognitive Assessment, mean ± SD **	24.6 ± 4.1	27.4 ± 1.9
Memory Composite (z-score), mean ± SD **	-1.27 ± 1.98	0.07 ± 0.60
EF Composite (z-score), mean ± SD **	-0.65 ± 0.98	-0.07 ± 0.72
Attention Composite (z-score), mean ± SD **	-0.67 ± 0.84	-0.10 ± 0.75
Geriatric Depression Scale, mean ± SD **	2.8 ± 3.1	0.7 ± 1.1

[a] Indicated with amyloid PET scans, CSF analyses, or if not available; pTau217. [b] 3 individuals with inconclusive TES diagnosis. *p < 0.05, **p < 0.001 (independent t-test, Chi-square tests). Abbreviations; RHI = repetitive head impacts, SD = standard deviation, AD = Alzheimer's disease, ApoE = Apolipoproteine E, TES = traumatic encephalopathy syndrome, CTE = chronic traumatic encephalopathy, EF = executive functioning

Results: No significant differences in plasma biomarkers were found between RHI-exposed and unexposed participants (**Figure 1**). After excluding individuals with underlying Alzheimer's disease (AD) pathology, Aβ-40 (*p*=.007) and SNAP25 (*p*=.007) were significantly lower in those exposed to RHI compared to unexposed individuals. Low plasma Aβ-42 and Aβ-42/40 ratio showed strongest associations with TES-related symptoms, and neuropsychological test results (**Figure 2**) in RHI-exposed individuals, mainly driven by those individuals with underlying AD.

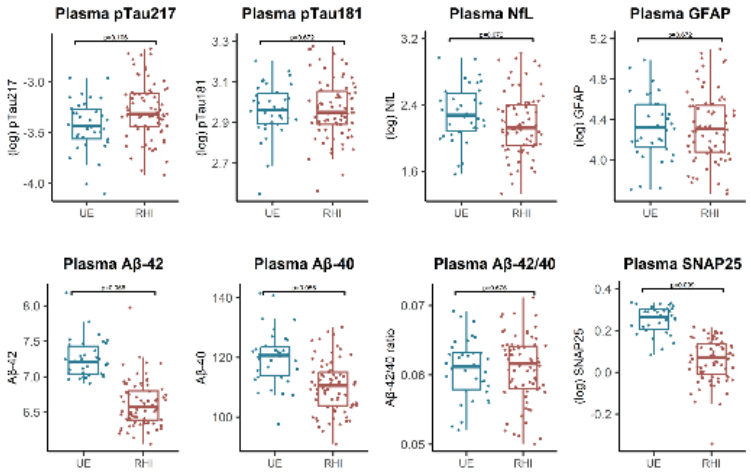

Figure 1. Boxplots with adjusted mean biomarker concentrations in plasma, p-values are FDR-corrected (ANCOVA models), including covariates: age, sex, and body mass index.
Abbreviations: UE = unexposed individuals, RHI = repetitive head impact exposed individuals, pTau = hyper-phosphorylated tau, Aβ = beta-amyloid, Nfl. = neurofilament light chain, GFAP = glial fibrillary acidic protein, SNAP25 = synaptosomal-associated

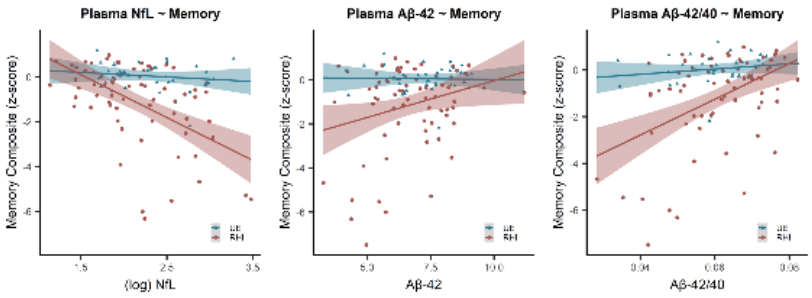

Figure 2. Plots illustrate the associations between selected biomarkers and memory composite scores, adjusted for covariates age, sex, body mass index, and educational level. Abbreviations; NfL = neurofilament light chain, Aβ = beta-amyloid, UE = unexposed individuals, RHI = individuals with repetitive head impact exposure

Conclusions: No evidence was found for the utility of NfL or GFAP in detecting pathophysiological changes related to RHI exposure. Low Aβ-40 and SNAP25 found in those with RHI may reflect disturbances in glymphatic clearance. RHI exposure may not increase the risk of AD neuropathology, but, when present, AD pathology significantly contributes to the clinical picture of TES in RHI-exposed

individuals.

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SHIFT 01-653

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

INVERSE ASSOCIATIONS BETWEEN PLASMA DOCOSAHEXAENOIC ACID (DHA) AND P-TAU181, PTAU217, AND P-TAU231 IN THE PRECLINICAL STAGES OF ALZHEIMER'S DISEASE.

Rosalie Cottez[1], Patrick Blondin Tsafack[1,2,3], Hélèna Denis[1], Chuck Chen[4], Cyntia Tremblay[1], Vincent Emond[1], Henrik Zetterberg[5,6], Sophie Layé[7], Richard Bazinet[4], Consortium For The Early Identification Of Alzheimer's Disease – Quebec (Cima-Q)[8], Frederic Calon[1,2,3]
[1]Centre de recherche du CHU de Québec, Neurosciences, Québec, Canada, [2]Université Laval, Faculté De Pharmacie, Québec, Canada, [3]Institut sur la Nutrition et les Aliments Fonctionnels (INAF), Québec, Canada, [4]University of Toronto, Faculty of Medicine, Department Of Nutritional Sciences, Toronto, Canada, [5]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, [6]UCL Institute of Neurology Queen Square, Department Of Neurodegenerative Disease, London, United Kingdom, [7]Nutrition and Integrative Neurobiology, INRA, Université de Bordeaux, Umr 1286, Bordeaux, France, [8]the Consortium for the Early Identification of Alzheimer's Disease – Quebec (CIMA-Q; cima-q.ca), Montréal/Québec/Sherbrooke, Canada

Aims: Explore the relationship between circulating omega-3 polyunsaturated fatty acids (n-3 PUFA) and plasma biomarkers of Alzheimer's disease (AD) neuropathology, in a clinically characterized cohort of participants at preclinical stages of cognitive impairments.
Methods: Plasma samples were collected from 54 cognitively healthy individuals (CH), 114 with subjective cognitive decline (SCD), 82 with mild cognitive impairment (MCI), and 29 with early-stage AD, all from the CIMA-Q cohort (mean age 74 years; 63.4% women). P-tau biomarkers were quantified using the Simoa HD-X platform for p-tau181 and p-tau231, and the S-PLEX MesoScale platform for p-tau217. Fatty acid profiles were analyzed by gas chromatography with a flame ionization detector. To mitigate the effects of lipid profiles, body weight, and sex on absolute concentrations (in nM), fatty acid levels were expressed as percentages of total fatty acids (%mol). Multiple linear regressions evaluated the relationships between relative plasma fatty acid levels, p-tau biomarkers (p-tau181, p-tau217, p-tau231), and clinical, biochemical, and neuroimaging data, adjusting for age and sex.
Results: Inverse associations were observed between the n-3:n-6 PUFA ratio, the percentage of n-3 PUFA (especially DHA), and plasma p-tau181 (ρ=-0.16, $p<0.01$). DHA also inversely correlated with ptau217 and p-tau231 (ρ217=-0.14; ρ231=-0.15, all $p<0.05$). Conversely, higher levels of saturated fatty acids (SFA) were associated with elevated p-tau181 and p-tau217. Proportions of n-3 PUFA and SFA correlated with waist circumference and body weight, respectively. Fatty acid profiles were similar across diagnostic groups, except for reduced C23:0 in AD. No associations were found between fatty acid profiles and age or MRI-determined BrainAge.
Conclusions: This study reveals an inverse relationship between omega-3 PUFA, especially DHA, and key AD biomarkers in the blood, suggesting a potential protective role against tau pathology.

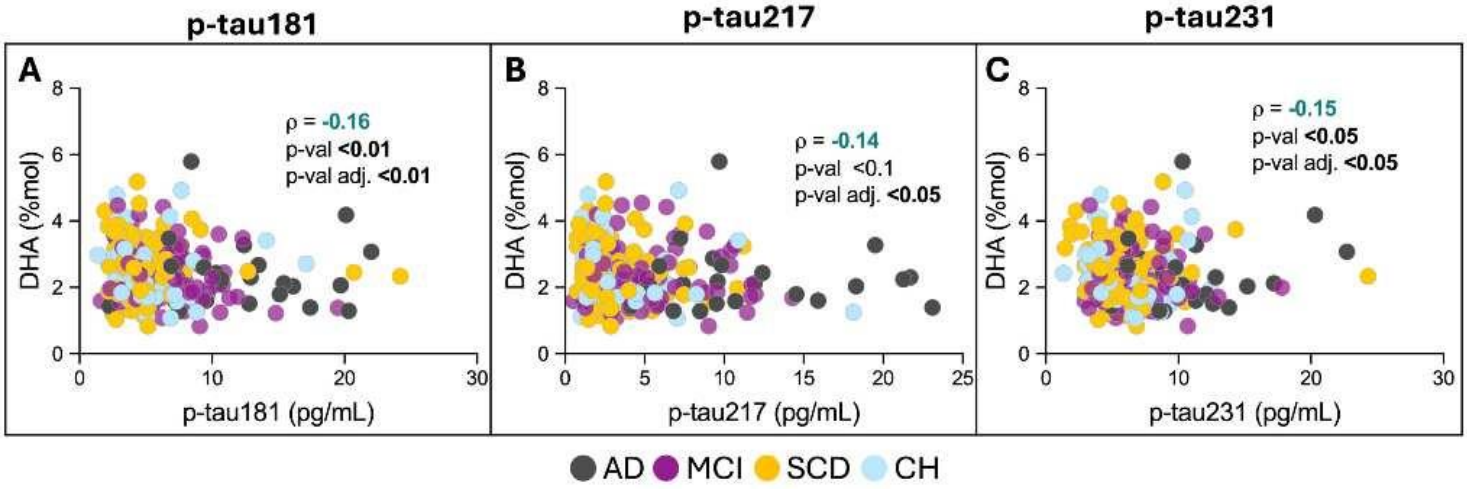

Figure 1. Inverse association between plasma p-tau levels and docosahexaenoic acid (DHA). Linear regression analyses were controlled for age and sex as covariates. p(Spearman) test, p-value and adjusted p-value (adj) are shown. *AD, Alzheimer's disease; CH, cognitively healthy; DHA, docosahexaenoic acid; MCI, mild cognitive impairment; p-tau, plasma phosphorylated tau protein; SCD, subjective cognitive decline.*

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SHIFT 01-654

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

PLASMA P-TAU217 AND ITS ASSOCIATIONS TO CSF, MMSE, CT AND INCIDENT DEMENTIA IN VERY OLD MEN.

Elisabeth Maria Hellquist[1], Lena Kilander[1], Bodil Weidung[1], Kristin Franzon[1], Vilmantas Giedraitis[1], Martin Ingelsson[2], Oskar Hansson[3], Shorena Janelidze[4]
[1]Uppsala University, Department Of Public Health And Caring Sciences, Clinical Geriatrics, Uppsala, Sweden, [2]Department of Public Health and Caring Sciences, Molecular Geriatrics, Rudbeck Laboratory, Uppsala University, Uppsala, Uppsala, Sweden, [3]Lund University, Clinical Sciences Malmo, Lund, Sweden, [4]Lund University, Lund, Sweden

Aims: Increased concentrations of plasma phosphorylated tau (p-tau) have been shown to be robust biomarkers of Alzheimer's Disease (AD) pathology. The full potential needs to be verified also in population-based cohorts, not the least in very old persons, i.e. those with the highest AD incidence. We examined the associations between plasma p-tau$_{217}$ concentrations and cerebrospinal fluid (CSF) amyloid beta (Aβ42), p-tau$_{181}$ and total tau (t-tau) concentrations, neuroradiological findings, Mini Mental State Examination (MMSE) results and incident dementia in a very old population.
Methods: Thirty-six men from the Uppsala Longitudinal Study of Adult Men underwent lumbar punctures with analyses of CSF AD biomarkers together with plasma p-tau$_{217}$, CT scans and MMSE at age approximately 87-89 years. Plasma p-tau$_{217}$ concentrations were measured using immunoassays and CSF Aβ42, p-tau$_{181}$ and t-tau concentrations using ELISA. Incident dementia diagnoses were identified through medical records up to 20 years follow up.
Results: Concentrations of plasma p-tau$_{217}$ strongly correlated with CSF Aβ42 and CSF p-tau$_{181}$ (Spearman *ρ*: rho = -0.68, $p<0.001$ and rho = 0.33, $p<0.05$, resp.) but not to CSF t-tau. We found no significant correlations between plasma p-tau$_{217}$ and MMSE scores, nor with medial temporal lobe atrophy. The concentrations of plasma p-tau were higher and the CSF Aβ42 concentrations lower in those who developed dementia, however not statistically significant.
Conclusions: Plasma p-tau$_{217}$ and CSF Aβ42 concentrations were strongly correlated, suggesting that plasma p-tau$_{217}$ concentrations primarily reflect brain amyloid beta deposition even in the very old. There was a trend for higher concentrations of plasma p-tau in those who developed dementia, but further studies in larger cohorts are needed.

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SHIFT 01-655

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2 - 3 April 2025

REPETITIVE HEAD IMPACTS DURING CONTACT SPORTS AND FLUID BIOMARKERS OF NEURAL DAMAGE – A META-ANALYSIS

Marloes Hoppen[1,2,3], Suzie Kamps[3,4], Everard Vijverberg[3,4], J Daams[5], Charlotte Teunissen[3,4,6], Jaap Oosterlaan[2,7], Marsh Königs[1,2,3]
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Aims: To systematically aggregate the available evidence for acute effects of contact sport participation on fluid biomarkers reflecting neural damage, while differentiating between contact sports and individual fluid biomarkers.
Methods: MEDLINE, Embase and SPORTdiscus were searched from inception until 18/07/2024. Studies were included that reported on fluid biomarkers of neural damage assessed in one session of contact sport participation. Risk of Bias was assessed using the Bias In Non-randomized Studies of Exposure tool and the Risk of Bias Tool. The level of evidence was synthesized according to the GRADE methodology.
Results: A total of 35 studies (847 participants) was included. Across blood biomarkers of neural damage and across contact sports, meta-analysis revealed statistically significant and medium-sized elevation of blood biomarkers after natural exposure to RHI during participation. Subsequent meta-analyses revealed statistically significant and medium-large-sized elevations across blood biomarkers for fight sports, American football and football specifically. Moreover, meta-analysis of individual biomarkers revealed statistically significant and medium-large-sized elevation of S100B calcium-binding-protein in fight sports, American football and football, large-sized elevation of total tau in American football and medium-sized elevation in neuron-specific enolase in football. Meta-analysis of experimental exposure to football heading showed no significant change in blood biomarkers of neural damage and also no significant difference in change compared to a control group.
Conclusions: Due to considerable risk of bias, the level of evidence regarding the effects of natural exposure to RHI is downgraded to very low quality evidence for a negative effect of RHI on brain integrity. Furthermore, based on moderate quality evidence, this meta-analysis provides no indication for negative effects of football heading in football on brain integrity as assessed with blood biomarkers.

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SHIFT 01-662

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2 - 3 April 2025

RELATIONSHIPS BETWEEN HYPOMETABOLISM AND BOTH B-AMYLOID AND TAU PET IN CORTICOBASAL SYNDROME

Alma Ghirelli[1], Austin Goodrich[2], Yehkyoung Stephens[1], Jonathan Graff-Radford[3], Farwa Ali[1], Mary Machulda[3], Christopher Schwarz[4], Matthew Senjem[3], Federica Agosta[5], Massimo Filippi[6], Clifford Jack[3], Val Lowe[3], Keith Josephs[1], Jennifer Whitwell[4]
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Aims: Corticobasal syndrome (CBS) is commonly caused by corticobasal degeneration, although Alzheimer's disease (AD) is the underlying pathology in 21-50% of patients and is associated with more widespread cortical degeneration. Studies have assessed hypometabolism in CBS according to amyloid (A) PET but understanding the association of both AD-tau (T) and amyloid to hypometabolism is still incomplete.
Methods: Thirty-three patients meeting research criteria for possible or probable CBS and 45 controls were recruited by the Neurodegenerative Research Group, Mayo Clinic, and underwent FDG-PET, flortaucipir PET, and Pittsburgh compound B (PiB) PET. A global PiB and temporal flortaucipir meta-ROI were used to define patients as A+/- and T+/-. FDG-PET uptake was extracted for 12 cortical and subcortical regions-of-interest in dominant (most affected) and non-dominant (lesser affected) hemispheres. Neurological and metabolic measures were compared across patients with different A/T status.
Results: Of 33 CBS patients, 5 were A+T+, 7 were A+T- and 21 were A-T-. A+T+ patients had greater hypometabolism in postcentral, parietal, and occipital cortices than A+T- and A-T- groups, with no differences observed between the A+T- and A-T- groups. Hemispheric asymmetry of FDG uptake was also more accentuated in A+T+ patients in frontal, parietal, lateral temporal, and occipital regions than other groups. Medial temporal and basal ganglia metabolism did not differ across AT groups.
Conclusions: Hypometabolism becomes more severe, widespread and lateralized as β-amyloid and tau synergistically act on the neurodegenerative processes. Asymmetry at FDG PET and a temporo-parieto-occipital hypometabolism pattern should be further investigated as a non-invasive and accessible biomarker of CBS-AD. This study sets the path for the use of FDG PET as a biomarker in CBS that could be used as a potential tool to enroll CBS patient into clinical trials

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SHIFT 01-664

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

DEFINING BRAIN ATROPHY SUBTYPES IN PARKINSON'S DISEASE WITH DISTINCT THERAPEUTIC EFFECTS OF DEEP BRAIN STIMULATION

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Aims: Determining the phenotypes of Parkinson's disease (PD) prior to surgery is crucial for predicting the therapeutic efficacy of deep brain stimulation (DBS).
Methods: To this end, clinical and MRI data from 1,192 PD patients who were candidates for DBS were collected prospectively. Deviations in brain regional volumes from 3D T1-weighted images of PD patients were obtained using normative references from 12,060 healthy individuals. Motor-related brain regions were selected for analysis. The Subtype and Stage Inference (SuStaIn) model was then used to identify distinct brain atrophy subtypes among PD patients.
Results: We identified two brain types in PD: "atrophied" brains, present in 56% of patients, characterized by more severe cognitive and motor decline, and "normal-appearing" brains, which responded better to DBS. Patients with "atrophied" brains were further classified into three subtypes: (1) PD-putamen subtype, marked by dominant putamen atrophy, severe motor, mood, and autonomic dysfunctions, worsening with advanced atrophy stages, and significantly reduced post-DBS motor outcomes; (2) PD-cerebellum subtype, defined by cerebellar atrophy, severe motor dysfunction, and poor DBS response, worsening with disease progression; (3) PD-cortex subtype, with atrophy in sensory-motor cortex, milder dysfunctions, and relatively better post-DBS outcomes, though mood dysfunction and DBS response worsened with disease progression.
Conclusions: It can be concluded that distinct spatiotemporal brain atrophy subtypes were identified in PD, each with distinct clinical and prognostic features. A poor post-DBS outcome was associated with cerebellum leading atrophy and advanced atrophy stages in all atrophy subtypes. These insights can inform clinical decision-making, optimizing patient selection and timing for DBS therapy.

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SHIFT 01-665

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

IRON DYSREGULATION IN ALZHEIMER'S DISEASE: INCREASED CONTENT AND REDUCED MOBILIZATION CAPACITY

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Aims: In Alzheimer's disease (AD), impaired iron metabolism is linked to its pathophysiology, with regional increases in iron, particularly in cortical regions (CX). Other brain regions also show disrupted iron metabolism. The superficial white matter (SWM), consisting of short-range association fibers beneath the cortex, is crucial for integrating information across brain regions. In AD, SWM undergoes microstructural changes that may contribute to cognitive decline. While cortical and white matter (WM) alterations in AD are well-studied, SWM pathology remains less understood. This imaging study focuses on assessing iron content and iron mobilization capacity in AD, particularly within the SWM.
Methods: We performed quantitative magnetic resonance imaging on post-mortem frontal lobe tissue from three cases with AD neuropathological change (ADNC) and one healthy control (HC). R_2* and R_1 mapping were used to assess r_1-r_2* relaxivity in WM, SWM, and CX.
Results: Increased R_2* values, indicating higher iron content, were observed in all ADNC tissue regions (WM=24.0 ± 0.54 1/s; SWM=27.1 ± 0.69 1/s; and CX=20.1 ± 0.35 1/s) compared to the HC (WM=23.4 ± 0.14 1/s; SWM=24.4 ± 0.10 1/s; and CX=16.0 ± 0.63 1/s). The r_1-r_2* relaxivity, representing the iron mobilization capacity, was decreased in ADNC as compared to the control in WM (0.114 ± 0.01 versus 0.056 ± 0.07), SWM (0.150 ± 0.01 versus 0.122 ± 0.14) and CX (0.112 ± 0.01 versus 0.032 ± 0.01), respectively.
Conclusions: Our findings confirm increased brain iron in AD, consistent with previous studies, and reveal reduced iron mobilization capacity in ADNC, potentially leading to iron accumulation. Interestingly, the highest iron mobilization capacity was observed in SWM for both ADNC and HC, which could reflect that iron trafficking peaks between the WM and the CX.

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SHIFT 01-666

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2 - 3 April 2025

LOCUS COERULEUS NEURODEGENERATION AND ALZHEIMER'S DISEASE RISK FACTORS: A PATHWAY TO WIDESPREAD CORTICAL ATROPHY

Emilie Foyard, Tao Blanchard, Brigitte Landeau, Léa Chauveau, Mikaël Naveau, Géraldine Poisnel, Gaël Chetelat, Robin De Flores, The Medit-Ageing Research Group
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Aims: The locus coeruleus (LC) is the first brain area affected by tau pathology in Alzheimer's disease (AD). Neuromelanin-sensitive (NM) MRI sequences can measure LC integrity, which declines with aging and increasing AD severity, disrupting the widespread neuroprotective norepinephrine LC release. While associations between LC integrity and cortical structure have been reported in unimpaired older adults, results are sparse and inconsistent. In addition, the moderating effects of AD risk factors, such as amyloid or ApoE4 status, on these associations are still unknown.
Methods: We used data from 71 unimpaired older adults (age: 73.7 ± 3.7 years) from the Age-Well randomized controlled trial with available standard T1 MRI (1x1x1mm^3), NM MRI (0.3x0.3x0.7mm^3), plasma Aβ42/40 and *APOE* genotype. Using a voxelwise approach, we evaluated the association between LC integrity, measured as LC intensity using an automatic segmentation algorithm, and grey matter volume (GMV), as well as interactions with plasma Aβ42/40 (continuous) and ApoE4 status (carriers versus non-carriers of the ApoE4 allele).
Results: LC integrity significantly and positively correlated with GMV in medial and lateral frontal cortices, medial temporal lobes, inferior, middle and superior temporal gyri, and the right primary somatosensory area. Interestingly, individuals with lower plasma Aβ42/40 showed stronger positive associations in Brodmann areas 45, insula, anterior cingulate, cunei, and the left middle temporal cortex than those with higher plasma Aβ42/40. Similarly, APOE4 carriers showed stronger positive associations in the right pars opercularis, caudate and accumbens nuclei, right inferior parietal lobule and the right inferior temporal area compared to non-carriers. Findings are illustrated in Figure1.

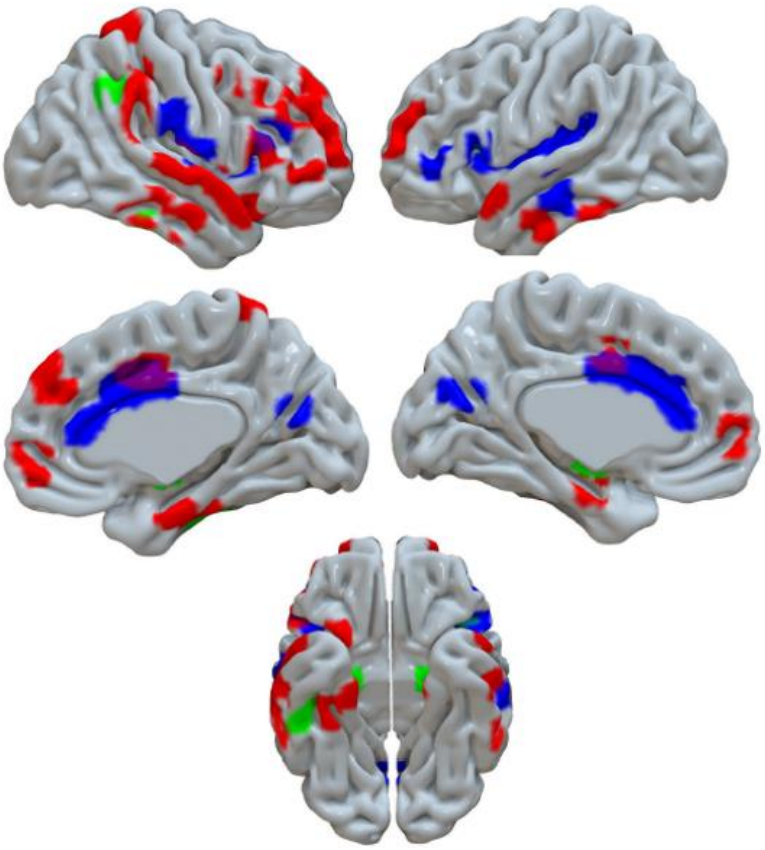

Figure 1: Representation of the voxelwise positive correlation between LC intensity and grey matter volume and its interactions with Aβ42/40 and ApoE4 status.
In red: Positive correlation between LC intensity and grey matter volume.
In blue: Negative interaction between LC intensity and Aβ42/40 on grey matter volume.
In green: Positive interaction between LC intensity and ApoE4 status on grey matter volume.
Multiple regressions, corrected for age, sex, level of education and experimental group (AGEWELL being a randomized controlled trial). p=0.001, min cluster size=50. Uncorrected for multiple comparisons.

Conclusions: Our results suggest that LC neurodegeneration leads to cortical atrophy in regions typically affected in aging, and that AD risk factors moderate this effect, extending it to more widespread regions.

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SHIFT 01-668

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2 - 3 April 2025

PRECLINICAL EVALUATION OF A TREG-TARGETING IMMUNOMODULATORY TREATMENT IN A MOUSE MODEL OF ALZHEIMER-LIKE TAU PATHOLOGY

Inès El Haddad[1], Mingli Chou[1], Karen Matta[1], Kevin Carvalho[2], Thibaut Gauvrit[2], Virginie Puchois[1], Thomas Chaigneau[1], David Blum[2], Eliane Piaggio[3], Guillaume Dorothée[1]
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Aims: Chronic innate neuroinflammation mediated by microglia and astrocytes plays a critical and complex role in the pathophysiology of Alzheimer's disease (AD). Besides innate neuroinflammation, increasing evidence also highlight an instrumental involvement of peripheral immunity and peripheral-central immune crosstalk in AD. Our previous studies in a mouse model of AD-like amyloid pathology evidenced a beneficial role of regulatory T cells (Tregs), which modulate the rate of disease progression and the onset of cognitive deficits, at least partially by rebalancing microglial responses and reactive astrocytes in favor of beneficial neuroinflammation. In parallel, in a mouse model of AD-like Tauopathy we previously evidenced that Tau pathology is associated with detrimental T-cell-mediated processes that contribute to promote Tau-related detrimental neuroinflammation and cognitive deficits. Considering the unique capacity of Tregs to inhibit T cell responses, our data raise the hypothesis that amplifying Tregs may allow controlling Tau-driven T-cell-mediated detrimental processes in the course of AD and other Tauopathies. Our aim was to evaluate preclinically the impact on disease progression of an optimized IL-2-based Treg-targeting immunomodulatory treatment in the THY-Tau22 mouse model of Tauopathy.
Methods: Mice were treated from early disease stages until the development of cognitive deficits. We then evaluated the impact of treatment on i) Spatial memory deficits with the Barnes Maze test, ii) innate neuroinflammation using transcriptomic analyses, iii) Tau pathology by Western Blot.
Results: Our data support that such treatment aimed at selectively amplifying Tregs i) restores cognitive functions, ii) modulates functional profiles of microglia and astrocytes, and iii) may partly alter pathological Tau protein deposition.
Conclusions: Our study supports the therapeutic potential in Tauopathies of Treg-targeting immunomodulatory approaches.

SHIFT 01-669

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2 - 3 April 2025

THE SYSTEMIC TRANSFER OF NATURAL KILLER CELLS SIGNIFICANTLY ATTENUATES DISEASE PHENOTYPES IN A PRECLINICAL MOUSE MODEL OF PARKINSON'S DISEASE.

Jae Kyung Lee, Adetutu Adebowale, Jungha Byun, Jaegwon Chung, Hyun Joon Lee, Declan Gresham
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Aims: Natural killer (NK) cells are present in the parenchyma of Parkinson's disease (PD) and have the capability to clear abnormally aggregated α-synuclein (α-syn). In a preclinical mouse model of PD, the depletion of NK cells led to worsened motor deficits and an increase in insoluble α-syn deposits, suggesting a neuroprotective role for NK cells in disease development. This study investigated the direct effect of transferring NK cells on the progression of α-syn pathology and neurodegeneration using a mouse model of PD.
Methods: We utilized M83 transgenic mice, which overexpress the human A53T α-syn mutant protein. These mice were given intrastriatal injections of recombinant human α-syn fibrils (PFF α-syn) or α-syn monomers. Mice injected with PFF α-syn) developed mild motor deficits three weeks post-surgery, with symptoms progressing over eight to ten weeks. To assess the protective effect of NK cells in PD progression, we transferred NK cells into the mice and compared them to a control group treated with saline. Motor function was evaluated using the clasping task and immunohistological analysis using phosphorylated serine 129 α-syn (pSer129) antibodies was performed to evaluate α-syn pathology.
Results: The results showed that mice receiving NK cell transfers exhibited a significant improvement in motor deficits compared to the control group. Additionally, immunohistological analysis using pSer129 antibodies revealed a marked decrease in synuclein aggregations in the SNpc of NK cell-transferred mice. Current studies are focused on examining dopaminergic (DA) neurodegeneration, microglial activation, and peripheral immune cell profile.
Conclusions: This study provides the direct evidence of the protective role of NK cells in the progression of synucleopathies, highlighting NK cells as a promising novel therapeutic target for PD.

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SHIFT 01-674

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2 - 3 April 2025

OLFACTORY TRAINING AMELIORATES COGNITION CONCURRENT WITH CHANGES IN ARTERIAL DIAMETERS AND MECHANISTIC INSIGHT UNDERLYING THE CADO OLFACTOPRINT.

Rona Graham[1], Melissa Lessard-Beaudoin[1], Gemma Camara[1], Tamas Fulop[2], Dominique Lorrain[3], Christiane Auray[4], Kevin Whittingstall[5], Richard Doty[6], Joseph Desouza[7]
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Aims: There is a substantial gap between the burden of neurodegenerative diseases and the resources available to prevent and treat them. Evidence suggests that olfactory therapy (OT) may improve olfactory functions and importantly affect functional connectivity networks and lead to restoration of neural circuits. The aim of our study is to evaluate the olfactory system and cognition levels in control and MCI individuals at baseline, one-year later (pre-OT), and post-OT.
Methods: Olfactory tests (UPSIT and ODMT), cognitive tests (MoCA, HVLT-R, BVMT-R, Tail Making Test, Stroop D-KEFS, Boston Naming Test) and MRIs were performed at each time point in seniors and individuals with MCI (60-75 years, both sexes).
Results: Baseline measurements reveal the presence of deficits in olfaction, odor memory and several cognitive functions in the MCI individuals. In contrast, post-OT, our data show improvements in smell identification, verbal learning, visuospatial memory, and cognitive flexibility scores. Differences were also observed in cerebral artery diameters between pre and post-OT. An important question also to be addressed is whether there is specificity within the olfactory dysfunction. Our study confirms that olfactory deficit patterns are observed in MCI and that misidentification of certain odors correlated strongly with cognitive scores. This lead to the development of the Cognitive Associated Diagnostic Odours (CADO) signature. An analysis of the physicochemical characteristics of the CADO is currently underway.
Conclusions: Despite extensive evidence showing olfactory system dysfunction is observed in MCI there has been limited investigation of olfactory memory and studies of olfactory training as a therapy. Our results show that OT may provide benefit for individuals with MCI and we identify a tool that may help to provide early diagnosis for individuals with impending cognitive decline.

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SHIFT 01-676

On-Demand Oral Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
2 - 3 April 2025

LITHIUM CHLORIDE DIFFERENTIALLY MODULATES TAU PHOSPHORYLATION AT DIFFERENT SITES IN CELL-BASED MODELS

Dorit Hoffmann[1], Virpi Ahola[2], Nadine Huber[1], Teemu Natunen[2], Stina Leskelä[1], Pekka Kallio[3], Ian Pike[4], Jouni Sirviö[5], Annakaisa Haapasalo[1], Mikko Hiltunen[2]
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Aims: Hyperphosphorylation and intracellular aggregation of Tau is a pathological hallmark of several neurodegenerative diseases, including Alzheimer's disease. Modulation of Tau phosphorylation using phosphatase 2 A activators and protein kinase inhibitors have been used in clinical trials for Alzheimer's patients with varying results so far. Here, we have explored in detail how treatment with LiCl, a potent inhibitor of the serine/threonine kinase GSK-3β, affects Tau phosphorylation at several different sites in two cell models.
Methods: We assessed the effect of LiCl on Tau phosphorylation at different sites using two different models: A U2OS cell line overexpressing human triple mutant Tau-tGFP and a co-culture model of mouse embryonic primary cortical neurons and mouse BV-2 microglial cells, in which inflammation and subsequent Tau hyperphosphorylation was induced with lipopolysaccharide and interferon-γ. We assessed changes in Tau phosphorylation after treatment with LiCl using Western blot in the co-culture model and Western blot and proteomics analyses in the U2OS cells.
Results: We show that in the co-culture model, inflammation was successfully induced, leading to a strong increase in nitric oxide and TNF-α in the cell culture media. Tau phosphorylation was increased at several sites. Treatment with LiCl reduced Tau phosphorylation depending on the concentration and examined phosphosites. Proteomics data from the U2OS cell line showed that treatment with LiCl led to decreased phosphorylation at most of the examined phosphosites, matching the Western blot data.
Conclusions: We identified several new phosphorylation sites affected by LiCl treatment, while also showing that the effect of LiCl can vary depending on the concentration, examined phosphosites, and also the cell model, suggesting that in-depth analysis in suitable models is necessary to properly ascertain its usefulness in alleviating Tau phosphorylation.

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SHIFT 01-680

On-Demand Oral Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2 - 3 April 2025

TOXIC INTERPLAY BETWEEN SMALL DIPEPTIDE PROTEIN REPEATS AND TAU IN TAUOPATHIES

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Aims: Tauopathies, including Alzheimer's Disease and Frontotemporal Dementia, are characterized as intracellular lesions composed of aggregated tau proteins. Soluble tau oligomers are shown to be one of the most toxic species and are responsible for the spread of tau pathology. Recent studies have found that several proteins such as amyloid b, a-synuclein, and TDP-43 can aggregate tau. In this study, we investigated the ability of small metabolites like *C9orf72* associated dipeptide protein repeats (DPRs) to interact with and aggregate tau to form toxic soluble tau oligomers.
Methods: We have developed various models which express dipeptide protein repeats to understand the interaction between short peptides and tau. Using imaging techniques, we have evaluated the production of dipeptide repeat induced tau aggregates. We have also evaluated the downstream neuronal implications of tau aggregation in the synaptic landscape. Furthermore, we evaluated their toxicity, and seeding potency to understand the biological effects of this interaction.
Results: Our results suggest the propensity for DPRs, especially glycine-arginine and proline-arginine repeats to form oligomeric structures which interact and seed tau in a prion like fashion. This leads to the production of tau oligomers causing alterations in the microtubule dynamics in cell lines as well as primary neuronal culture systems. We also observe tau mediated synaptic degeneration.
Conclusions: Many studies have investigated the toxicity of small protein repeats, however, the role of DPR oligomers in inducing tau aggregation is still unclear. Thus, the ability to understand the toxic interplay between small peptide repeats and tau oligomers has great potential to further the understanding of tau progression and aid in the development of targeted therapeutics. This interaction leads to the production of tau oligomers, which trigger subsequent neurodegeneration.

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SHIFT 01-685

On-Demand Oral Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

BLOOD NEURON-DERIVED EXTRACELLULAR VESICLES FOR THE ANALYSIS OF TDP43 PATHOLOGY

Erez Eitan, Olga Volpert, Ahmed Elsherbini
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Aims: TAR DNA-binding protein 43 (TDP43) mislocalization and aggregation are pathologies found in about 90% of amyotrophic lateral sclerosis (ALS) patients, 40% of frontotemporal dementia (FTD) patients, and 40% of Alzheimer's disease patients. While CSF and blood biomarkers for Amyloid-beta, Tau, and alpha-synuclein have emerged in recent years, no TDP43 biomarker is available. Here, we develop a neuron-derived extracellular vesicle (NDE) based blood biomarker for TDP43.
Methods: NDEs were isolated from plasma samples using ExoSORT, and P-TDP43/TDP43 was measured by ELISA and Luminex assays. All assays were rigorously qualified for specificity and precision, ensuring the reliability of our results.
Results: TDP43 and P-TDP43 can be detected in the NDEs of both diseased and healthy individuals. Two operators ran the assay across three different days, and the coefficient of variance was below 15%. Recombinant protein from two different sources is detected, immune depletion reduces the signal, and there are significant differences in TDP43 knock-down cells. The level of TDP43 is 1.46-fold higher in ALS plasma samples than in healthy controls (N=95, $P<0.001$). TDP43 correlates with ALSFRS-R (N=58, R=0.46, P=0.007). P-TDP43 shows a lower level of separation in early diseases but strongly increases with disease progression (N=15). TDP43 associated with NDEs was significantly higher in rNLS8 mice (N=28, $P<0.001$). TDP43 associated with NDEs was 1.8-fold higher in dementia patients regardless of classical AD biomarkers (N=80, $P<0.02$). In FTD, we found an inverse correlation between TDP43 and Tau (R=0.65, $P<0.01$).
Conclusions: TDP43 and P-TDP43 can be measured in plasma NDEs from mice and humans. The procedure is semi-automated, robust, and specific. Our proof-of-concept studies across a variety of diseases demonstrate the potential of NDEs TDP43 to serve as a blood biomarker that identifies this pathology.

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SHIFT 01-690

On-Demand Oral Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2 - 3 April 2025

GRANULINS RESCUE INFLAMMATION, LYSOSOME DYSFUNCTION, AND NEUROPATHOLOGY IN A MOUSE MODEL OF PROGRANULIN DEFICIENCY

Thomas Kukar[1], Anarmaa Mendsaikhan[1], Jessica Root[2], Georgia Taylor[1], Paola Merino[1], Ludmilla Troiano Araujo[1], Danny Ryu[1], Christopher Holler[3], Bonne Thompson[3], Giuseppe Astarita[3], Jean-François Blain[3]
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Aims: Heterozygous, loss-of-function mutations in the granulin gene (*GRN)* cause frontotemporal dementia (FTD) by decreasing progranulin (PGRN) levels. The function of PGRN is still debated. We previously discovered that PGRN is rapidly processed into stable ~6 kDa granulin proteins in the lysosome. Granulin levels are also decreased in cells and tissue of GRN mutation carriers. Based on these findings we hypothesized that granulins are the functional subunits of PGRN. Here we report *in vivo* efficacy studies testing the hypothesis that delivery and replacement of a single granulin protein to the brains of *Grn*$^{-/-}$ mice is sufficient to ameliorate neuropathology.
Methods: We used *Grn*$^{-/-}$ mice which replicate many pathological features of human *GRN*-FTD cases including lysosome dysfunction, neuroinflammation, lipid alterations, and neurodegeneration. We performed intracerebroventricular injections of recombinant adeno-associated virus (rAAV2/1) encoding granulin-2/F, granulin-4/A, full-length PGRN (positive control), or GFP (negative control) in neonatal wild-type and *Grn*$^{-/-}$ mice. After AAV injections, mice were aged for 12 months, tissues collected, and analyzed using proteomics, lipidomics, biochemistry, and IHC.
Results: We find that expression of a single granulin broadly rescues disease pathology in *Grn*$^{-/-}$ mice. AAV-mediated expression of human granulin-2/F or granulin-4/A in *Grn*$^{-/-}$ mouse brain ameliorates dysregulated lysosomal proteins, microgliosis, and lipofuscinosis like full-length PGRN. Using lysosome immunoprecipitation and fluorescent microscopy, we find that granulins accumulate inside lysosomes in *Grn*$^{-/-}$ brains or cells.
Conclusions: These data support the hypothesis that PGRN is a precursor to granulins, which share a beneficial function inside the lysosome to maintain lipid and protein homeostasis to prevent neurodegeneration. Therefore, granulins are potential therapeutics to treat FTD-*GRN* and related diseases.

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SHIFT 01-694

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2 - 3 April 2025

LIFESTYLE FACTORS ASSOCIATE WITH COGNITIVE FUNCTION IN ELDERLY PARTICIPANTS OF THE GOTHENBURG MILD COGNITIVE IMPAIRMENT STUDY

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Aims: Cognitive diseases and dementia are thought to be caused by both genetic and environmental factors, such as lifestyle risk factors. The roles of lifestyle variables, as well as socioeconomic status, on cognitive function and dementia risk are not fully known. This is problematic as several of these risk factors are potentially modifiable and understanding their relationship with cognitive status could assist preventive approaches for dementia.
Methods: We investigated how lifestyle and socioeconomic variables were associated with cognitive functions in 901 participants from the Gothenburg Mild Cognitive Impairment study using Spearman correlations and linear regression models. The cohort consisted of healthy controls, individuals with preclinical stages of disease (subjective and mild cognitive impairment) as well as patients with Alzheimer 's disease, mixed dementia or subcortical small-vessel disease. Lifestyle and socioeconomic variables included education, civil status, physical activity, smoking, alcohol use, body mass index (BMI) and blood pressure (BP). Neuropsychological tests included, for example, cognitive screening by mini-mental state examination (MMSE), memory function using the Rey-auditory verbal learning test (RAVLT), verbal function from the Boston naming test (BNT) and processing speed and executive functions by trail making tests (TMT) and parallel serial mental operations (PASMO).
Results: Correlations of lifestyle/socioeconomic variables with cognition indicated that education was associated with the majority of cognitive test scores. Smoking status correlated with BNT and PASMO. Alcohol use correlated with TMT-A, TMT-B and BNT. BMI correlated with MMSE, RAVLT and BNT. Interestingly BP correlated with a large portion of the investigated cognitive test scores.
Conclusions: Our findings indicate that potentially modifiable lifestyle factors could have an important effect on cognitive function in older age. This speaks towards the importance of future intervention trials to prevent cognitive decline and cognitive diseases.

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SHIFT 01-695

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2 - 3 April 2025

INTRAVENOUS THROMBOLYSIS THERAPY AND DEMENTIA RISK IN ACUTE ISCHEMIC STROKE PATIENTS: A RETROSPECTIVE COHORT STUDY IN TAIWAN

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Aims: Intravenous thrombolysis (IVT) is the standard treatment for acute ischemic stroke (AIS) to improve functional outcomes. Furthermore, AIS is an important risk factor for dementia. Limited evidence has shown the long-term benefit of IVT on dementia in Western countries. We aim to investigate the association between IVT and the risk of dementia in acute ischemic stroke patients in Asian population.
Methods: A retrospective cohort study using medical records from a medical center in Taiwan between 2017 and 2022 was conducted. We included acute ischemic stroke patients aged over 55 years old who had not previously been diagnosed with dementia. The primary outcome was incident dementia ascertained through dementia diagnosis in medical records. The inverse probability of treatment-weighted Cox proportional hazard models were used to estimate the association between IVT and incident dementia.
Results: A total of 1,471 patients with AIS were included. 939(63.8%) were male, and the mean age was 70.7(SD=9.6) years. Among them, 19.1% of patients (n=281) received IVT. The mean follow-up year was 2.64 (SD=1.71) years. Although not statistically significant, the IVT was associated with a decreased risk of dementia (HR: 0.88 [95%CI 0.54-1.41)]).
Conclusions: The IVT showed a potentially protective effect, although not statistically significant, in reducing the incidence of dementia in Asian patients with ischemic stroke. Studies with larger sample sizes will be needed in the future.

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SHIFT 01-696

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2 - 3 April 2025

INHIBITION OF TNFA SHOWS PATHOLOGY SPECIFIC ALTERATIONS OF INFLAMMATION IN VCID MODELS

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Aims: Neuroinflammation is a well-documented contributor to vascular contributions to cognitive impairment and dementia (VCID), though studies elucidating inflammatory mechanisms of VCID are scarce. Our lab has identified TNFα as a potential driver of early inflammation in etiology of VCID. This study seeks to identify the role of TNFα in cerebral small vessel disease (cSVD) and cerebral amyloid angiopathy (CAA), as measured by vascular and inflammatory outcomes including microhemorrhage and microinfarct pathology, vascular amyloid assessment, and microglial Iba1 expression.
Methods: 16-month-old C57Bl6/SJL mice and Tg2576 were placed on our hyperhomocysteinemia-inducing diet for ten weeks to promote cSVD and CAA pathologies, respectively. XPro1595, a novel soluble TNFα inhibitor, was administered subcutaneously twice weekly at 2mg/ml throughout this timeframe. The right hemibrain was dissected and frontal cortex tissue was utilized for RNA extraction and subsequent NanoString nCounter analysis using the Mouse Neuroinflammation panel. The left hemibrain was fixed in PFA and used for histology, including Prussian blue for microhemorrhage assessment, H&E for microinfarct identification, and Congo Red for amyloid deposition in our CAA model. Immunohistochemical assessment for Iba1 was also performed.
Results: Gene expression data showed changes following soluble TNFα inhibition compared to vehicle controls. In cSVD, several genes were upregulated including Duoxa1, Bik, and Ikbke. In CAA, there were several altered genes including Tnfrsf1b, Trem1, Nod1, and Mavs. While both disease models had an upregulation of Slfn8, there was opposing expression of Itga7 between models. Histological analysis is ongoing.
Conclusions: Inhibition of soluble TNFα differentially impacts gene expression in models of cSVD and CAA compared to vehicle controls. Interestingly, this inhibition affects each disease model differently and suggests distinct mechanistic roles of TNFα-driven inflammation in cSVD and CAA.

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SHIFT 01-698

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / GENETICS, EPIDEMIOLOGY
2 - 3 April 2025

EFFECT OF LIFESTYLE AND SOCIOECONOMIC VARIABLES ON THE RISK OF CONVERTING TO COGNITIVE DISEASES IN THE GOTHENBURG MILD COGNITIVE IMPAIRMENT STUDY

Francesco Locatelli[1], Tahira Irum[2], Emir Basic[1], Zina Abed Al Sattar[2], Anders Wallin[2], Petronella Kettunen[1,2]
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Aims: The roles of lifestyle variables, as well as socioeconomic status, on cognitive function and dementia risk are not fully known. This is problematic as several of these risk factors are potentially modifiable and increased understanding of their relationship with progression to cognitive diseases could assist preventive approaches for dementia.
Methods: The cohort consisted of 901 participants from the Gothenburg Mild Cognitive Impairment study and included healthy controls, individuals with preclinical stages of disease (subjective and mild cognitive impairment) as well as patients with a dementia diagnosis of either Alzheimer's disease (AD), mixed dementia (MIX) or subcortical small-vessel disease (SSVD). Lifestyle and socioeconomic variables included education, civic status, physical activity, smoking, alcohol use, body mass index (BMI) and blood pressure (BP). First, we explored how lifestyle and socioeconomic variables correlated with the global deterioration scale (GDS). Next, the associations between lifestyle/socioeconomic variables and CSF biomarkers, such as the main AD biomarkers and APP metabolites, were investigated. Finally, survival analysis with Kaplan-Meier estimates were performed in preclinical patients to investigate how these variables impacted the number of persons converting to manifest cognitive diseases over the 10 year follow-up time of participants.
Results: Spearman correlations of lifestyle/socioeconomic variables, CSF biomarkes and GDS scores showed that education, alcohol use, BMI and BP were associated with cognitive function as well as CSF biomarkers representative for both amyloid and vascular pathologies. Moreover, survival analyses revealed that education level impacted the conversion to MIX and SSVD, and smoking the conversion to SSVD.
Conclusions: Our findings indicate that potentially modifiable lifestyle factors and socioeconomic status could have an important effect on risk of developing cognitive disease. This speaks towards the importance of future intervention trials to prevent cognitive decline and dementia.

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SHIFT 01-699

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

INVESTIGATING THE IMPACT OF LIFESTYLE AND SOCIOECONOMIC FACTORS ON REGIONAL BRAIN VOLUMES IN THE GOTHENBURG MILD COGNITIVE IMPAIRMENT STUDY

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Aims: The Gothenburg MCI study investigates patients with cognitive complaints at the Sahlgrenska University Hospital's memory clinic. Diagnoses include Alzheimer's disease (AD), subcortical small-vessel disease (SSVD), mixed AD/SSVD, and preclinical conditions like subjective cognitive impairment (SCI) and mild cognitive impairment (MCI), as well as healthy controls. While lifestyle factors like smoking, physical activity, blood pressure (BP), body mass index (BMI), and alcohol consumption are thought to influence cognitive decline, their impact on brain region volumes remains unclear. This study aimed at analyzing the associations between lifestyle and socioeconomic factors, and brain region volumes using MRI data from our cohort.
Methods: We studied 217 individuals, including healthy controls and patients with SCI, MCI, AD, MIX, and SSVD. MRI scans were analyzed for brain volumes using FreeSurfer software and adjusted for intracranial volume. Spearman correlation analyses and linear regression models with relevant covariates were used to assess the associations between the demographic and lifestyle variables sex, age, education, BMI, BP, smoking, alcohol consumption, physical activity, marital status, and employment, and brain region volumes.
Results: Our correlation analyses revealed significant associations between many lifestyle factors and brain region volumes. Interestingly, education had little impact on the examined regions. BMI affected several regions, and in turn, only the amygdala showed an influence on BMI. Elevated BP negatively impacted multiple brain regions, and smoking was regularly linked to reduced brain volumes.
Conclusions: Our findings indicate that several modifiable lifestyle factors significantly affect brain region volumes in an elderly population. Additionally, differences in brain volumes could possibly underlie lifestyle choices, highlighting the complexity of developing effective strategies for maintaining brain health and cognitive function.

SHIFT 01-700

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2 - 3 April 2025

BIOMARKERS OF NEURODEGENERATION, INFLAMMATION, AND MICROVASCULAR DISEASE DISCRIMINATE BETWEEN TRAJECTORIES OF RECOVERY AFTER TRAUMATIC BRAIN INJURY (TBI).

Ramon Diaz-Arrastia[1], Sonia Jain[2], Xiaying Sun[2], Catherine Demos[3], Nikhil Padmanabhan[3], Taron Gorham[3], Jacob Wohlstadter[3], Kevin Wang[4], Ava Puccio[5], Andrea Schneider[1], Danielle Sandsmark[1], Geoffrey Manley[6]
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Aims: TBI is a recognized risk factor for neurodegenerative disease in late life. Understanding the molecular mechanism(s) of neurodegeneration after brain injury will be required to develop effective disease-modifying therapies.
Methods: Plasma was collected on the day of injury from 394 patients with TBI (200 Glasgow Coma Scale (GCS) score 13-15; 194 GCS 3-12). Levels of 45 biomarkers were measured using Meso Scale Diagnostics assays, including proteins related to neurodegeneration, inflammation, and vascular injury. K-means clustering was performed to classify subjects into subgroups based on biomarker levels. The model was built on k=3 identified as the elbow of the scree plot of within-cluster sum of squares. We compared measures of injury severity and 6-month functional outcomes among the three clusters.
Results: 56 subjects compromised cluster 1, while 98 compromised cluster 2 and 97 cluster 3. There was no difference in age, race, ethnicity, of injury mechanisms across the clusters. Cluster 2 had significantly more females ($p<0.0001$). Admission GCS score, cranial CT findings, and 6-month Glasgow Outcome Scale-Extended (GOSE) scores differed significantly across the clusters ($p<0.0001$ for all comparisons). Cluster 1 consisted of those with primarily moderate to severe injuries (89% GCS 3-12; 93% CT positive), the majority of whom experienced an unfavorable outcome (64% with GOSE 1-6). Cluster 2 consisted primarily of those with minor injuries (97% GCS 13-15, 76% CT negative), and mostly experienced a favorable outcome (68% with GOSE 7-8). Cluster 3 defined a group with relatively moderate-to-severe injuries (64% GCS 3-12; 75% CT positive), who experienced relatively favorable outcomes (52% GOSE 7-8).
Conclusions: Protein biomarkers of neurodegeneration, inflammation, and vascular injury measured in the first day after TBI show promise as tools for classifying injury severity and predicting functional outcome.

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SHIFT 01-704

On-Demand Oral Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2 - 3 April 2025

MECHANISMS FOR MICRO-HEMORRHAGE INDUCED NEUROLOGICAL DECLINE WITH THERAPEUTIC IMPLICATIONS

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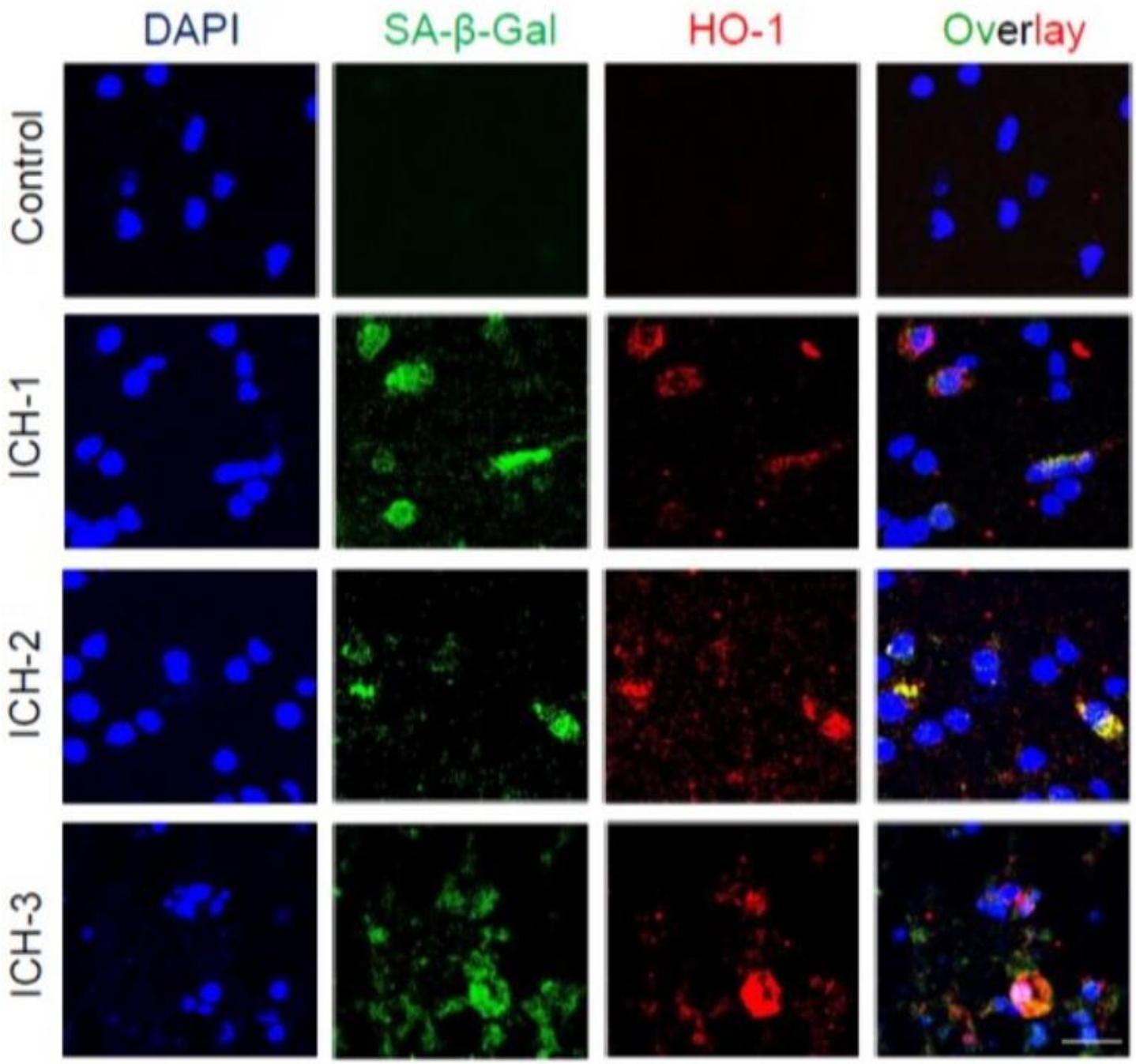
Aims: Brain micro- and macro-hemorrhage (ICH) are associated with cognitive decline. We investigated injury mechanisms of hemorrhage breakdown products, hemin and iron. We previously reported hemin and iron rapidly induce double strand DNA breaks and DNA damage response (DDR). These signals induced senescence that may explain the cognitive decline. However, senescence is known to protect against ferroptosis and apoptosis, therefore senolytic therapy may unleash iron-mediated cell death in the context of hemorrhage. Here, we characterize hemin induced phenotypic changes and test a pleiotropic oxidized carbon nanozyme developed to target hemorrhage.
Methods: Senescence associated beta-galactosidase (beta-Gal) and the heme-degrading enzyme heme-oxygenase 1 (HO-1) staining were performed in human IPSC-derived neurons after exposure to hemin, and in 3 human ICH post-operative and matched control brain sections. Signals reflecting apoptosis and ferroptosis were assessed by Western blot. We tested effects of a previously reported neuroprotective superoxide dismutase mimetic, oxidized, and PEGylated carbon nanozyme (PEG-OAC) w/wo the iron chelator deferoxamine covalently bonded (DEF-OAC-PEG).
Results: In IPSC-neurons, hemin rapidly induced DDR and b-Gal expression. while HO-1 expression lagged, indicating a vulnerable neuronal population. Inhibition of DDR was cytotoxic while inhibition of HO-1 transcription or PEG-OAC significantly reduced senescence but increased apoptosis and ferroptosis. DEF-OAC-PEG reduced all pathological phenotypes. Human ICH (Figure) showed neighboring neurons with b-Gal and HO-1 expression, indicating similar signals seen in our pre-clinical models.



Conclusions: Because HO-1 is not constitutively expressed in neurons, they are selectively vulnerable to hemin toxicity. The duality of phenotypes induced following hemorrhage is revealed in while senescence protects against ferroptosis and apoptosis but if selectively targeted, unleashes these cell death pathways. A dual-acting bespoke deferoxamine-linked nanozyme was most effective, suggesting no individual therapeutic target will be sufficient to improve cognition following hemorrhage.

On-Demand Orals
Posters on Board
Shift 02
4 – 5 April 2025

SHIFT 02-004

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / A-SYNUCLEIN
4 - 5 April

ALPHA-SYNUCLEIN MODULATES THE PHASE SEPARATION PROPERTIES OF SYNAPTIC CONDENSATES

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Aims: Compeling evidence indicates that liquid-liquid phase separation organizes macromolecules, especially proteins with intrinsically disordered regions, into membrane-free compartments. Hundreds of synaptic vesicles (SVs) form biomolecular condensates through the interaction with synapsins, the highly abundant family of synaptic phosphoproteins. Another key presynaptic protein family, including alpha-synuclein, plays a role in SV dynamics. Although alpha-synuclein's precise function in synaptic physiology is unclear, it is involved in nearly all steps of the SV cycle. This work focuses on understanding alpha-synuclein's role in SV clustering in synaptic physiology and disease.
Methods: To determine the effect of α-synuclein on the synapsin phase, we employ the reconstitution approaches using natively purified SVs from rat brains and the heterologous cell system to generate synapsin condensates. We demonstrate that synapsin condensates recruit alpha-synuclein, and while enriched into these synapsin condensates, alpha-synuclein still maintains its high mobility.
Results: The presence of SVs enhances the rate of synapsin/ alpha-synuclein condensation, suggesting that SVs act as catalyzers for the formation of synapsin condensates. At physiological salt and protein concentrations, alpha-synuclein alone cannot trigger the phase separation of SVs. The excess of alpha-synuclein attenuates the kinetics of synapsin/SV condensate formation, indicating that the molar ratio between synapsin and alpha-synuclein is important in assembling the functional condensates of SVs. alpha-Synuclein can be depleted from synapsin condensates by synphilin 1, another intrinsically disordered, scaffold protein at the presynapse implicated in Parkinson's Disease. Interestingly, synphilin 1 can form fluid condensates by itself, and alpha-synuclein shows the ability to fully wet synphilin condensates in a salt-dependent manner.
Conclusions: Understanding the molecular mechanism of alpha-synuclein interactions at the nerve terminals is crucial for clarifying the pathogenesis of synucleinopathies, where alpha-synuclein, synaptic proteins, and lipid organelles all accumulate as insoluble intracellular inclusions.

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SHIFT 02-005

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / A-SYNUCLEIN
4 - 5 April

THE SYSTEMATIC INVESTIGATION OF SELECTIVE NEURONAL VULNERABILITY IN PARKINSON'S DISEASE USING SPATIAL AND SINGLE-NUCLEI TRANSCRIPTOMICS INTEGRATION

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Aims: In Parkinson's disease, dopaminergic neurons of the substantia nigra (SN) show selective cell loss and build-up of α-synuclein aggregates in the remaining cells. Our study aims to investigate the molecular mechanisms that contribute to this vulnerability by integrating spatial and single-nuclei transcriptomics (ST).
Methods: We used GeoMx ST platform together with immunofluorescence staining with C-terminus α-synuclein antibody, LB509 which is less susceptible to Protein Kinase that is required for GeoMx workflow. The pathologist marked manually SN neurons with and without α-synuclein-positive Lewy bodies (LB) in 12 segmented areas in total. GeoMx enabled us to collect expression information only from these segmented areas and sequence them. We integrated our ST results with a single-nuclei in-house and published datasets that included 8 donors with PD. We created and implemented a computational framework to manage the quality, integrate, and analyse spatial and single-nuclei transcriptomics datasets.
Results: We projected 1303 scRNA-seq neurons onto the vulnerable (with LBs) and resistant (without LBs) neurons that were identified during the ST experiment. Integration resulted in an increase of the number of neurons in the ST profile from 12 to 916 cells. There were 253 genes that differentially expressed, with 152 being upregulated and 101 being downregulated ($P < 0.05$). The organization of microtubule cytoskeleton was impacted by the differentially regulated genes such as *NEFM, SOD1 and KLC1*. This indicates that there may be a problem with the assembly or degradation of microtubules in neurons that are vulnerable.
Conclusions: Our study showed that there are variations in the gene expression between neurons that are vulnerable and resilient, which can lead to significant insights. This knowledge can lead to targeted therapies that protect vulnerable neurons and slow disease progression.

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SHIFT 02-011

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS
4 - 5 April

A TRANSCRIPTOMIC AND CONNECTOMIC MODEL FOR NEURAL ATROPHIES INDUCED BY ALPHA-SYNUCLEIN INJECTION

Vikram Nathan[1,2], Stephanie Tullo[1], Janice Park[1,2], Yohan Yee[1], Gabriel A. Devenyi[1,3], Shady Rahayel[4,5], Ying-Qiu Zheng[6], Alain Dagher[7], Bratislav Misic[7], M. Mallar Chakravarty[1,3,8]
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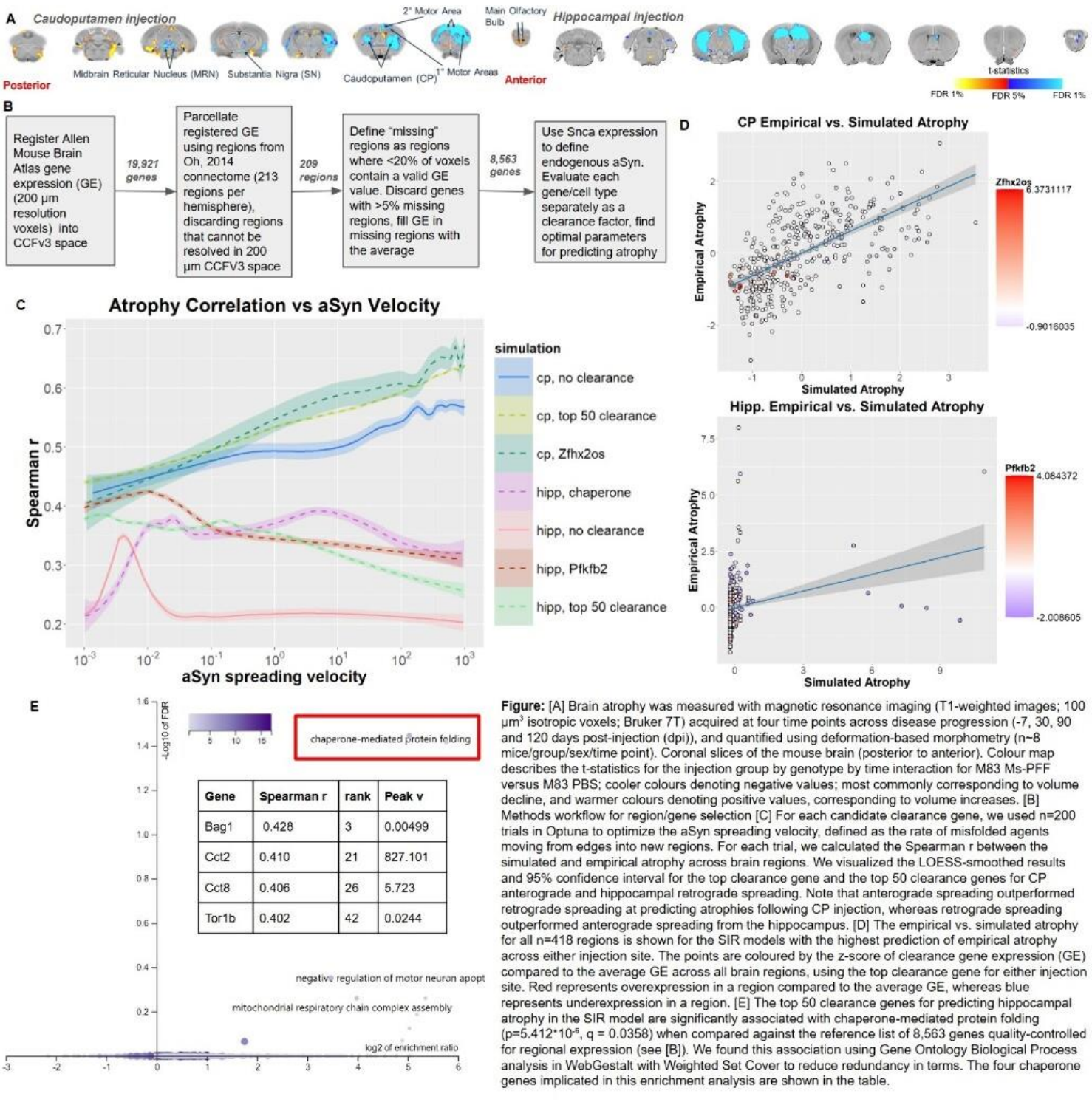
Aims: Previous work from our group adapted a Susceptible-Infected-Removed (SIR) agent-based model of alpha synuclein (αSyn) spreading to predict magnetic resonance imaging (MRI)-derived atrophy upon preformed fibril (hu-PFF) injection into the caudoputamen (CP). We injected hu-PFFs into the hippocampus as a positive control for prion-like αSyn spreading and observed atrophy localized around the hippocampi that was not well predicted by the SIR model, suggesting regional resilience to αSyn propagation. To elucidate putative mechanisms, we independently optimized model parameters for CP and hippocampal epicenters to discover potential differences in rate and clearance mechanisms.
Methods: We used an SIR model to predict αSyn spreading across the brain following injections of hu-PFF into the CP and hippocampus in different M83 transgenic mice injected at 11 weeks of age (n~8 mice/group/sex; 2.5 µL saline vs. hu-PFF). Deformation-based morphometry (DBM) derived from MRI data was used to quantify brain atrophy. Gene expression data from the Allen Mouse Brain Atlas was used to define the probability of αSyn clearance across regions. We used Bayesian parameter tuning with a number of candidate clearance genes to optimize the model's prediction of empirical atrophies.
Results: We improved the predictions from the fast, anterograde αSyn spreading from the CP with the addition of clearance genes (top gene Zfhx2os with r=0.679 vs. r=0.588). In contrast, we found that slower, retrograde spreading with clearance genes maximized atrophy prediction for hippocampal injection (highest Spearman r=.430 with Pfkfb2 vs. r=0.357), and the top 50 clearance genes were significantly enriched in chaperone folding processes (GO:0061077; $p=5.412*10^{-6}$, q=0.0358).



Gene	Spearman r	rank	Peak v
Bag1	0.428	3	0.00499
Cct2	0.410	21	827.101
Cct8	0.406	26	5.723
Tor1b	0.402	42	0.0244

Figure: [A] Brain atrophy was measured with magnetic resonance imaging (T1-weighted images; 100 µm^3 isotropic voxels; Bruker 7T) acquired at four time points across disease progression (-7, 30, 90 and 120 days post-injection (dpi)), and quantified using deformation-based morphometry (n~8 mice/group/sex/time point). Coronal slices of the mouse brain (posterior to anterior). Colour map describes the t-statistics for the injection group by genotype by time interaction for M83 Ms-PFF versus M83 PBS; cooler colours denoting negative values; most commonly corresponding to volume decline, and warmer colours denoting positive values, corresponding to volume increases. [B] Methods workflow for region/gene selection [C] For each candidate clearance gene, we used n=200 trials in Optuna to optimize the aSyn spreading velocity, defined as the rate of misfolded agents moving from edges into new regions. For each trial, we calculated the Spearman r between the simulated and empirical atrophy across brain regions. We visualized the LOESS-smoothed results and 95% confidence interval for the top clearance gene and the top 50 clearance genes for CP anterograde and hippocampal retrograde spreading. Note that anterograde spreading outperformed retrograde spreading at predicting atrophies following CP injection, whereas retrograde spreading outperformed anterograde spreading from the hippocampus. [D] The empirical vs. simulated atrophy for all n=418 regions is shown for the SIR models with the highest prediction of empirical atrophy across either injection site. The points are coloured by the z-score of clearance gene expression (GE) compared to the average GE across all brain regions, using the top clearance gene for either injection site. Red represents overexpression in a region compared to the average GE, whereas blue represents underexpression in a region. [E] The top 50 clearance genes for predicting hippocampal atrophy in the SIR model are significantly associated with chaperone-mediated protein folding ($p=5.412*10^{-6}$, q = 0.0358) when compared against the reference list of 8,563 genes quality-controlled for regional expression (see [B]). We found this association using Gene Ontology Biological Process analysis in WebGestalt with Weighted Set Cover to reduce redundancy in terms. The four chaperone genes implicated in this enrichment analysis are shown in the table.

Conclusions: Our work leverages the heterogeneity of αSyn spreading to highlight clearance genes as targets for therapeutic intervention, consistent with novel chaperone-derived drugs preventing αSyn aggregation.

SHIFT 02-012

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4 - 5 April

INTRATHCAL MRI CONTRAST REVEALS CSF-BRAIN FLUID DYNAMICS IN PARKINSON'S DISEASE AND CONTROLS

Sofie Lian[1,2], Jørgen Riseth[3,4], Markus Hovd[5,6], Ingrid Mossige[1,7], Tryggve Storås[8], Hilde Uggerud[9], Kent Andre Mardal[3,4], Mathias Toft[1,2], Kaja Nordengen[1,2]
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Aims: To investigate the efficiency of extracellular waste clearance using intrathecal gadobutrol in patients with Parkinson's disease (PD) compared to healthy controls.
Methods: We enrolled 10 healthy controls (mean age 66.1 years, 50% females) and 10 PD patients (mean disease duration 8.4 years, mean age 66.7 years, 70% females), diagnosed according to MDS criteria with positive DAT scans. Participants underwent baseline MRI before a 0.25 mmol intrathecal gadobutrol injection, followed by MRI at 5, 24, 48, and 72 hours post-injection using a 3T Philips Ingenia scanner. T1 signals in FreeSurfer-segmented regions were used for influx and efflux modeling. Blood samples were collected from 0 to 72 hours, and CSF was sampled pre-injection and at 72 hours. Gadobutrol levels were analyzed using ICP-MS with pharmacokinetic modeling. Sleep patterns were monitored with actigraphy and a sleep diary. This study received ethics approval (REC#282297) and hospital authority clearance (Data-protection #21/19051). All participants provided informed consent.
Results: Our study confirms the exchange between CSF and brain parenchyma in all participants, providing the first documented findings in both PD patients and healthy controls. We observed significant individual variations in the clearance of the contrast agent from CSF to peripheral blood in both groups, corresponding to intracranial CSF flow. Notably, gadobutrol was still detectable in the subarachnoid space 72 hours post-injection.
Conclusions: The observed influx and efflux of gadobutrol support the concept of active CSF circulation potentially contributing to waste product dynamics in PD. The substantial individual variability emphasizes the need for further research, particularly to investigate differences between PD patients with varying disease durations. Additionally, understanding the pharmacokinetics of gadobutrol in blood and CSF could provide deeper
insights into CSF clearance mechanisms in PD compared to healthy controls.

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SHIFT 02-023

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
4 - 5 April

IMMUNOPROTEASOME DYSREGULATION IN SYNUCLEINOPATHIES: ORTHOGONAL APPROACHES TO UNVEILING ITS THERAPEUTIC POTENTIAL IN PARKINSON'S DISEASE AND MSA

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Aims: Parkinson's disease (PD) and multiple system atrophy (MSA) are characterized by alpha-synuclein aggregation and immune dysregulation. Emerging evidence highlights the immunoproteasome (IP), a specialized proteasome with dual roles in immune modulation and protein homeostasis, as a key player in these disorders. However, its precise contribution remains to be fully clarified. Therefore, this study aimed to elucidate the role of the immunoproteasome, with a focus on both peripheral blood and central nervous system compartments, and to assess the therapeutic potential of its inhibition.
Methods: A total of 214 PBMC samples from healthy controls, PD, and MSA patients were analyzed for the immunoproteasome mRNA, protein expression alongside catalytic activity measurements. In parallel, a dry-lab analysis was conducted using data from the PPMI cohort. Flow cytometry was employed to evaluate the effect of inhibition on immune cell profiles. Additionally, neuronal exosomes from PD and MSA patients were isolated to be analyzed. Besides, human dopaminergic neurons, with or without co-cultured microglia, were used to model PD in vitro.
Results: RT-qPCR, Western blot, and native-gel revealed upregulation of IP expression and activity in both peripheral blood and neuronal exosomes from PD and MSA patients compared to healthy controls, corroborating findings from the PPMI cohort analysis. IP inhibition led to notable alterations in immune profiles, particularly in PD samples, with minimal impact on proteostasis stress. In the PD neuronal models, immunoproteasome expression and activity were markedly elevated. Notably, its inhibition demonstrated neuroprotective effects, as evidenced by a significant reduction in early apoptosis, which was attributed to improved mitochondrial mass without a concomitant increase in reactive oxygen species.
Conclusions: These findings revealed immunoproteasome increase, and its inhibition shows promise as a potential therapeutic strategy, offering neuroprotective benefits in PD models

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SHIFT 02-027

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4 - 5 April

DIFFERENTIAL TOXICITY INDUCED BY ALPHA-SYNUCLEIN CONFORMATIONAL STRAINS IN PRIMARY NEURONS

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Aims: Progressive accumulation of intracellular alpha-synuclein (asyn) aggregates is observed PD, DLB, and MSA. These synucleinopathies can be partly replicated in rodents following intracerebral seeding with recombinant asyn pre-formed fibrils (PFF) or human synucleinopathy-derived brain homogenates. In addition, distinct asyn PFF with unique conformational properties spread pathology differentially in various mouse brain regions, raising the possibility that distinct clinicopathological features of human synucleinopathies may be explained by differential toxicity to asyn conformers. Conformer properties are also sustained and refined by serial passaging in mice. We hypothesize that the mechanism for selective targeting of specific neuronal populations may be identified by measuring PFF internalization, trafficking, and mixing with cellular asyn. Here, we use primary neuron cultures to assess the susceptibility or resistance to distinct asyn conformers.
Methods: Hippocampal neurons isolated at E17 were exposed for 7-14 days to 7.5 ug/ml brain homogenate from A53T asyn transgenic (TgM83) mice inoculated with different asyn conformers, including PFF generated by adjusting NaCl concentration during aggregation ('no salt' (NS) and 'salt' (S) fibrils), human MSA brain homogenate, or spontaneously ill (SI) TgM83 brain homogenate.
Results: S PFF- and MSA-derived homogenates induced pronounced Ser129 phosphorylated-asyn (pS129) puncta, whereas NS PFF- and SI-derived homogenates generated lower levels of pathology. These differences were not due to the amount of misfolded asyn or pS129 in the inoculum. Cell lysates contained sufficient asyn seed to faithfully propagate parent conformer pathology. We observed a loss of lysosome integrity in correlation with asyn pathology and aberrant trafficking of presynaptic markers, suggesting that asyn conformers disrupt proteostasis and induce synaptic reorganization.
Conclusions: These neuronal cultures offer a simple biological assay to assess mechanisms governing seeding capacity of asyn fibrils.

SHIFT 02-031

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
4 - 5 April

TRANSIENT DOPAMINE DEPLETION INCREASES VESICULAR GLUTAMATE TRANSPORTER (VGLUT2) EXPRESSION IN MIDBRAIN DOPAMINE NEURONS – IMPLICATIONS FOR PARKINSON'S DISEASE

Thomas Steinkellner
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Aims: Though many neuronal populations are affected in Parkinson's disease (PD), its cardinal motor symptoms are a consequence of dopamine (DA) neuron loss in the substantia nigra (SNc). The precise mechanisms underlying DA neuron vulnerability remain unclear, but include oxidative stress, mitochondrial dysfunction, inflammation and aggregation of alpha-synuclein. More recently, a glutamate driven process has been implicated in disease progression, and there is now proof that DA neurons express the vesicular glutamate transporter VGLUT2 and co-release glutamate. In fact, we discovered that the majority of midbrain DA neurons transiently express VGLUT2 in development, but most shut down expression in the adult. Interestingly, DA neurons expressing VGLUT2 were shown to be more protected in various models of PD and are enriched in the SNc of human PD patients suggesting that VGLUT2 confers neuroprotective properties. However, it remains unclear whether DA neurons already expressing VGLUT2 are simply protected over non-VGLUT2 DA neurons, and/or whether VGLUT2 expression can also re-emerge in DA neurons not expressing VGLUT2 prior to neuronal injury.
Methods: We use different mouse models of experimental parkinsonism, viral vectors, biochemistry, behavior and histology.
Results: Our results indicate that transient DA depletion or inhibition of DA receptors can lead to re-emergence of VGLUT2 in subsets of DA neurons without concomitant DA neuron loss.
Conclusions: This suggests that pharmacological treatments that upregulate VGLUT2 expression in DA neurons may be a disease-modifying treatment strategy protecting against PD.

SHIFT 02-040

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LRKK2, PARKIN, PINK1, DJ-1
4 - 5 April

UNCOVERING GENETIC AND EPIGENETIC MECHANISMS OF DISEASE RESISTANCE IN PARKINSON'S RISK CARRIERS

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Aims: Numerous genetic risk factors for Parkinson's disease (PD), including GBA1, LRRK2, SNCA, PINK1, and PARK, have been identified in previous studies. However, not all individuals carrying these mutations develop PD, suggesting the presence of protective mechanisms that confer resistance. To better understand this phenomenon, we investigate the genetic and epigenetic factors that contribute to disease resistance in individuals with known PD risk factors.
Methods: We conducted an in-depth analysis of dopaminergic neurons derived from induced pluripotent stem cells (iPSCs) from five groups: healthy controls, GBA1 N370S mutants (with and without PD), and LRRK2 G2019S mutants (with and without PD). Three independent analyses approaches were employed: RNA sequencing (RNA-seq), ATAC-seq, and genome-wide CRISPR screening using a BiFC-α-Synuclein platform, aimed at identifying genes involving α-Synuclein aggregation, a hallmark of PD pathology.
Results: Through these analyses, we identified candidate genes consistently present at least two datasets. Notably, *Novel Gene A* was significantly downregulated in both human and animal PD models and appears to play a critical role in regulating the endoplasmic reticulum (ER)-related pathway. Furthermore, overexpression of *Novel Gene A* in dopaminergic neurons successfully restored the expression of genes downregulated in PD, shedding light on the potential molecular mechanisms underlying resistance to PD in mutation carriers.
Conclusions: Our findings highlight the importance of genetic and epigenetic factors in influencing disease resistance in individuals carrying Parkinson's disease (PD) risk factors. The identification of Novel Gene A and its role in regulating ER-related pathways offers new insights into the molecular mechanisms that may protect against PD development.

SHIFT 02-042

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4 - 5 April

PARAQUAT PRIMES AND ACTIVATES THE NLRP3 INFLAMMASOME LEADING TO NEUROINFLAMMATION AND NEURODEGENERATION VIA THE VOLTAGE-GATED PROTON CHANNEL HV1

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Aims: Paraquat (PQ) is a widely used herbicide that has been linked to increased risk of developing Parkinson's disease (PD). PQ exposure in mice induces selective nigrostriatal degeneration, aggregation of a-synuclein, and increased neuroinflammation that requires a priming dose. However, the mechanism(s) behind this priming are unclear.
Methods: C57BL/6J (C57) and Hv1 knockout (Hv1KO) primary microglia (PMG) were treated with 10 µM of paraquat for 6 (qPCR) and 12 hours (Western blot). To evaluate the priming effects, PMG were primed to PQ (10µM) for 6 hours, followed by 6 hours of PQ (10µM) treatment. 20-week-old male C57 and Hv1KO mice were injected with paraquat (PQ, 10 mg/Kg, i.p., once or twice separated by 7 days) and sacrificed 48 hours after the first dose or 7 days after the second dose. Brain regions were dissected for gene expression and fixed hemispheres were sectioned and stained for unbiased stereological counting of dopamine neurons.
Results: Hvcn1 mRNA levels were increased 2-fold in C57 PMG and 6-fold in C57 striatum following PQ treatement. This was accompanied by increased expression levels of NLRP3 inflammasome-related proteins, including NLRP3, ASC, cleaved caspase-1, cleaved IL-1b, secreted IL-1b, and secreted IL-18, which were abolished in Hv1KO PMG. A single PQ injection in C57 mice elevated NLRP3 and ASC protein levels in striatum by 6-fold and 5-fold, respectively, but not in Hv1KO mice. Following the second dose, PQ treatment resulted in 40% loss of TH^+ neurons in C57, but not in Hv1 or NLRP3 KO mice.
Conclusions: These data demonstrate that NLRP3 priming and activation is required for PQ-induced dopaminergic cell death and this is regulated by Hv1. Targeting Hv1 may be a novel means to reduce neuroinflammation and neurodegeneration.

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SHIFT 02-044

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4 - 5 April

1. MILD CI IMPAIRMENT IS SUFFICIENT TO INDUCE DEFECTS IN A-SYNUCLEIN PROTEOSTASIS

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Aims: Mild mitochondrial complex I (CI) deficits have been observed in the SN of idiopathic Parkinson's disease (PD) patients. Yet, it remains unclear if CI deficit is a cause or consequence of disease. CI is a proton-pumping NADH: ubiquinone oxidoreductase crucial for energy production. We developed highly viable systems (cellular and animal) with genetic loss of *NDUFAF2* resulting in a partial CI deficit, mimicking idiopathic PD brain and tested the hypothesis that mild CI deficit increases the propensity for αSyn aggregation.
Methods: In the cellular system, we employed HEK293 lines exhibiting different levels of CI deficits. To model abnormal αSyn aggregation, cells were induced to transiently overexpress αSyn in the presence of synthetic pre-formed fibrils (PFFs). In the mouse *Ndufaf2* KO model, bilateral intrastriatal injections were conducted with WT mouse PFFs. Brains were analyzed three months post-injection via immunohistochemistry for αSyn inclusions.
Results: Partial CI deficiency resulted in elevated levels of aggregated total and pS129 αSyn. In the mouse model of PFF-induced synucleinopathy, we observed a significant increase in pS129 pathology in the prefrontal cortex and motor cortex of the *Ndufaf2* KO compared to WT. These results support our hypothesis that mild CI defects promote αSyn aggregation both *in vitro* and *in vivo.* Surprisingly, the degree of αSyn aggregation was not worsened by severe CI deficiency suggesting that even mild CI deficit is maximally detrimental to αSyn homeostasis.
Conclusions: Our study reveals the novel finding that mild CI deficit, mimicking idiopathic PD brain, is sufficient to cause a greater propensity for abnormal αSyn aggregation in both cellular and animal models of synucleinopathy. Ongoing studies are being conducted to elucidate the mechanism by which mitochondrial CI impairment promotes αSyn dyshomeostasis.

SHIFT 02-047

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4 - 5 April

MODELING CORTICAL A-SYNUCLEIN PATHOLOGY IN CEREBRAL ORGANOIDS (CO)

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Aims: Lewy Body Dementia (LBD) accounts for 10-15% of all pathologically defined dementia cases. The defining pathological features of LBD is the misfolding and accumulation of α-synuclein (aSyn) aggregates in cortical neurons and neurites, which are associated with cognitive decline. Currently, no disease-modifying treatments exist to slow or halt the progression of LBD. One of the challenges in therapeutic development is the lack of experimental models that faithfully replicate the cortical pathology seen in LBD. Here, we present the development of a robust CO model of cortical aSyn pathology.
Methods: CO were generated from induced pluripotent stem cells (iPSCs) derived from a familial Parkinson's disease (fPD) patient carrying the α-synuclein gene (*SNCA*) triplication, as well as from healthy control subjects. We conducted longitudinal analyses of aSyn and phosphorylated aSyn (p-aSyn) accumulation, as well as Lewy body (LB) markers such as p62 and ubiquitin.
Results: Our findings demonstrated a progressive and substantial accumulation of p-aSyn in the fPD-COs, which morphologically resemble cortical LBs. Additionally, the fPD-CO exhibited substantial p-aSyn accumulation in neurites resembling Lewy neurites (LNs). Notably, we did not observe significant accumulation of p62-positive inclusions in the fPD-CO. We are currently investigating these results in the context of recent findings demonstrating the existence of two distinct types of aSyn inclusions: lipid-rich cytotoxic inclusions and p62-positive inclusions enriched in filamentous material. Further analyses are ongoing to assess the seeding capacity of these aSyn inclusions and their effects on synaptic integrity, gliosis, and neuronal loss.
Conclusions: The cellular diversity and the physiological levels of cell type-specific human transcriptome expression make the CO an excellent model to study the mechanisms of cortical aSyn pathology and to develop novel therapeutics.

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SHIFT 02-057

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
4 - 5 April

LOCUS COERULEUS CIRCUIT DYSFUNCTION IN A PRODROMAL PARKINSON'S DISEASE MOUSE MODEL

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Aims: Breathing is a resilient behavior, yet respiratory dysfunction occurs in neurodegenerative diseases, including Parkinson's Disease (PD). The precise mechanistic cause of PD is not completely understood; however, the disease is classically characterized by aggregated alpha-synuclein (α-syn). Years prior to diagnosis, individuals with PD often experience various non-motor symptoms, including respiratory dysfunction. This potentially correlates with pathology and cell death in brain regions afflicted early in the disease progression, such as the Locus Coeruleus (LC). The overarching goal of this project is to investigate the impact of local LC α-syn accumulation on the intrinsic properties of LC neurons and its subsequent impact on the control of breathing.
Methods: To study prodromal PD progression, we induced pathology with bilateral injections of α-syn pre-formed fibrils (PFF) into the LC region of C57BL/6J mice. At 1-week, 1-month, and 3-months post-injection, mice were assessed for changes in sleep/wake cycles (passive infrared motion detectors, Aurora; Ademco®) and breathing function (whole-body plethysmography with ventilatory challenges). Following this, we used immunohistochemistry to assess cellular pathology and neuronal death. Whole-cell patch clamp recordings were utilized to measure intrinsic LC neuron properties, such as excitability, firing rate, afterhyperpolarization, and action potential characteristics.
Results: At each time point assessed, PFF-injected mice exhibit significant increases in baseline respiratory rate, indicating dysfunction in LC-based networks involved in breathing. This is also evidenced in whole-cell patch clamp recordings indicating changes in LC neuronal properties, as well as behavioral data assessing circadian rhythm.
Conclusions: The complex relationship between α-syn pathology, respiratory irregularities, and dysfunction at the neuronal level in PD is not fully understood. Our results indicate that LC pathology in a prodromal PD mouse model correlates with disruption of respiration, sleep-wake cycles, and intrinsic properties of LC neurons.

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SHIFT 02-058

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
4 - 5 April

N370S AND L444P GBA1 MUTATIONS IMPAIR DOPAMINE NEURON MOLECULAR AND FUNCTIONAL PHENOTYPE IN PARKINSON´S DISEASE

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Aims: Mutations in the glucocerebrosidase 1 (*GBA1*) gene, encoding a lysosomal enzyme, are major risk factors for Parkinson´s disease (PD), but their role in PD pathology is not fully understood. The impact of *GBA1* mutations on neuronal maturation, function, and degeneration was investigated in human dopaminergic (DA) neurons.
Methods: DA neurons were obtained by differentiation of induced pluripotent stem cells (iPS cells or iPSCs) derived from PD patients carrying the heterozygous N370S or L444P mutation in *GBA1* or from healthy controls and then analyzed by immunocytochemistry, confocal microscopy, RT-qPCR, ELISA, electrophysiology, and electron microscopy.
Results: Expression of markers of mesencephalic dopaminergic progenitors and neurons (including LMX1A, LMX1B, FOXA2, NURR1, TH, VMAT2, GIRK2, and DAT) was detected in differentiating cultures. Electrophysiological recordings revealed a significant increase in the firing rate of N370S but not L444P DA neurons, whereas evoked dopamine release was stronger from neurons carrying either mutation than from the controls. Furthermore, there was a significant accumulation of α-synuclein aggregates in the cell body and dendrites of N370S neurons. Remarkably, neurons carrying either *GBA1* mutation accumulated abundant degenerative bodies, multilamellar bodies, autophagosomes, and Golgi apparatus vacuolated dictyosomes, with some differences in neurons carrying the N370S or L444P mutation.
Conclusions: Our findings indicate that N370S and L444P *GBA1* mutations produce similar and distinct molecular, electrical, and ultrastructural alterations in DA neurons. They suggest that these mutations provoke stress responses early in the neuronal differentiation program, which could be involved in PD pathology.

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SHIFT 02-063

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4 - 5 April

RESEARCH INFORMATION DISCLOSURE IN THE PPMI STUDY: PARTICIPANT IMPRESSIONS IMMEDIATELY AFTER DISCLOSURE

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Aims: Disclosure of personal research information to participants in observational studies remains controversial due to ethical and logistical challenges. The Parkinson Progression Markers Initiative (PPMI) is a multinational, longitudinal observational study that collects clinical, imaging, and biologic data from participants with or at risk of Parkinson's disease (PD) and healthy controls. Our objective is to ascertain PPMI participant impressions of learning personal research information after disclosure.
Methods: PD participants in the PPMI study in the United States were invited to access their alpha-synuclein seed amplification assay (aSyn-SAA), MDS-UPDRS Part III, and DaT scan research information. This information is made available on the myPPMI participant portal. Educational material and tele-counseling were provided and access to research information was voluntary. Participants were asked to complete surveys after disclosure to ascertain utility and comprehension of the educational content and regret in learning their research information.
Results: 255 participants accessed at least 1 research data point. The mean age at the most recent clinic visit was 65.6 (SD 8.9), with age at onset of 61.8 (SD 9.3). 57% were male and the mean years of education was 17 (SD 2). 52 (20% of 255) participants completed a survey after aSyn SAA disclosure, 53 (20%) after MDS-UPDRSIII disclosure, and 92 (36%) after DaT scan disclosure. After reviewing their research information, roughly 2% (SAA), 22% (DaT), and 25% (MDS-UPDRSIII) of participants reported not understating their information. Over 90% of respondents reported that they did not regret the decision to learn their research information.
Conclusions: PD PPMI participants reported good comprehension of educational materials, and a low level of regret in learning their research information. Future clinical research studies should consider disclosing research information to participants.

SHIFT 02-064

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4 - 5 April

COGNITION IN EARLY-STAGE NEURONAL ALPHA-SYNUCLEIN DISEASE WITH HYPOSMIA

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Aims: Objectives: To determine if cognitive deficits are detectable in early-stage neuronal alpha-synuclein Disease (NSD) with hyposmia, with and without REM sleep behavior disorder (RBD).
Methods: Methods: Using Parkinson's Progression Markers Initiative baseline data, cognitive performance was assessed with a cognitive summary score (CSS) developed from a multi-domain battery and applying regression-based internal norms derived from a robust healthy control (HC) group. Performance was examined for participants with hyposmia classified as NSD-Integrated Staging System (NSD-ISS) Stage 2, either Stage 2A (CSF synuclein seed amplification assay [SAA]+, SPECT dopamine transporter scan [DaTscan]-) or 2B (SAA+, DaTscan+).
Results: Results: Participants were Stage 2A (N=175), Stage 2B (N=318) and HCs (N=158). Although Stage 2 overall had intact Montreal Cognitive Assessment scores[WD1] (mean (SD) =XX.X (X.X), Stage 2A had a numerically worse CSS (z-score mean difference =0.10, p-value NS; effect size=0.16) and Stage 2B had a statistically worse CSS (z-score mean difference =0.26, p-value <0.05; effect size=0.40) compared with HCs. In Stage 2A participants with hyposmia alone had normal cognition, but the presence of comorbid RBD was associated with a significant decline in cognition (z-score mean difference =0.33, p-value <0.05, effect size =0.49). In Stage 2B participants with hyposmia alone cognition was abnormal[WD2] , and superimposed RBD had a non-statistically-significant additive effect.
Conclusions: Interpretation: Early NSD with hyposmia is associated with detectable cognitive deficits using a cognitive summary score compared with a robust HC comparator group, particularly when dopamine system impairment is superimposed or comorbid iRBD is present, supporting the inclusion of a cognitive track in early-stage NSD-ISS.

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SHIFT 02-072

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / ENZYME MODULATORS
4 - 5 April

DESIGN OF A PHASE 1B STUDY TO EVALUATE THE GCASE-TARGETING MOLECULE GT-02287 IN GBA1-PD AND SPORADIC PD.

Jonas Hannestad[1], Raffaella Pozzi[2], Terenzio Ignoni[2], Manuela Bosetti[2], Sara Cano[3], Joanne Taylor[4]
[1]Gain Therapeutics, Bethesda, United States of America, [2]Gain Therapeutics, Lugano, Switzerland, [3]Gain Therapeutics, Barcelona, Spain, [4]Gain Therapeutics Inc, London, United Kingdom

Aims: This is a 3-month, open-label study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the brain-penetrant small molecule GT-02287 in approximately 15 participants with GBA1-PD or sporadic PD who are treatment-naïve or on stable dopaminergic treatment.
Methods: This study will be conducted in Australia. Recruitment will start in December 2024. The primary endpoint, safety and tolerabilty, will be evaluated through the incidence, nature, and severity of adverse events and the incidence of clinically significant findings for laboratory tests, physical examinations, body weight, vital signs, and 12-lead electrocardiograms. Plasma PK will include C_{max}, T_{max}, AUC_{tau}, AUC_{last}, C_{min}, and other parameters as appropriate. Levels of GT-02287 in CSF will also be measured. Target engagement and disease biomarkers in blood and CSF will include GCase activity, levels of glucosylsphingosine and glucosylceramide, levels of phosphorylated and total α-synuclein, neurofilament light chain, and inflammatory markers. Additional exploratory endpoints will include sleep EEG, the Movement Disorder Society Unified Parkinson's Disease Rating Scale, the Montreal Cognitive Assessment, and other scales. Participants will receive a daily oral dose of GT-02287 of approximately 13.5 mg/kg/day (range 11.3 to 15.0 mg/kg) for 90 days. This dose level was safe and generally well tolerated in healthy volunteers for 14 days of dosing, produced therapeutic plasma levels, and increased GCase activity in the blood.
Results: Recruitment for this study will initiate in December 2024, and the study is projected to be completed in Q4 2025.
Conclusions: GT-02287 is a novel brain-penetrant, GCase-targeting small molecule that has successfully completed Phase 1 in healthy volunteers and that is now being evaluated in the first study in people with PD. Based on extensive preclinical data, GT-02287 has the potential to slow disease progression in both GBA1-PD and sporadic PD.

SHIFT 02-074

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / IMMUNOTHERAPY
4 - 5 April

NOVEL OUTCOME MEASURES FOR PROOF-OF-CONCEPT CLINICAL TRIAL OF THE IMMUNOMODULATORY AND DOPAMINERGIC NEUROPROTECTANT RXR AGONIST IRX4204 IN PD

Martin Sanders, Vidyasagar Vuligonda
Io Therapeutics, Inc., The Woodlands, United States of America

Aims: IRX4204 is a highly potent, highly selective, brain penetrant, RXR nuclear receptor agonist. It has immunomodulatory effects of promoting Tregs, and inhibiting Th17 cells and production of IL-17. It has anti-inflammatory effects of inhibiting production of IL-6, nitric oxide, and other inflammatory mediators by microglia and monocytes. It has dopaminergic neuron protective effects, mediated by activation of RXR-Nurr1 heterodimers. IRX4204 has been evaluated in a an open label, 28-day dose ranging clinical trial in early PD patients, in which it demonstrated tolerability and safety of oral dosing at 5 mg/day, brain penetrance, and improvement in UPDRS Total Scores and Motor Scores in 13 of 15 patients. Our aim is to conduct a follow-on proof of concept placebo-controlled trial with novel outcome measures.
Methods: We are initiating a follow-on phase II, randomized, double-blind, placebo-controlled proof of concept clinical trial in PD patients using an expanded panel of novel assessments of efficacy. The trial utilizes biomarkers, including quantitation of brain derived exosomes for RXR, Nurr1, Nur77, DAT, and DDC, all of which are promoted by IRX4204 in preclinical studies; CSF and plasma assays for IL-17, IL-6, and other cytokines; a newly developed multi-symptom questionnaire, the University of Rochester PD Health Inventory; and quantitative recording of patient motor activities by a wearable device; in addition to the UPDRS. The trial will be conducted with IRB and regulatory agency approvals.
Results: It is expected the trial conclusion will not have been reached at the time of the presentation and the trial blinding will not have been broken.
Conclusions: It is expected that the trial will provide placebo-controlled proof-of-concept evidence of safety and efficacy of IRX4204 for treatment of PD by utilizing multiple new types of assessments of biologic and clinical outcomes.

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SHIFT 02-076

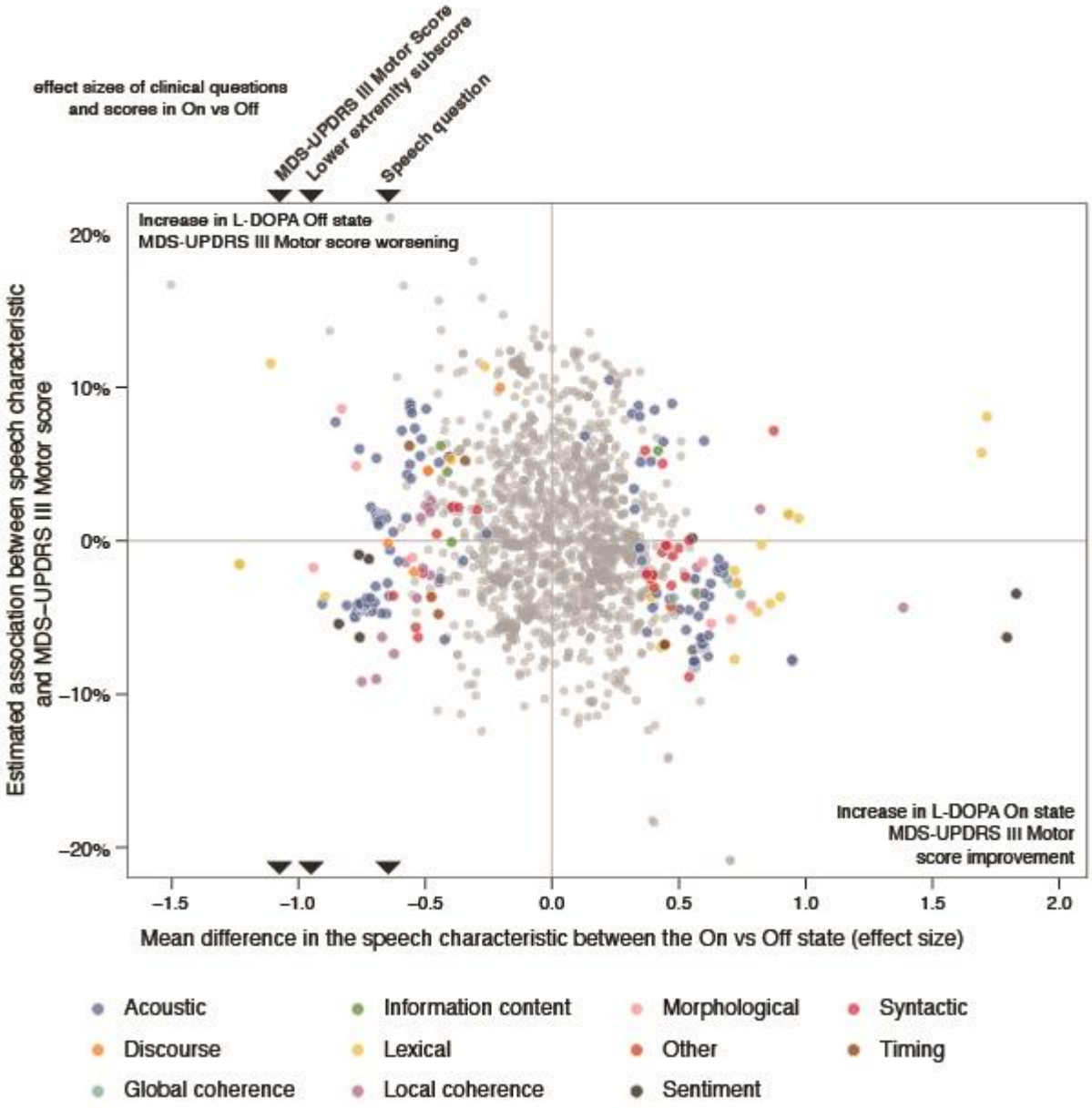
On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY
4 - 5 April

COMPARISON OF CLINICAL ENDPOINTS AND DERIVED SPEECH CHARACTERISTICS FOR TRACKING MOTOR SYMPTOM CHANGES WITH LEVODOPA ADMINISTRATION IN PARKINSON'S DISEASE

Matthew Wipperman[1], Rolando Acosta[1], William Simpson[2], Erica Chio[1], Erin Robertson[1], Bharatkumar Koyani[1], Emily Timm[3], Nicollette Purcell[3], Joan O'keefe[3], Dhanesh Patel[1], Michael Spilka[2], Mengdan Xu[2], Martina De Lillo[2], Jessica Robin[2], Laureano Moro Velázquez[4], Ana-Maria Visoiu-Knapp[1], Andreja Avbersek[1], Rinol Alaj[1], Sara Hamon[1], Jacek Urbanek[1], Olivier Harari[1], Oren Levy[1], Deborah Hall[3], Kimberly Kwei[5]
[1]Regeneron Pharmaceuticals, Inc., Tarrytown, United States of America, [2]Cambridge Cognition, Toronto, Canada, [3]Rush University Medical Center, Chicago, United States of America, [4]Johns Hopkins University, Baltimore, United States of America, [5]Columbia University Medical Center, Department Of Neurology, Movement Disorders, New York, United States of America

Aims: Patients with Parkinson's disease experience significant changes in aspects of speech, but existing clinical instruments fail to fully capture the range of these changes (the speech question alone having insufficient dynamic range). Our objective was to develop and use a signal and natural language processing platform to measure and evaluate changes in speech before (OFF) and after (ON) levodopa administration, examine how these measures associate with existing clinical endpoints, and establish criteria to further refine such characteristics for digital biomarker development.
Methods: Ten females and 11 males had a mean (standard deviation [SD]) age of 64 (11) years, a disease duration of 10 (6) years, and a Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) motor score of 43 (18), and completed a battery of digital speech assessments. Participants' responses were recorded, transcribed, and processed using the Winterlight speech platform to derive speech characteristics, which were evaluated for ON versus OFF change, as well as for their changes associated to the MDS-UPDRS III motor score.
Results: Raw data were processed into >800 speech characteristics covering a broad range of categories. Characteristics were plotted with respect to their change in ON versus OFF state, and association with MDS-UPDRS III motor score to thoroughly evaluate various aspects of speech. While many characteristics followed expected trends, several did not (labeled quadrants). Interestingly, some individual characteristics had effect sizes within the range of composite clinical scores.
Conclusions: Digital speech assessments have promise to measure characteristics of speech in Parkinson's disease. Next steps are to filter the most promising characteristics for face validity on the directionality of change and validate them in an independent dataset.

Figure. Speech characteristics associated with nominally significant mean changes (P<0.05) between medication states are colored.



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SHIFT 02-079

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
4 - 5 April

RAB32 VARIANTS IN A HISPANIC PD COHORT, ENRICHED FOR CARIBBEAN HISPANICS.

Karen Nuytemans[1], Genesis Soriano[1], Liena Infante[1], Anisley Matinez[1], Tianjie Gu[1], Corneliu Luca[2], Carlos Singer[2], Jason Margolesky[2], Henry Moore[2], Ihtsham Haq[2], Margaret Pericak-Vance[1], Jeffery Vance[1]
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Aims: Recently identified variants in novel PD gene, *RAB32*, seem to be located on mostly European ancestry. To determine the contribution of this gene in the admixed Hispanic population, we screened 162 PD patients from the Miami Hispanic PD research study.
Methods: Illumina Global Diversity Array with Neurobooster content genotyping data were generated for all samples through the HiPD study and the Global Parkinson's Genetics Program (GP2). Genotyping data was used to determine local ancestry surrounding the *RAB32* gene using RFMIx. We performed Sanger sequencing for all four exons of *RAB32* in all PD patients.
Results: We did not identify previously reported variant p.S71R in any of our patients. We did identify novel variant p.D107G in one patient on European ancestry. *In-silico* functional evidence supports a pathogenic role of this variant; gnomAD frequency < 0.01%, CADD = 33, functional predictions on amino acid change consistently (highly) pathogenic, highly conserved). No data on other family members is available.
Conclusions: Our analyses show potential pathogenic variants in *RAB32* underlying disease in Hispanic populations. More experimental functional analyses will be needed to determine the impact of this variant on protein function. Additional screenings of this variant in larger (Hispanic) PD dataset will further elucidate the impact of this variant in admixed and all PD patients.

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SHIFT 02-080

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

A COMPREHENSIVE SINGLE-CELL RNA SEQUENCING ANALYSIS EVALUATING THE ROLE OF T-LYMPHOCYTES IN IDIOPATHIC AND GENETIC PARKINSON'S DISEASE

Mikaela Rosen[1], Oriol Narcis[1], Tatsuhiko Naito[2,3], Elena Mejia[1], Carlos Perez Mandry[1], Amanda Allan[1], Tarek Khashan[1], Charlie Argyrou[1], Rachel Saunders-Pullman[4], Giulietta Riboldi[5], Towfique Raj[1]
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Aims: T-lymphocytes are key in Parkinson's disease (PD) pathology, influencing the inflammatory response from the periphery to the brain. Genetic studies link human leukocyte antigen (HLA) class II alleles to PD risk, suggesting CD4 T-cells' crucial role with antigen-presenting cells. Our goal is to rigorously characterize T-cells' transcriptional profiles and T-cell receptor repertoires during PD progression.
Methods: We performed a large-scale, comprehensive single-cell RNA-seq analysis of human peripheral blood mononuclear cells (PBMC) from two well-characterized cohorts of PD, encompassing 157 donors. Our processed cohort include controls (n=28), individuals with idiopathic PD (iPD; n=30), genetic PD with GBA or LRRK2 mutations (gPD; n=29), and carriers of GBA or LRRK2 mutations (n=10). We obtain gene expression, V(D)J immune receptor expression, genotypes and HLA alleles. We perform standard single-cell data processing, differential cell type composition, differential expression, TCR-HLA association and clonal expansion analysis.
Results: We found a main effect of disease on regulatory T-cell proportions, with more cells present in control blood (p=0.04). We also identified an interaction effect between disease and sex on cytotoxic effector CD8 T-cell proportions (p=0.02). Furthermore, we have observed distinct V(D)J gene expression patterns indicating clonal expansion in CD8 activated T-cells. The degree of clonal expansion differs between control and PD patients, with more clonal expansion in control blood and more diversity in PD blood. Interestingly, we also observe more clonal expansion of cytotoxic GZMK+ or GZMB+ CD8+ T-cells in female PD patients compared to male PD patients.
Conclusions: Overall, these results further our understanding of the role of T-cells in PD and help determine the potential for targeted immune-based therapeutic interventions or biomarker capabilities.

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SHIFT 02-083

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
4 - 5 April

LONG-READ SEQUENCING IN COMPLEX CASES OF PARKINSON'S DISEASE: ADVANCES AND CHALLENGES

Ngan Tran[1,2,3], Rhett Rautsaw[4], Michael Heckman[5], Alexandra Soto-Beasley[1], Wolfdieter Springer[1,3], Ryan Uitti[6], Zbigniew Wszolek[6], Owen Ross[1,3]
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Aims: Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, and currently, no treatments effectively halt/slow disease progression. Two primary cellular mechanisms implicated in PD are mitochondrial dysfunction and alpha-synuclein aggregation. We believe that mitochondrial dysfunction plays a particularly important role in early-onset PD (EOPD). To date, less than 10% of patients with EOPD are genetically explained. In this project, we utilize long-read sequencing(LRS) to capture complex structural variants in the nuclear and mitochondrial genome (mtDNA).
Methods: We generated both SR-WGS and LR-WGS for a subset of 24 EOPD patients(AAO<39). We utilized a CNN deep-learning based caller DeepVariant(Google) to call genetic variations. We also overlapped SVs and SNVs for compound heterozygotes identification. Finally, we evaluated the use of LRS on mtDNA and weight the impact based on functional relevance.
Results: We find that at the individual sample level, there are significant higher number of coding variants captured by LRS. We also found highly biological-relevant variants captured only by LRS, that may partially explain clinical phenotypic heterogeneity, e.g. 62 bp deletion in *COL6A2*. The 16.5kb mtDNA, uniquely captured in a single read showcase robust capability to identify stable and acquired SNPs.
Conclusions: Our study provides a comprehensive approach for cases that has been ruled out by other methods(whole exome; MLPA) and not typical PD with pathogenic variants in *PINK1/PRKN*. LR-WGS facilitates the identification of variants that likely have a phenotypic impact. The robust capture of mtDNA highlights potential mitochondrial therapies-targeted approach. However, prioritization strategies to pinpoint a disease modifier remains challenging due to the lack of mechanism to gather supporting evidence simultaneously and a lack of large control cohort. We believe that deciphering the genetic variation using LRS could provide novel insights for unsolved neurological cases.

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SHIFT 02-084

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
4 - 5 April

NOVEL SPATIAL TRANSCRIPTOMIC TOOLS TO IDENTIFY CHANGES IN VULNERABLE ANATOMICAL REGIONS AND CELLS IN PARKINSON'S DISEASE

Annie Ziyi Zhao[1], Alan Liu[1], Isar Nassiri[1], Jimena Monzón-Sandoval[2], Michal Rokicki[2], Caleb Webber[2,3], Laura Parkkinen[1,3]
[1]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom, [2]Cardiff University, Cardiff, United Kingdom, [3]University of Oxford, Oxford Parkinson's Disease Centre, Oxford, United Kingdom

Aims: Recent advancements in spatial transcriptomics technology have enabled the analysis of gene expression changes within vulnerable cells and regions in Parkinson's disease (PD). However, such techniques have yet to be fully utilised with archival formalin-fixed, paraffin-embedded (FFPE) human brain tissues. In this study, we aim to use 10x Genomics Visium to compare the differential gene expression (DEGs) between anatomical regions in PD and aged controls, and to explore if DEGs exist in cells around alpha-synuclein (aSyn)-positive Lewy body (LB) pathologies.
Methods: The substantia nigra (SN) and entorhinal cortex from 3 PD and 3 healthy controls with the greatest DV200 values were processed. The recommended antigen retrieval method from Visium protocol (70°C Tris-EDTA buffer) did not reveal the aSyn staining, thus we performed Visium with H&E and carried out aSyn immunohistochemistry (IHC) in the consecutive section, then superimposed IHC and H&E images to reprocess spot transcriptomics.
Results: The number of genes per spot from 14 samples averaged 337 UMI with 2 samples achieving > 1000 UMI. This did not correlate with DV200, but negatively correlated with fixation time (p=0.0016). Using the SN sample with >1000 UMI, we identified 8 unique cell clusters where the dopaminergic neuron cluster aligned with the pigmented dopaminergic neurons of SN. By combining Visium data with publicly available SN snRNA-seq data, we identified DEGs between anatomical subregions. Aligned IHC and H&E sections allowed us to compare DEGs between regions with and without LBs.
Conclusions: Our work established that Visium works on human FFPE tissue even with increased RNA fragmentation and can be combined with histology in consecutive sections. The results enabled us to compare vulnerable anatomical subfields in PD, as well as the LB-affected and surrounding regions.

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SHIFT 02-085

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4 - 5 April

SPATIAL ORIENTATION SKILLS ARE SIGNIFICANTLY IMPAIRED IN PATIENTS WITH LEWY BODY DISEASE USING THE REAL-SPACE ORIENTATION TEST AND ARE ASSOCIATED WITH FOCAL BRAIN ATROPHY

Zuzana Nedelská, Martina Laczo, Jan Laczo, Jakub Hort
Second Faculty of Medicine, Charles University, Motol University Hospital, Memory Clinic, Department Of Neurology, Prague, Czech Republic

Aims: Spatial navigation (SN) is impaired in Alzheimer disease (AD) patients using real-space and computerized tests, which may address SN more comprehensively than paper-and-pencil-based neuropsychology.Visuospatial impairment is prominent in dementia with Lewy bodies (DLB) too, but studies other than pencil-and-paper-based are scarce. We assessed pattern and magnitude of SN impairment using real-space and computerized environments in DLB and Parkinson disease (PD) compared to AD, including prodromal patients, and controls. We determined associations of SN impairment with regional brain atrophy.
Methods: 24 biomarker-based prodromal AD (MCI-AD) and 20 overt AD-dementia grouped as AD (n=44), 7 prodromal DLB (MCI-LB), 9 overt DLB, and 8 MCI-PD grouped as LBD (n=24), and 48 cognitively unimpaired (controls) underwent comprehensive evaluations and MRI. Pattern and magnitude of SN impairment were assessed in a real-space and 2D-computerized version of a human analogue of the Morris water maze, where participants searched for a hidden goal that shifted its position across several trials to challenge the utilization of various SN strategies: 1.solely own body position (no external cues, egocentric SN), 2.solely external cues (allocentric SN), 3.mixed (allo-egocentric SN), and 4.delayed allocentric recall.
Results: Overall, LBD had the worst SN using allocentric and mixed strategies (p's<0.0001) in both real-space and computerized environments (p's<0.0001). AD were the worst in delayed allocentric recall (p=0.00169). Adjusting for age, education, clinical status (unimpaired/MCI/dementia), findings remained significant. MCI-LB tended to perform worse than MCI-AD in most tests and were similar to MCI-PD. DLB tended to perform the worst. SN impairment correlated with atrophy in basal forebrain and other regions (p's<0.05)
Conclusions: LBD showed the worst SN impairment, potentially interfering with every-day functioning. Patterns of SN impairment may be differential in LBD vs AD and are associated with focal atrophy.

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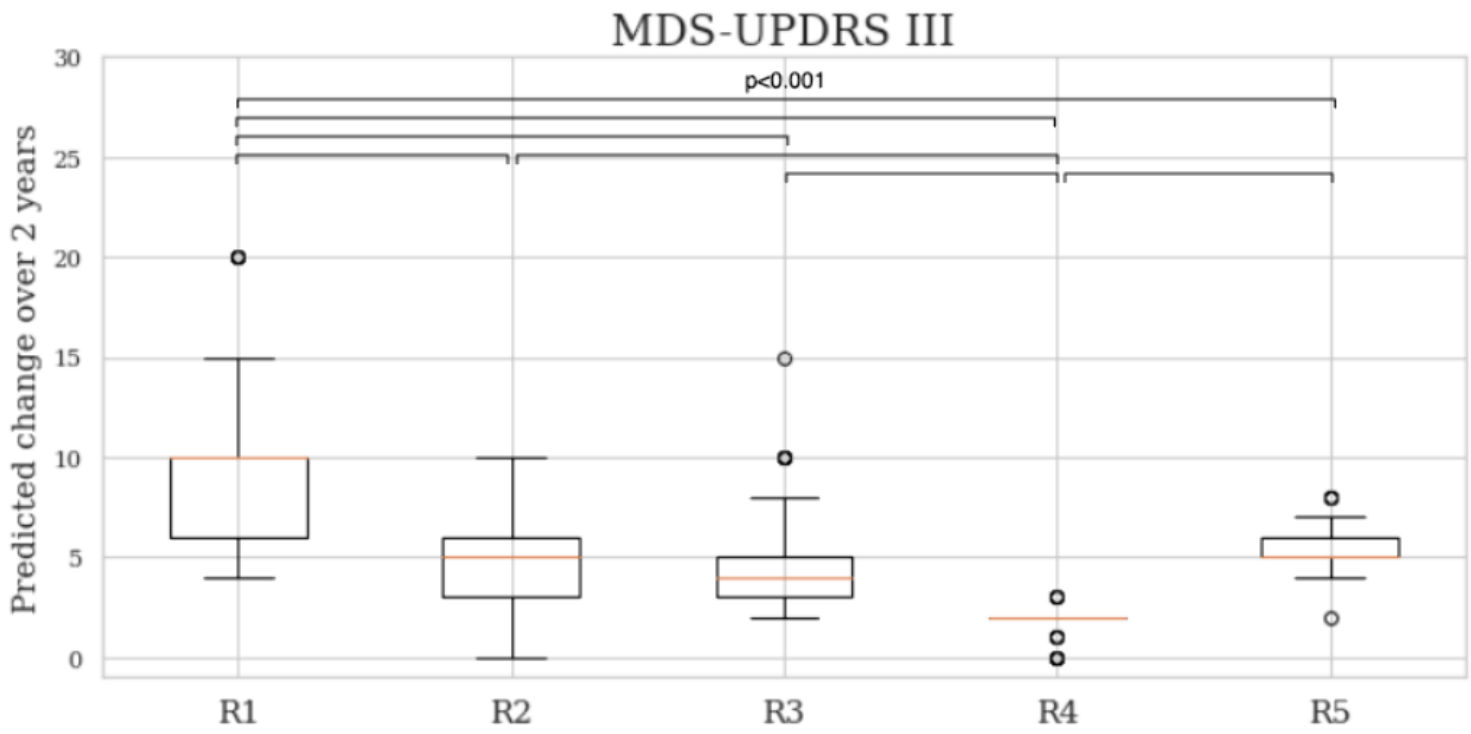
SHIFT 02-086

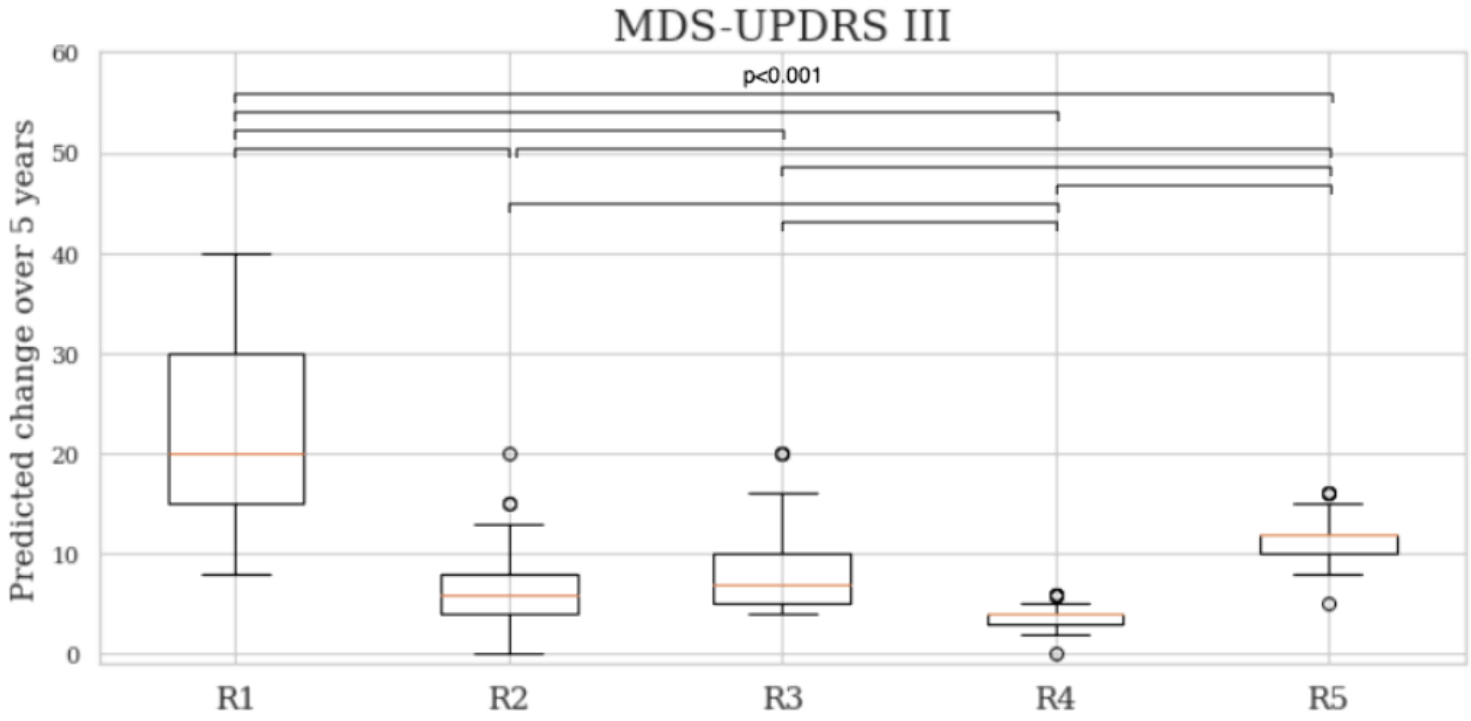
On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4 - 5 April

PROGNOSTIC VARIABILITY IN MDS-UPDRS-III

Jaime Simarro[1], Thibo Billiet[1], Elnaz Ghasemi[2], Thanh Vân Phan[1], Shahid Shahid[2], Nuno Pedrosa De Barros[1], Annemie Ribbens[1], Kathleen Poston[2]
[1]icometrix, Leuven, Belgium, [2]Stanford University School of Medicine, Department Of Neurology & Neurological Sciences, Stanford, United States of America

Aims: The MDS-UPDRS-III is a standard tool for monitoring motor symptoms in Parkinson's disease (PD) patients. This study aims to assess the variability in predicting MDS-UPDRS-III over 2 and 5 years, based on information at baseline only, as assessed by neurologists specializing in movement disorders. We hypothesize a similar predicted average between the specialists.
Methods: In this prospective evaluation, 5 movement disorder specialists reviewed retrospective baseline data from 45 patients with Parkinson's disease (mean age 65.89 ± 8.08 years, disease duration 2.09 ± 2.29 years) obtained from the PPMI database and Stanford University. Each neurologist predicted the change in MDS-UPDRS-III for the next 2 and 5 years, given limited information at baseline, including raw MRI scans, age, disease duration, sex, MoCA, MDS-UPDRS-III, Hoehn and Yahr stage, and PD medication status. The statistical analysis included a descriptive analysis of the predicted MDS-UPDRS-III values and a one-way repeated measures ANOVA, followed by post-hoc analysis using pairwise t-tests.
Results: Figures 1 and 2 illustrate the predicted changes from the baseline at 2 and 5 years, respectively, as estimated by the readers. There was significant variability in the mean prognosis of MDS-UPDRS-III among readers in both 2 and 5 years, as evidenced by the ANOVA analysis ($p<0.001$). In the post-hoc analysis, when predicting the 2-year change, a significant difference was observed between the means of two out of the five readers ($p<0.001$). When predicting the change over 5 years, all pairs of reader combinations except one showed a significant difference in mean predicted MDS-UPDRS-III ($p<0.001$).





Conclusions: Given limited clinical information including raw MRI scans, there is a significant lack of consensus regarding the average expected decline in MDS-UPDRS-III.

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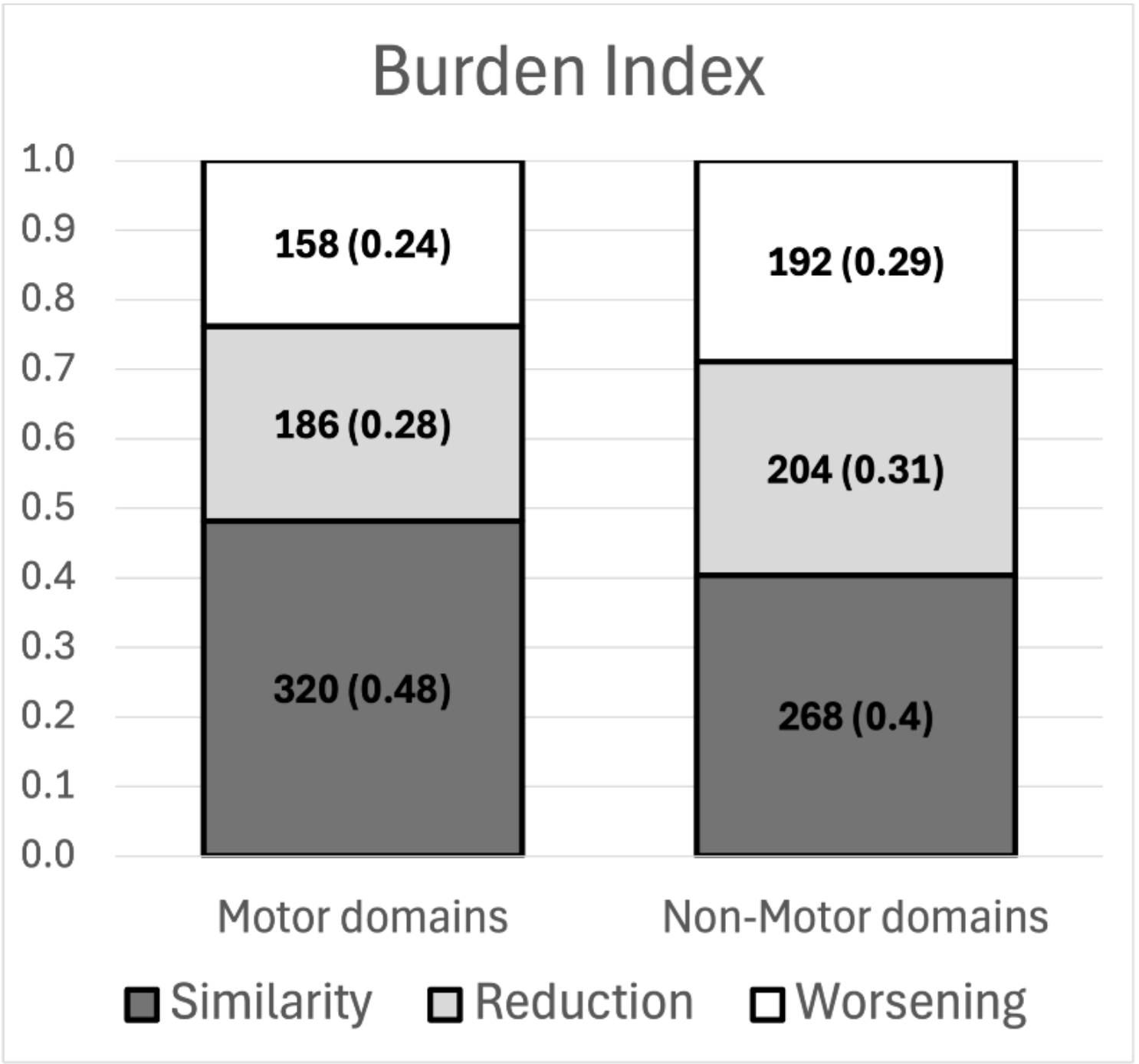
SHIFT 02-087

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4 - 5 April

TOWARD QUANTIFYING HOW THE BURDEN OF PROBLEMS REPORTED BY PATIENTS EVOLVES IN PARKINSON'S DISEASE

Abhishek Hosamath[1], Lakshmi Arbatti[1], Karl Kieburtz[2], Andrew Mcgarry[3], Ira Shoulson[1], David Suendermann-Oeft[1], Vikram Ramanarayanan[1]
[1]Modality.AI, Inc., San Francisco, United States of America, [2]University of Rochester, Rochester, United States of America, [3]Clintrex Research Corporation, Sarasota, United States of America

Aims: To track longitudinal change in a quantitative measure of the Parkinson's Disease (PD) - Patient Reports of Problems (PROP™), an instrument that asks participants questions about what bothers them about PD. Clinical utility of PD-PROP was shown in over 30,000 participants in the FoxInsight (FI) study sponsored by the Michael J Fox Foundation. We developed a computed metric, to complement the descriptive utility of PD-PROP, potentially to be used as a quantitative endpoint in clinical trials.
Methods: A subset of 664 participants with PD (years since diagnosis 0-3; age: 65.36±8.56; males: 57%) were selected from the FI cohort. Recorded verbatim PD-PROP™ responses were allocated into 14 domains using an established custom curation and classification methodology. Occurrence probabilities of a specific triad of reported motor (Gait, Postural Instability, Bradykinesia) and non-motor (Psychiatric, Fatigue, Sleep) domains were compared between baseline and 24 months. These triads were arbitrarily chosen to assay a breadth of PD features. Participants were categorized based on the number of domains with reported symptoms (within each triad). An index was calculated comparing the baseline reports to those 2 years later. Changes were classified 'Similar' if the number of domains reported remained unchanged, 'Worsening' if the number increased, and 'Reduction' if the number decreased.
Results: While the 'Reduction' index was comparable between motor (0.28) and non-motor (0.30) triad domains, the 'Worsening' index was higher for the non-motor triad (0.29) than for the motor triad (0.23) (figure), in line with clinical observations that motor features remain stable (in this time frame) in treated PD, while non-motor features worsen.



Conclusions: Through statistical methods, we can effectively quantify how the burden of PD patient-reported problems evolves to serve as a quantitative endpoint for clinical trials.

SHIFT 02-088

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4 - 5 April

DIFFERENTIAL ASSOCIATIONS OF PLASMA NFL AND COGNITIVE PERFORMANCE IN LEWY BODIES DISEASE PATIENTS WITH AND WITHOUT ALZHEIMER'S DISEASE CO-PATHOLOGY

Elena Vera[1], Iñigo Rodríguez-Baz[1,2], Javier Arranz[1], Carla Abdelnour[3], Sara Rubio[1,2], Mª Belen Sanchez Saudinos[1,2], Sílvia Valldeneu Castells[1,2], Laura Videla[1,2,4], Judit Selma-Gonzalez[1], Nuole Zhu[1,2], José Arriola-Infante[1], Lucia Maure[1,4], Jesús García Castro[1], Isabel Barroeta[1,2,4], María Carmona Iragui[1,2,4], Miguel Angel Santos[1,2], Ignacio Illán Gala[1,2], Juan Fortea[1,2,4], Alberto Lleó[1,2], Isabel Sala-Matavera[1,2], Alexandre Bejanin[1,2], Daniel Alcolea[1,2]
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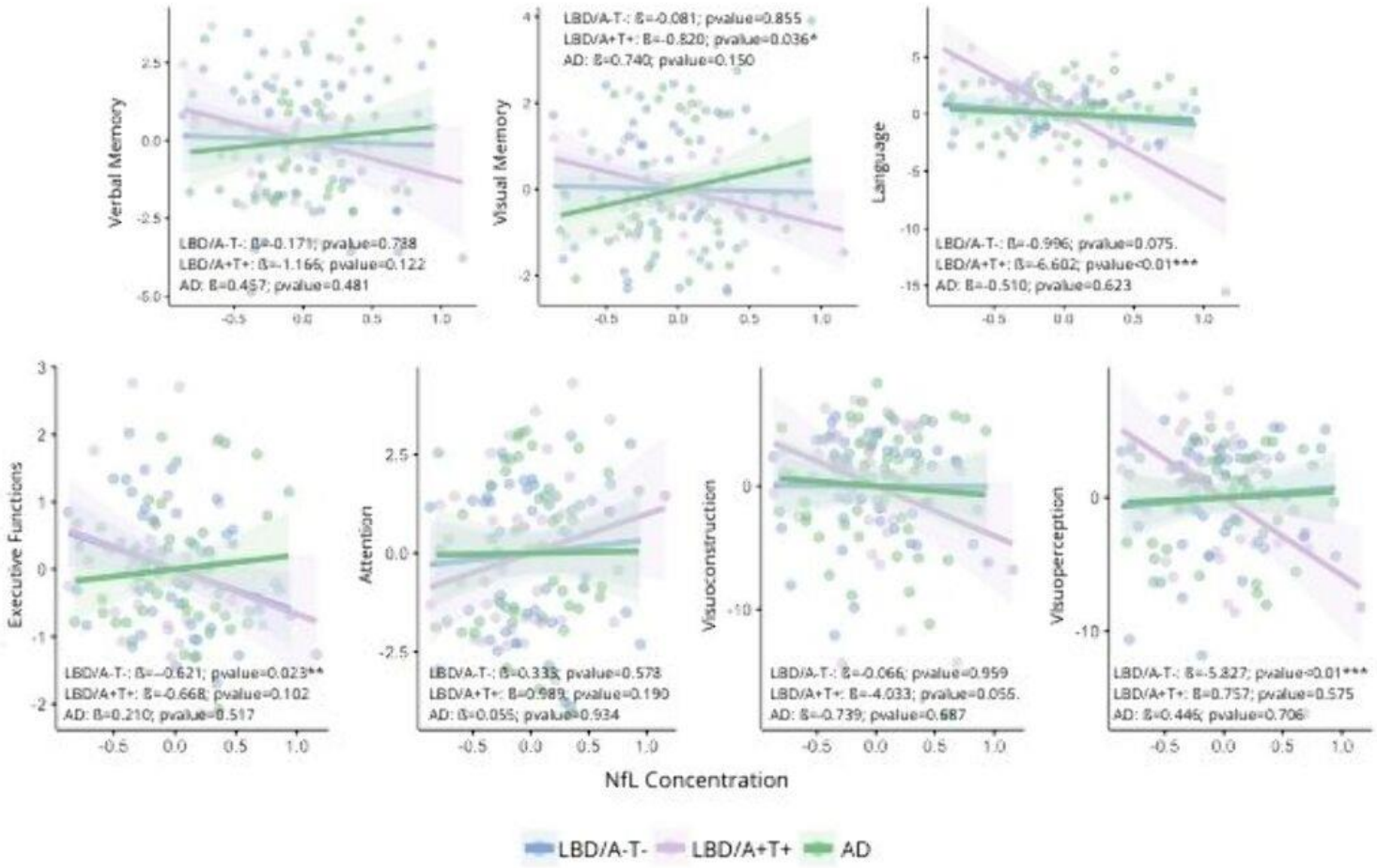
Aims: Alzheimer's pathology (amyloid-β plaques and tau tangles) is present in 50–80% of Lewy Body Disease (LBD) patients, contributing to cognitive variability and complicating diagnosis. Plasma Neurofilament Light Chain (NfL), a neurodegeneration biomarker, predicts early LBD diagnosis and is linked to cognitive performance in individuals at high risk for both LBD and AD. This study examines whether Alzheimer's co-pathology influences the relationship between plasma NfL levels and cognitive function in LBD patients.
Methods: Cross-sectional study. We included 50 cognitively normal volunteers and 139 patients (either in prodromal or dementia stages): 52 with probable LBD clinical diagnosis ("pure" LBD), 50 "pure" AD and 37 mixed probable LBD/AD. AD co-pathology was defined by abnormal CSF Aβ42/40 ratio (A+:<0.062) and abnormal pTau181 levels (T+:>63pg/mL). A composite score was calculated for each cognitive domain using scores adjusted for age, sex, and education. We performed age- and sex-adjusted linear regression models to assess the association between plasma NfL levels and performance in cognitive domains in all groups.
Results: Plasma NfL concentrations were higher in the LBD/AD ($\bar{x}$=3.08±0.46) and "pure" AD ($\bar{x}$=2.97±0.43) groups compared to "pure" LBD ($\bar{x}$=2.71±0.57), with significant differences (LBD/AD vs "pure" LBD p=0.002; "pure" AD vs "pure" LBD p=0.023). In LBD/AD group, higher concentrations of plasma NfL were associated with worse performance in visual memory (β=-0.82;p=0.036), language (β=-6.60;p<0.001) and visuoperception (β=-5.82;p=0.003). By contrast, higher plasma NfL concentration was only associated with worse performance in executive functions (β=-0.62;p=0.023) in the "pure" LBD group, and no significant associations were found with cognitive performances in pure AD.

Table 1. Demographics Table

	'Pure' AD	'Pure' LBD	LBD/AD	p.overall	p.'Pure' AD vs 'Pure' LBD	p.'Pure' AD vs LBD/AD	p.'Pure' LBD vs LBD/AD	N
	N=50	*N=52*	*N=37*					
AGE (years)	75.7 (5.58)	74.0 (5.43)	76.9 (4.88)	0.034	0.235	0.540	0.030	139
SEX:				0.179	0.468	0.468	0.308	139
Male	24 (48.0%)	30 (57.7%)	14 (37.8%)					
Female	26 (52.0%)	22 (42.3%)	23 (62.2%)					
EDUCATION (years)	9.08 (4.84)	9.38 (5.28)	9.24 (5.00)	0.955	0.950	0.988	0.991	139
GDS:				0.632	0.882	0.715	0.715	139
3	26 (52.0%)	25 (48.1%)	16 (43.2%)					
4	22 (44.0%)	25 (48.1%)	17 (45.9%)					
5	2 (4.00%)	2 (3.85%)	2 (5.41%)					
6	0 (0.00%)	0 (0.00%)	2 (5.41%)					
Plasma NfL (pg/mL)	2.97 (0.43)	2.71 (0.57)	3.08 (0.46)	0.002	0.023	0.586	0.002	139

Note: Mean (SD); GDS: Global Deterioration Scale Score

Figure 1. Associations of Plasma NfL Concentration with Cognitive Domains



* ***Note:*** ß= Beta Coefficient of the Linear Model

Conclusions: Plasma NfL levels were associated to cognitive performance differences in LBD patients, influenced by AD co-pathology. Our results suggest that mixed LBD/AD patients have more neurodegeneration and a worse cognitive profile.

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SHIFT 02-092

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

THE SYN-D STUDY: DETECTION OF CUTANEOUS PHOSPHORYLATED ALPHA-SYNUCLEIN AND BLOOD P-TAU 217 IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Aims: Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterized by progressive accumulation of a misfolded protein, phosphorylated a-synuclein (PSYN). Up to 30% of patients with Alzheimer's disease (AD) may exhibit synuclein co-pathology in the central nervous system. An important unmet need exists for a validated, simple, reproducible marker of synuclein pathology in neurogenerative diseases at the prodromal stage. Aim:To quantify the deposition of cutaneous PSYN and blood P-Tau217 in patients with suspected DLB and AD at the mild cognitive impairment (MCI) stage and track clinical and pathologic changes over time.
Methods: After informed consent, detailed neurologic examinations, cognitive evaluation, orthostatic vital signs and questionnaires were completed. An independent expert panel of reviewers, blinded to pathology, reviewed de-identified medical records to confirm clinical diagnoses. Skin biopsies at the distal leg, distal thigh and posterior cervical sites were performed. Phosphorylated alpha-synuclein immunostaining was performed blinded to any clinical data. Serum biomarkers for AD pathology (P-Tau217) were measured.
Results: To date, 98 subjects have been enrolled (44 with MCI-AD and 54 with MCI-DLB) from 15 study sites across the United States out of an anticipated 100 subjects. The mean age of the enrolled subjects is 73.5±6.4 years. Of the 98 enrolled subjects, 57/98 are P-SYN positive (58%). Complete unblinded baseline data will be presented at the conference.
Conclusions: Skin biopsies are a simple, low-risk outpatient procedure to test for phosphorylated alpha-synuclein as a diagnostic biomarker for the synucleinopathies. We will report the sensitivity of PSYN detection in patients with suspected MCI-DLB, and the rate of peripheral co-pathology in suspected MCI-AD cases. Although still blinded the data suggest that skin biopsy is an early, sensitive marker of synuclein detection prior to a clinical diagnosis of dementia.

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SHIFT 02-093

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

APPLICABILITY OF SELF-ADMINISTERED MEASURES DERIVED FROM MDS-UPDRS PARTS 2 AND 3 TO EVALUATE PARKINSON'S DISEASE (PD) PROGRESSION: INTERIM ANALYSIS

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Aims: To evaluate the applicability of at-home smartphone-administered assessments of motor function and speech in participants with early Parkinson's disease (PD), we evaluated compliance, usability of the assessments, reliability, and construct validity of derived measures from the LEARNS (NCT06219629) study.
Methods: Smartphone-based assessments are completed weekly over the course of 12 months, in both the on- and off-state where applicable, and during one-week bursts of daily assessments at baseline and 90-day intervals. We calculated compliance as a percentage of expected assessments completed to date, assessed usability with a questionnaire following one week of use, and calculated test-retest reliability for 36 derived digital motor and speech measures within bursts. These measures were compared to aligned MDS-UPDRS subparts completed in-clinic on Days 1 and 30. This interim analysis includes up to two months of data from 22 participants.
Results: Of completed bursts, on average 95% of assessments were completed, with slightly higher compliance in off-state versus on-state. Most participants found the smartphone easy to use, with clear instructions (>75% responded with "Agree" or "Strongly Agree" to all questions). Of the 36 measures, 26 showed excellent or good reliability (17 with intraclass correlation coefficient [ICC] >0.9 and nine with ICC >0.75). Comparisons between individual items on MDS-UPDRS Parts 2 and 3 and aligned digital measures indicated association with severity for measures of speech, bradykinesia, gait, and tremor (see Figure).
Conclusions: The smartphone-based assessments demonstrated high compliance and usability, and digital motor and speech measures derived from these assessments demonstrated high test-retest reliability and construct validity. These interim results suggest strong potential for clinical validity of at-home digital measures in PD clinical studies. Longitudinal evaluation in a larger sample is planned.

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SHIFT 02-094

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

SEX AFFECTS REM SLEEP BEHAVIOR DISORDER IDENTIFICATION: A COMPARATIVE ANALYSIS OF CLINICAL DATA, SCREENING QUESTIONNAIRES AND REM SLEEP WITHOUT ATONIA IN WOMEN AND MEN

Abubaker Ibrahim[1], Monica Serradelll[2], Matteo Cesari[1], Carles Gaig[2], Evi Holzknecht[1], Paula Marrero[2], Elisabeth Brandauer[1], Laura Perez-Carbonell[2], Melanie Bergamnn[1], Ana Fernandez-Arcos[2], Nuria Matos[2], Joan Santamaria[2], Birgit Högl[1], Alex Iranzo[2], Ambra Stefani[1]
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Aims: Although REM sleep behavior disorder (RBD) is more frequently reported in men, epidemiological studies reported equal prevalence in both sexs, suggesting underdiagnosis in women. We investigated sex differences in RBD identification by evaluating clinical data, three validated RBD screening questionnaires, and REM sleep without atonia (RWA).
Methods: In this bicentric prospective study, 300 subjects (159 men and 141 women) referred to a sleep center for the first time, completed three RBD screening questionnaires, i.e. RBD screening questionnaire (RBDSQ), RBD single question (RBD1-Q), and Innsbruck RBD inventory (RBD-IBK) before sleep expert interview, and underwent 8-hour video polysomnography (v-PSG). Clinical history, questionnaires, and RWA were compared between men and women with and without RBD.
Results: More women than men were above the cut-off for at least one RBD questionnaire (74.5% vs. 63.5%,*P*=0.046), and RWA quantification revealed lower flexor digitorum superficialis activity in women (*P*=0.003). For women, only being above the RBD-IBK was associated with RBD diagnosis (LOR 1.812 (0.635 - 3.347), *P*= 0.023). For men, being above the cut-off for all three RBD questionnaires was associated with RBD diagnosis (RBDSQ: LOR 3.076 (1.671 - 5.362), *P*= 0.003; RBD1Q: LOR 2.837 (1.716 - 4.347),*P* <0.001; RBD-IBK: LOR 3.076 (1.671 - 5.362),*P*= 0.003). Among RBD patients (N =30(10.0%), women:12 (8.5%), men:18 (11.3%), *P*= 0.446), women were less likely to have bed partners (*P*=0.002) and to report abnormal sleep behaviors (*P*=0.006). All RWA scores, except chin tonic, had a higher identification performance compared to the questionnaires in women (AUC >0.82) and comparable identification performance for men.
Conclusions: This study demonstrated sex-related variability in RBD screening questionnaires probably related to sex-specific differences in RBD awareness, likely affecting referral to v-PSG. These findings emphasize the need for sex-specific approaches for RBD screening and diagnosis.

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SHIFT 02-095

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

METHODOLOGY FOR DEVELOPING DIAGNOSTICS OF PARKINSON'S DISEASE AT THE PRODROMAL STAGE

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Aims: Developing early diagnostics for Parkinson's disease (PD) is a priority in neurology. Therefore, we aimed to identify changes in the blood of patients at risk of developing PD at the prodromal stage that could be considered diagnostic biomarkers.
Methods: The methodology used included: (i) searching for patients at risk of developing prodromal PD based on premotor symptoms; (ii) searching for changes in their blood plasma composition and gene expression in lymphocytes according to 27 parameters; (iii) validating the diagnosis of prodromal PD and diagnostic biomarkers using positron emission tomography (PET) and the appearance of motor symptoms over time; (iv) estimating the probability of detection of each marker at the prodromal stage of PD.
Results: Of 1835 patients, 26 had premotor symptoms - sleep disorders (RBD-REM), olfactory disorders, etc. The main changes in plasma were a decrease in the concentrations of L-3,4-dihydroxyphenylalanine, urates and some microRNAs, as well as an increase in the general oxidant status. In lymphocytes of patients at risk, an increase in the expression of the dopamine receptor gene (D3) and the lymphocyte activation gene 3, as well as a decrease in the expression of the protein deglycase DJ-1 (PARK7) gene were observed. According to the PET study, most patients at risk of PD had pronounced interhemispheric asymmetric inclusion of 18F-dihydroxyphenylalanine in dopamine synthesis in the striatum. In some patients, motor disorders developed within one to five years. The identified blood markers were ranked according to the probability of their detection in prodromal PD patients.
Conclusions: Blood changes detected in patients at risk of developing PD at the prodromal stage, validated by PET and the appearance of motor symptoms over time, can be considered diagnostic biomarkers. **Funding:** Russian Science Foundation, grant №24-14-00374.

SHIFT 02-104

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4 - 5 April

DEVELOPMENT OF NOVEL PET TRACERS SPECIFICALLY TARGETING PATHOLOGICAL ALPHA-SYNUCLEIN AGGREGATES IN THE BRAIN

Felix Schmidt[1], Daniel Bleher[2], Ann-Kathrin Grotegerd[2], Andreas Maurer[2], Daniel Weckbecker[1], Sergey Ryazanov[1,3], Andrei Leonov[1,3], Christian Griesinger[3], Viktoria Ruf[4], Christian La Fougère[5], Benjamin Röben[6], Gerald Reischl[2], Johannes Levin[1], Bernd Pichler[2], Kristina Herfert[2], Armin Giese[1]
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Aims: Based on an established pipeline, we are developing PET tracers for pathologically aggregated alpha-synuclein (αSyn), the key pathological hallmark of synucleinopathies such as Parkinson's disease (PD) and Multiple System Atrophy (MSA). This work aims at improving the available diagnosic tools for synucleinopathies, enabling molecular biomarker-based quantification of disease progression, and therefore supporting the development of αSyn targeting therapeutics.
Methods: We conducted a systematic PET tracer development program including competition assays and saturation binding assays using recombinant fibrils and human patient-derived brain tissue, (micro)autoradiography, a range of animal models, animal PET in rodents and non-human primates, as well as the required IND-enabling studies.
Results: We previously developed MODAG-005, which shows a very high affinity for αSyn (Kd ≈ 0.2 nM) and target selectivity regarding Tau and Aβ with a difference in binding potential of approximately 200-fold and 6000-fold, respectively. Autoradiography proves specific target binding and lack of relevant off-target MAOB-binding in human brain tissue. In vivo, [^{11}C]MODAG-005 shows good brain penetration, rapid clearance from brain tissue and low metabolite formation in rodents and non-human primates. In animal PET, target binding was shown in fibril-inoculation-based models and in a transgenic mouse model of familial PD. First imaging results in humans are encouraging. In parallel, we successfully used our validated pipeline to develop next-generation compounds suitable for ^{18}F-labeling. The longer half-life of ^{18}F makes clinical use more efficient and facilitates tracer availability for the entire patient community.
Conclusions: Our work identified promising αSyn PET tracer candidates. The available evidence supports further testing in patients in first-in-human trials.

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SHIFT 02-105

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4 - 5 April

IDENTIFICATION OF NOVEL AND HIGHLY SELECTIVE ALPHA-SYNUCLEIN LIGANDS FOR PET TRACER DEVELOPMENT

Stella Vukelic[1], Manolo Mugnaini[2], Frauke Pohlki[1], Stefan Barghorn[2], Marc Skaddan[3], Robert Comley[3], Gero Fink[2], Sjoerd Finnema[3]
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Aims: Pathological alpha-synuclein aggregates are the neuropathological hallmarks of neurodegenerative diseases like Parkinson's disease (PD) and Multiple System Atrophy (MSA). A positron emission tomography (PET) tracer for imaging alpha-synuclein in living subjects would enable monitoring of disease progression and efficacy measurements of novel disease-modifying therapeutics targeting alpha-synuclein. Aim of this work was to implement a process for the discovery of PET tracers for aggregated alpha-synuclein.
Methods: Targeted design campaign was carried out and a miniaturized radioligand binding assay on idiopathic PD (iPD) brain-derived material was developed to rank order compounds' affinity for native alpha-synuclein. Affinity for AD tau and amyloid-beta aggregates was measured using AD brain homogenates and competition with 3H-NFT-355 and 3H-PiB, respectively. Selectivity against monoamine-oxidase (MAO) was assessed in human MAO-A and MAO-B expressed in microsomes. Promising compounds were radiolabeled with 3H for characterization in pathological tissue (by means of autoradiography and micro-autoradiography) and with 18F to determine PET pharmacokinetic (PK) profile in normal non-human primates (NHPs).
Results: A process for the discovery of alpha-synuclein in PET tracers was successfully implemented. Current lead compound has a high affinity for native alpha-synuclein aggregates in both iPD and MSA, high selectivity against off-targets and a favorable PET PK profile in NHPs.
Conclusions: With the experience of >500 compounds evaluated in a miniaturized assay format based on PD-extracts, the team is in a good position to explore compounds with single digit nanomolar alpha-synuclein affinity to develop a PET tracer with higher likelihood to image alpha-synuclein in iPD, where the alpha-synuclein load is lower than in other synucleinopathies (like familial PD and MSA).

SHIFT 02-106

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4 - 5 April

MICROGLIAL ACTIVATION IN PARKINSON'S DISEASE: AN IN VIVO TSPO-PET STUDY EVALUATING LIPOPOLYSACCHARIDE PHARMACOLOGICAL CHALLENGE

Edoardo De Natale[1], Joji Verghese[1], Alana Terry[1], Heather Wilson[1], Savvas Antoniadis[1], Pegah Khosropanah[1], Martin Howard[1], Holly Wright[1], Lisa Cashmore[1], Alessandra Elena Thomann[2], Venissa Machado[2], Bastian Zinnhardt[2], Gennaro Pagano[1], Marios Politis[1]
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Aims: Neuroinflammation plays a critical role in Parkinson's disease (PD) pathophysiology, but the exact underlying mechanisms are still unclear. We present preliminary data of an *in vivo* Positron Emission Tomography (PET) study with [^{11}C]PBR28 and a pharmacological challenge with Lipopolysaccharide (LPS), aiming to visualise acute translocator protein (TSPO) changes reflecting microglial activation in PD.
Methods: Five people with Parkinson's (PwP; mean age 65.6±11.6 years; disease duration 28.7±15 months) and five healthy controls (mean age 64.8±8.2 years), underwent a PET/MR scan with [^{11}C]PBR28 before, and four hours after intravenous administration of LPS (dose: 1 ng/Kg). Percentage change of volume distribution (V_T) in cortical and subcortical regions of interest was calculated with the formula $\%\Delta V_T=[(V_T\text{postLPS}/V_T\text{preLPS}) -1] \times 100$.
Results: Healthy controls and PwP showed increased post-LPS TSPO levels in frontal cortex (30% vs 36%), temporal cortex (27% vs 34%), putamen (30% vs 33%), thalamus (33% vs 39%), and midbrain (18% vs 31%).
Conclusions: These preliminary data show that TSPO-PET can be used to measure microglial activation in PwP and healthy controls. Pharmacological challenge with LPS may provide valuable insights in the understanding of innate immune response in PwP. The process of gathering more data from additional PwP and healthy control subjects is currently in progress.

SHIFT 02-120

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

DIGITAL AMPLIFICATION REVEALS THE INCREASE IN AGGREGATES IN PARKINSON'S PATIENTS CSF

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Aims: Parkinson's disease is an increasingly prevalent and currently incurable neurodegenerative disease. Sensitive biomarkers that allow early diagnosis, track disease progression, and support the development of future therapeutics are thus actively sought. Yet, measuring absolute numbers of pathological aggregates in clinical samples has remained elusive. Here, we develop and describe a digital seed amplification assay, which allows us to measure the numbers of α-synuclein aggregates in solution.
Methods: We use microdroplets to encapsulate individual aggregates and measure their seeding ability by monitoring the rate of conversion of soluble α-synuclein for individual encapsulated seed. This approach gives a high-throughput direct digital counting readout for the absolute seeding-competent aggregates numbers per unit volume.
Results: We apply this strategy to quantify the numbers of seeds in the CSF of PD patients and healthy individuals. Our data show that healthy CSF contains on average aM of α-synuclein aggregates, which dramatically increased for the CSF of PD patients and reaches levels on the pM order. We thus present a next generation digital microfluidics platform to detect and characterise single misfolded protein species in a complex biological background of correctly folded proteins; this platform can thus allow us to obtain a full picture of the molecular heterogeneity associated with protein aggregation and propagation.
Conclusions: These results open up a path to using number determination of α-synuclein seeds as a biomarker for PD. We believe that this high-throughput approach can be further applied to a variety of fundamental research questions along with opening up a new route for PD biomarkers and diagnostics.

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SHIFT 02-121

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

ASC SPECKS AS A SINGLE-MOLECULE FLUID BIOMARKER OF INFLAMMATION IN NEURODEGENERATIVE DISEASES

Evgeniia Lobanova[1,2], Yu Zhang[1,2], Clare Bryant[3], James Rowe[4,5], Henrik Zetterberg[6,7,8,9], Caroline Williams-Gray[5], David Klenerman[1,10]
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Aims: Given that inflammation is now recognized as a major contributor to the pathogenesis of a number of neurodegenerative disorders, biofluid-based methods are needed for sensitive and accurate detailed characterisation of inflammation in people with Parkinson's (PD), Alzheimer's (AD) and other related neurodegenerative conditions, both at an early stage and as disease progresses. One promising candidate biomarker of the inflammatory response is the inflammasome ASC protein (the adapter protein apoptosis associated speck-like protein containing a CARD) which undergoes a rapid intercellular aggregation into a cluster termed a 'speck' and is released into biofluids (blood, mucus and CSF) when the cells die due to inflammation-driven pyroptosis.
Methods: We have established an ultra-sensitive single-molecule pull-down assay combined with direct stochastic optical reconstruction microscopy for characterising the number, size and shape of individual extracellular inflammasome ASC specks in the serum, plasma, CSF and nasal swabs of people with PD and AD and compare them to those formed in healthy aging.
Results: Our novel ASC speck biomarker of inflammation demonstrates up to 4-fold change in the CSF, serum/plasma as well as nasal swabs of people with early-stage Parkinson's and Alzheimer's compared to controls. We find that the size of ASC specks is significantly decreased in early AD/PD CSF and serum compared to age-matched healthy controls giving an AUC of 98-100%.
Conclusions: Our findings confirm ASC specks as a novel fluid-based candidate biomarker of inflammation for AD and PD with blood and nasal swabs being the main focus for further development as convenient samples for diagnostics and monitoring.

SHIFT 02-123

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

LOAPI: A NOVEL NORMALIZATION METHOD TO HANDLE NONLINEAR COVARIATE EFFECTS IN PLASMA PROTEOMICS ANALYSIS

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Aims: Linear models are often used to study changes in the human plasma proteome, with age and sex as covariates. However, these models assume linearity and normal value distributions—assumptions frequently violated in biological data. To address this, we introduced a novel normalization method: Local Regression with Asymmetric Prediction Intervals (LOAPI).
Methods: Using repeated Olink measurements from PPMI, linear mixed effects models adjusted with age and sex were applied to 1461 proteins to predict their abundance. Significance was assessed using Likelihood Ratio Test (LRT) between two models with and without PD status. Analyzing proteins independently does not account for abundance ratios, which often drive biological function. We therefore examined all possible 1,066,530 abundance ratios between two proteins, requiring ratios to show at least 20-fold increase in significance than either interactor to be considered as PD-associated.
Results: From the original data, 440 PD-associated proteins were identified. LOAPI normalization indicated that 11 of them are possibly false-positives, while unmasking 69 associations, leading to 498 hits. Within this protein set, we found 30% more database-curated interactions (PPIs) and giant component size was also increased by 17%. Evaluating the original data led to 3087 PD-associated protein pairs. 589 found to be possible false-positive after LOAPI normalization and 5072 novel hits were introduced, leading to more than 2-fold increase of the signal. Focusing on 5517 database-curated PPIs, the original data linked 33 PPIs to PD. Normalization yielded 45 additional hits and removed one, increasing the network's diameter from 4 to 10 and giant component size from 13 to 41, revealing a more coherent, biologically interpretable PPI structure.
Conclusions: In conclusion, LOAPI normalization uncovers hidden aspects of PD biology and enhances proteomic data analysis, particularly when nonlinear covariate effects are present.

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SHIFT 02-124

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

INVESTIGATING ACCURACY OF A-SYNUCLEIN SEED AMPLIFICATION ASSAY IN DETECTING DIFFUSE SYNUCLEIN PATHOLOGY IN POST-MORTEM CONFIRMED CASES

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Aims: Lewy body disease (LBD), which includes Parkinson's disease (PD) and dementia with Lewy bodies (DLB), involve the aggregation of misfolded α-synuclein, with Lewy bodies and Lewy neurites as its neuropathological hallmarks. Historically, only post-mortem examination could confirm LBD, but α-synuclein seed amplification assay (synSAA) has emerged as a tool to identify underlying LBD in life by detecting misfolded α-synuclein (syn-seeds) in cerebrospinal fluid (CSF). While large longitudinal clinical cohort studies have shown CSF seeds are a robust biomarker for LBD, pathology-confirmed CSF results are scattered. Here, we compiled published and unpublished pathology-confirmed data to determine the accuracy of syn-seeds as a CSF biomarker for LBD in the context of PD, DLB, and Alzheimer's disease (AD).
Methods: We included 594 published and 98 unpublished pathology-confirmed samples tested by a synSAA. Of the 692 cases, 302 had LBD (LBD+) and 390 didn't (LBD-). Of the LBD+ cases, 152 were diffuse neocortical-predominant, 62 amygdala/brainstem-predominant, 25 limbic-predominant, and 63 unspecified. Sensitivity and specificity were calculated using neuropathology as gold-standard.
Results: Specificity for LBD- cases reached 96% (374/390), while sensitivity reached 74% (223/302) and varied depending on the brain region with predominant pathology. Sensitivity for diffuse neocortical-predominant LBD+ reached 97% (148/152), while amygdala/brainstem-, and limbic -predominant reached 35% (22/62) and 68% respectively (17/25).
Conclusions: These results unequivocally demonstrate that syn-seeds in CSF are a biomarker for LBD, which can be detected by synSAA with impressive specificity and >95% sensitivity for diffuse neocortical LBD. Lower detection of CSF syn-seeds in amygdala/brainstem-predominant cases has been reported and explained by low spreading and burden. These findings confirm that detection of syn-seeds in CSF equates to identification of underlying LBD during life and emphasize utility of synSAA in clinical practice.

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SHIFT 02-125

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY CONCORDANCE TO DEMENTIA WITH LEWY BODIES DIAGNOSTIC CRITERIA

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Aims: To investigate the results of the alpha-synuclein (aSyn) Seed Amplification Assay (SAA) in cerebrospinal fluid (CSF) from patients with a clinical diagnosis of Dementia with Lewy Bodies (DLB), and to examine the prevalence of core clinical features or abnormal indicative biomarkers in relation to the SAA results.
Methods: We assessed aSyn-SAA in CSF from patients that fulfilled criteria for either possible or probable DLB, recruited from the Sant Pau Memory Unit (Barcelona). We compared aSyn-SAA results with demographic characteristics, core clinical features (cognitive fluctuations, visual hallucinations, REM sleep behavior disorder [RBD], parkinsonism), and abnormalities in indicative biomarkers (dopamine transporter uptake by SPECT, myocardial scintigraphy, and absence of REM atonia in polysomnography). Amyloid pathology in CSF was also examined.
Results: We included 57 patients (mean age 77.3±5.0 years, 40.4% female). aSyn-SAA was positive in 24 (42.1%) patients and amyloid pathology was present in 30 (52.6%). Three subjects were excluded from further analysis due to diagnosis of prodromal DLB and one due to an inconclusive result in aSyn-SAA. aSyn-positive individuals were younger (76.2±4.9 vs 79.2±4.7 years, p=0.031), with a tendency for a larger age difference in the amyloid-positive group. Clinical RBD was more frequent in aSyn-positive patients (58% vs 42%, p=0.051), and clinical RBD with polysomnographic confirmation was significantly higher in this group (86% vs 14%, p=0.04). No other significant differences were observed.

Table 1. Characteristics of patients with Dementia with Lewy Bodies according to result of alpha-synuclein seed amplification assay and amyloid pathology in cerebrospinal fluid.

	Total				Amyloid Positive				Amyloid Negative			
	N	aSyn-SAA Positive N = 23	aSyn-SAA Negative N = 29	p-value	N	aSyn-SAA Positive N = 12	aSyn-SAA Negative N = 15	p-value	N	aSyn-SAA Positive N = 11	aSyn-SAA Negative N = 14	p-value
Age (years)*	52	76.2 (4.9)	79.2 (4.7)	0.031	27	75.8 (5.3)	80.0 (3.9)	0.053	25	76.6 (4.8)	78.3 (5.4)	0.3
Sex	52			0.2	27			0.5	25			0.2
Female		7 (33%)	14 (67%)			5 (38%)	8 (62%)			9 (53%)	8 (47%)	
Male		16 (52%)	15 (48%)			7 (50%)	7 (50%)			2 (25%)	6 (75%)	
Clinical Diagnosis	52			>0.9	27			0.7	25			0.6
DLB Possible		5 (45%)	6 (55%)			4 (57%)	3 (43%)			1 (25%)	3 (75%)	
DLB Probable		18 (44%)	23 (56%)			8 (40%)	12 (60%)			10 (48%)	11 (52%)	
APOE-E4 carrier	51	9 (56%)	7 (44%)	0.2	26	7 (58%)	5 (42%)	0.13	25	2 (50%)	2 (50%)	>0.9
MMSE score**	46	21.0 (18.5, 26.0)	22.5 (20.0, 24.0)	>0.9	25	21.0 (18.0, 26.0)	22.0 (19.0, 23.0)	>0.9	21	23.0 (19.0, 26.0)	24.0 (20.5, 26.5)	0.8
Core clinical features												
Visual hallucinations	52	12 (40%)	18 (60%)	0.5	27	7 (41%)	10 (59%)	0.7	25	5 (38%)	8 (62%)	0.6
RBD	52	15 (58%)	11 (42%)	0.051	27	8 (62%)	5 (38%)	0.085	25	7 (54%)	6 (46%)	0.3
Parkinsonism	52	23 (45%)	28 (55%)	>0.9	27	12 (44%)	15 (56%)	>0.9	25	11 (46%)	13 (54%)	>0.9
Cognitive fluctuations	52	15 (47%)	17 (53%)	0.6	27	6 (43%)	8 (57%)	0.9	25	9 (50%)	9 (50%)	0.4
Core clinical features accumulation	52			0.2	27			0.3	25			0.4
Two or less		6 (32%)	13 (68%)			4 (33%)	8 (67%)			2 (29%)	5 (71%)	
Three or four		17 (52%)	16 (48%)			8 (53%)	7 (47%)			9 (50%)	9 (50%)	
Indicative biomarkers												
DAT uptake by SPECT	25			0.2	12			0.2	13			>0.9
Normal		1 (14%)	6 (86%)			0 (0%)	3 (100%)			1 (25%)	3 (75%)	
Reduced		9 (50%)	9 (50%)			6 (67%)	3 (33%)			3 (33%)	6 (67%)	
Atonia during REM sleep by PSG	11			0.5	6			>0.9	5			0.4
Preserved		2 (50%)	2 (50%)			1 (50%)	1 (50%)			1 (50%)	1 (50%)	
Absent		6 (86%)	1 (14%)			3 (75%)	1 (25%)			3 (100%)	0 (0%)	
^{123}I-MIBG uptake on myocardial scintigraphy	4			>0.9	2			>0.9	2			>0.9
Normal		1 (50%)	1 (50%)			0 (0%)	1 (100%)			1 (100%)	0 (0%)	
Reduced		1 (50%)	1 (50%)			0 (0%)	1 (100%)			1 (100%)	0 (0%)	
Sleep disturbances	52			0.040	27			0.2	25			0.15
Absent		8 (31%)	18 (69%)			4 (29%)	10 (71%)			4 (33%)	8 (67%)	
Clinical RBD		9 (47%)	10 (53%)			5 (56%)	4 (44%)			4 (40%)	6 (60%)	
Clinical RBD and abnormal PSG		6 (86%)	1 (14%)			3 (75%)	1 (25%)			3 (100%)	0 (0%)	

*Mean (SD), **median (25p ; 75p). ^{123}I-MIBG= Iodine-123-metaiodobenzylguanidine αSyn-SAA= alpha-synuclein Seed Amplification Assays; DAT=Dopamine transporter; MMSE=Mini-mental state examination; PSG=polysomnography; RBD=REM sleep behavior disorder; SPECT=Single Photon Emission Computed Tomography.

Conclusions: This study highlights the discordance between current clinical criteria for DLB and aSyn-SAA results. While amyloid pathology might influence the age of symptom onset, it does not alter the overall clinical presentation. The potential for other etiologies to produce clinical phenotypes similar to DLB underscores the need for precise biological biomarkers to ensure an accurate etiological diagnosis.

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SHIFT 02-126

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-AND BLOOD-BASED BIOMARKERS
4 - 5 April

SEEDED AGGREGATION IMMUNOASSAY (SAIA) DETECTS AGGREGATED ALPHA-SYNUCLEIN IN SKIN TISSUE AND CAN DISTINGUISH SYNUCLEINOPATHIES FROM CONTROLS

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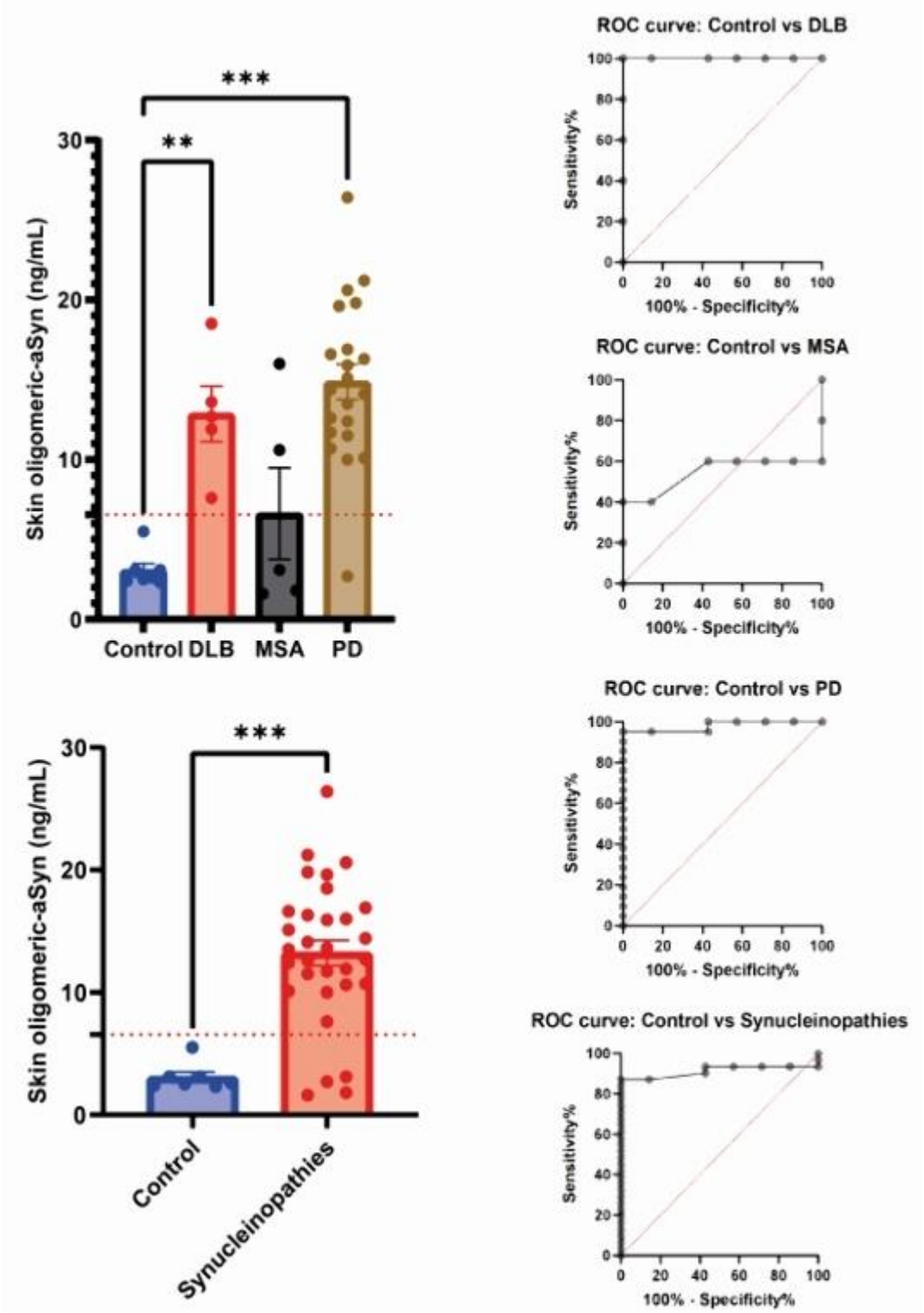
Aims: The main neuropathological hallmark of synucleinopathies is the presence of aggregated alpha-synuclein (aSyn) depositions in the human brain. Recent studies highlight the presence of aggregated aSyn in the skin of patients suffering from synucleinopathies using various methods, highlighting its potential to serve as a clinical biomarker. Herein, we describe a newly developed method to detect aggregated aSyn in skin tissue from synucleinopathy cases, which can distinguish synucleinopathies from controls with high diagnostic accuracy.
Methods: Postmortem skin tissue was collected from the back (C7) from neuropathologically confirmed Parkinson's disease (PD, n=21), Multiple System Atrophy (MSA, n=5), Dementia with Lewy Body (DLB, n=5) and control (n=7) cases. A seeded aggregation immunoassay (SAIA) was performed to determine the presence and amount of oligomeric aSyn in skin tissue homogenates.
Results: Group comparisons revealed significantly higher oligomeric aSyn values in the skin tissue homogenates from PD ($p < 0.001$) and DLB ($p < 0.01$) cases compared to controls, while there was no significant difference between MSA cases and controls. ROC analyses highlighted that SAIA could differentiate PD from controls with 95% sensitivity and 100% specificity and DLB from controls with 100% sensitivity and 100% specificity, while SAIA could differentiate MSA from controls with only 40% sensitivity but with 100% specificity. Overall, synucleinopathies showed significantly higher oligomeric aSyn values compared to controls ($p < 0.001$) and could be differentiated from controls with 87% sensitivity and 100% specificity using the SAIA method.



Conclusions: These results highlight that SAIA on skin tissue samples might prove to be a useful clinical biomarker for the detection of synucleinopathies.

SHIFT 02-128

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
4 - 5 April

FIRST IN CLASS ASO TARGETING A53T ALLELE: PRECLINICAL EFFICACY

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Aims: The Ala53Thr (A53T) *SNCA* mutation has been identified as one of the most significant risk factors in early-onset Parkinson's disease (PD) (Polymeropoulos et al., 1997). We propose an antisense oligonucleotide (ASO)-based allele-specific strategy to target the mutant A53T *SNCA* allele without downregulating the wild-type (WT) allele. This strategy is unique compared to existing SNCA-targeting ASOs, as these target general SNCA knockdown despite mutation status. As depletion of alpha-syn induces neurodegeneration, a therapeutic that only targets the mutant allele ensures healthy levels of alpha-syn are maintained.
Methods: We designed an ASO that targets the A53T *SNCA* allele. This ASO was designed to have a higher affinity for the mutant allele, predicted *in silico,* as opposed to the same sequence from WT of the same length. HEL cells were incubated for 72-hours with the A53T-specific ASO (1µM) using gymnotic uptake. This cell line was chosen due to its abundant SNCA expression.
Results: ASO treatment resulted in a 40% reduction of *SNCA* expression (qPCR), confirmed by RNAseq data. Positive control gapmers as well as siRNA were used as controls. Limited off-target effects were demonstrated *in silico*. Patient fibroblasts with confirmed A53T mutation were obtained and iPSCs were generated. Molecular characterization of this phenotype in an organ-on-a-chip system is planned to assess effects of A53T-specific ASO silencing.
Conclusions: CRISPR-Cas9 deletion of the A53T *SNCA* mutation can improve PD-related conditions, including alpha-syn overproduction, reactive microgliosis, dopaminergic neurodegeneration, and motor symptoms (Yoon et al., 2022). Achieving a ratio in favor of mutant allele downregulation is desirable as it does not knockdown the WT allele while targeting the aberrant gain-of-function, a phenomenon that is not possible with other proposed lines of treatment. We present a novel ASO that achieves this.

SHIFT 02-129

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
4 - 5 April

PROFILING OF AGGREGATION-PRONE MOTIFS IN ALPHA-SYNUCLEIN AND IMPLICATION FOR TARGETED THERAPEUTIC DEVELOPMENT

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Aims: Lewy bodies and neurites formed due to excessive accumulation of α-synuclein are the hallmarks of Parkinson's disease. Alongwith PD, α-synuclein aggregates have been prominently observed in Lewy Body Dementia(LBD), Multiple System Atrophy(MSA), and in a subset of Alzheimer's Disease(AD) patients. The structures of the fibrillar region across different synucleinopathies suggest the modification in each conformation is governed by the pathological condition. The structural heterogeneity between oligomers and fibrillar forms of aggregates derived from patient samples is elusive. The cryo-EM structures of post-mortem brain-derived samples of PD, LBS, and MSA patients have revealed the polymorphic nature of well-arranged fibrillar forms with overlapping stretches. The discordance in main aggregation forming segments remains unsolved even with numerous studies employing computational-tools and experimental investigations of selected short peptides.
Methods: We have synthesized a series of offsetting 15-mer peptides covering the entire stretches from recently reported cryo-EM structures of fibrils isolated from patients with all major synucleinopathies. Using ThT-based aggregation assay, we have thoroughly profiled aggregation propensity and zeroed on aggregation hotspots, which could be the nucleation centres. The congregation patterns were experimentally validated by in-vitro assays such as Thioflavin T assay and Congo red binding assay and microscopic methods such as CLSM, SEM, and AFM.
Results: The study identifies the sticky peptide regions which can act as nucleation points. We have discovered that the aggregation propensities are highly modulated by the flanking regions and PTMs particularly focusing on acetylation and carbamylation that render lysine residue chargeless.
Conclusions: The offsetting peptide library can be used as a target detection tool for potential therapeutic development. The mildly aggregation-prone sequences appear to be of high interest as they can act as standalone inhibitors or a target-site for degrader development.

SHIFT 02-132

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / CELL TRANSPLANTATION
4 - 5 April

THE IMPACT OF A PATHOLOGICAL ALPHA-SYNUCLEIN ENRICHED MICROENVIRONMENT ON GRAFTED HUMAN ES-DERIVED DOPAMINE NEURONS IN A PRECLINICAL PARKINSONIAN MOUSE MODEL.

Jinghua Piao[1], Lucia Perera[1], Vittoria Bocchi[2], Subhashini Joshi[1], Tae Wan Kim[2], Nidia Claros[1], Shkurte Donohue[1], Lorenz Studer[2], Viviane Tabar[1]
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Aims: Stem cell therapy offers a promising treatment approach for Parkinson's disease (PD) by replenishing lost dopamine neurons. However, the impact of the pathological PD environment on grafted neurons remains unclear. We aim to investigate the impact of the PD microenvironment on human dopamine neuron grafts, focusing on the roles of microglia and astrocytes.
Methods: Human ES-derived dopamine neuron progenitors were injected in the striatum of SNCA 3K mutant/RAG1 KO mice, which overexpress mutant α-synuclein, develop α-synuclein aggregates, and exhibit abnormal motor behavior. Behavior tests were conducted over time, and the grafts were analyzed by snRNAseq and immunohistochemistry.
Results: Grafted dopamine neuron progenitors led to behavioral amelioration in 3K mice 4 months post-grafting. Compared to the wild-type mice, microglia surrounding the grafts in 3K mice phagocytosed phosphorylated α-synuclein. Microglia in the 3K mice more prominently expressed complement components C1q and C5b9, and MHCII in the graft area. Genes associated with the activation of the innate immune response, cellular response to interferon-β, and IL-1β production were also more enriched in the grafted 3K striatum. Astrocytes in the 3K graft area showed greater activation with elevated expression of complement component C3d and a few contained phosphorylated α-synuclein inclusions. Additionally, higher expression of complement component C1q, and the deposition of C3d and C5b-9 were observed in grafted dopamine neurons in 3K mice. The presence of phosphorylated α-synuclein was observed in a few grafted dopamine neurons.
Conclusions: Neuroinflammation and phosphorylated α-synuclein accumulation are present in hES-derived dopamine neuron grafts in 3K mice, mimicking the observation in fetal cell therapy for Parkinson's disease. This model provides deeper insight into the underlying mechanisms and could potentially facilitate the development of strategies to counteract the inflammatory effects of the PD microenvironment.

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SHIFT 02-137

On-Demand Oral Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
4 - 5 April

DEVELOPMENT OF THERAPEUTIC SUBSTANCES FOR THE DISASSEMBLY OF ALPHA-SYNUCLEIN AGGREGATES AS TREATMENT OPTION AGAINST SYNUCLEINOPATHIES

Antje Willuweit[1], Marc Sevenich[1], Sara Reithofer[2], Kira Allmeroth[1], Wolfgang Hoyer[2], Janine Kutzsche[2], Nils-Alexander Lakomek[2], Lothar Gremer[2], Jeannine Mohrlueder[2], Gültekin Tamgüney[2], Dieter Willbold[2]
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Aims: Parkinson's disease (PD) belongs to the group of neurodegenerative diseases associated with the misfolding and aggregation of alpha-synuclein (a-syn). Multiple lines of evidence indicate that small soluble a-syn assemblies play a key role in prion-like cell-to-cell transmission and induction of cellular toxicity. Consequently, disassembly of these aggregates into physiological a-syn monomers is a very efficient way to interfere with neurodegeneration and progression of the disease. Here, we report on the development of a-syn specific all-D-enantiomeric peptide ligands that act as pharmacological chaperones disassembling preformed a-syn fibrils as disease-modifying therapy of synucleinopathies.
Methods: We have performed a mirror-image phage display selection against monomeric full-length a-syn and selected all-D-enantiomeric peptide ligands that were characterized using surface plasmon resonance, atomic forced microscopy (AFM), dynamic light scattering (DLS), size exclusion chromatography (SEC), nuclear magnetic resonance (NMR) spectroscopy, seeded Thioflavin-T aggregation, cell-viability, cellular aggregation, and in vivo proof-of-concept in an a-syn preformed fibril (PFF) seeded PD mouse model ($TgM83^{+/-}$ mice).
Results: Two lead compounds (SVD-1 and SVD-1a) were identified which inhibited de novo and seeded a-syn aggregation dose-dependently. The ligands showed high affinity to monomeric a-syn (picomolar K_D range) and the interaction with a-syn was further characterized by NMR analyses. Target engagement was shown by the compounds´ ability to specifically disassemble a-syn oligomers into monomers in vitro, as demonstrated by AFM, time dependent DLS and SEC analyses. SVD-1a reduced toxic effects and intracellular seeding capacity of a-syn PFFs in cell culture. Finally, a significant prolongation of the mean survival could be demonstrated in TgM83+/− mice.
Conclusions: The present work reports on promising lead compounds capable of destabilizing and disassembling a-syn aggregates as a new disease-modifying treatment strategy against PD and other synucleinopathies.

SHIFT 02-140

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4 - 5 April

COMPREHENSIVE HUMAN-MOUSE PROTEOMICS UNCOVERS CONSERVED PATHWAYS AND NOVEL MOLECULAR INSIGHTS OF DELAYED PROTEIN TURNOVER IN AMYLOIDOME

Junmin Peng
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Aims: Murine models of Alzheimer's disease (AD) cannot capture the full molecular complexity of AD. Our goal is to comprehensively characterize AD mouse models by proteomics to reveal mechanistic insights and compare with a unified human proteomic landerscape to uncover conserved pathways and identify limitations for future development.
Methods: We analyzed the whole proteome from 103 mice across five models (5xFAD, NLF, NLGF, 3xTG, and BiG), the phosphoproteome from 36 mice, and the amyloidome from 8 mouse samples using laser capture microdissection. Additionally, we assessed proteome turnover in 30 mice. Most datasets include over 10,000 proteins, enabled by our development of the latest tandem mass tag (TMT) and mass spectrometry pipeline.
Results: We generated the most comprehensive AD mouse brain proteomes to date. We profiled age-dependent brain proteomes and phosphoproteomes in 5xFAD and NLF/NLGF KI mice, identifying conserved pathways through integration with human metadata and prioritizing novel components via multi-omics analysis. While these models collectively replicate 30% of protein alterations found in humans, the additional genetic incorporation of tau (3xTG) and splicing pathologies (BiG) in mice increased this similarity to 42%. We further examined proteome-transcriptome inconsistencies in human AD and 5xFAD brains, revealing that inconsistent proteins are enriched within amyloid plaques (the amyloidome). Measuring proteome turnover in 5xFAD mice demonstrated that amyloid formation delays the degradation of amyloidome components, including Aβ-binding proteins and autophagy/lysosomal proteins. For instance, Apoe accumulation is driven by RNA upregulation and slow protein turnover in 5xFAD.
Conclusions: Our proteomic strategy defines conserved AD pathways, identifies new targets, and highlights protein turnover as a key factor contributing to proteome-transcriptome discrepancies. This proteomics resource allows researchers to select the most appropriate models for studying specific pathways.

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SHIFT 02-141

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4 - 5 April

CHARACTERIZATION OF DISEASE PROGRESSION IN THE APP-SAA MOUSE TO FACILITATE USE IN PRECLINICAL TESTING FOR ALZHEIMER'S DISEASE

Michael Sasner[1], Andy Tsai[2], Dylan Garceau[1], Ravi Pandey[3], Peter Bor-Chian Lin[4], Amber Sanders[5], Jason Hart[5], Sean-Paul Williams[6], Zach Cope[6], Tim Ragan[7], Gary Landreth[8], Bruce Lamb[2], Gregory Carter[1], Stacey Sukoff Rizzo[6], Adrian Oblak[2]
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Aims: The APP^{SAA} model was developed to provide an animal model of familial Alzheimer's disease (AD) that is accessible for preclinical research without licensing restrictions or artifacts due to transgenic overexpression (Xia et al, 2022). In order to establish this as a useful model for translational research, we have characterized numerous clinically relevant phenotypes throughout aging.
Methods: Assays at early and late ages include: quantification of amyloid deposition by brain region using the TissueCyte Serial Two-Photon Plus imaging platform; neuroinflammation and synaptic markers as assayed by iterative immunohistochemistry (IBEX); multi-omics including transcriptomics, proteomics and metabolomics; fluid biomarkers; spatial transcriptomics; electrophysiology; touchscreen-based cognitive tasks; and cortical electroencephalography (EEG).
Results: Amyloid plaque pathology begins at cortical regions by 4 months of age and progresses rapidly throughout the forebrain to 12 months, then increases only gradually. Plaques are parenchymal at early stages, with vascular amyloid detected after ~15 months of age. Bulk brain transcriptomics exhibits age-dependent correlations to AMP-AD differentially regulated pathways, with strongest correlation to immune modules. Hippocampal synaptophysin levels and LTP at the Schaffer collateral-CA1 synapse are reduced at 7.5 months of age. Prior to 12 months of age, there were no differences in cognitive function as measured by hippocampal-mediated pattern separation task in APP^{SAA} relative to hAPP littermate controls, despite significant amyloid accumulation. Handing-induced seizures were observed during daily cognitive training in subjects after 12 months of age but not at younger ages. Cognitive assessments and EEG analysis are in progress in aged animals.
Conclusions: This model improves upon historical transgenic overexpression models for studying early onset amyloidosis, and the data presented here will enable selection of appropriate ages and assays to be used in preclinical research.

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SHIFT 02-142

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4 - 5 April

DISTINCT GENDER-SPECIFIC BONE CHANGES SEEN IN MAPT P301S TG+, FDD, 5XFAD AND PSEN11 L166P KNOCK-IN PRECLINICAL MODELS OF AD

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Aims: Falls are fractures are predominant in patients with Alzheimer's disease (AD) and individuals with falls and fracture have faster cognitive decline. To evaluate changes in the bone microarchitecture during AD in the context of various mechanisms including accumulation of amyloid-ß plauques, Tau tanges leading to neurodegeneration, we studied prelcinical models of AD: MAPT P301S Tg+, FDD, 5xFAD and PSEN11 L166P knock-in for changes in the bone miscroarchitecture and function.
Methods: We studied 160 mice which are 9-12-months of age and gender-matched wild type and AD mouse inclduing MAPT P301S Tg+, FDD and PSEN11 L166P knock-in to evaluate for bone microarchitecture using microCT, mechanical properties using three-point bending test, histological assessment of the bone and gene expression of bone turnover markers from tibia.
Results: PSEN1/hAPP Tg+ mice had reduction in whole-body bone mineral density and bone mineral content, cortical and tarbecular properties compared to controls in female mice, but not males. PSEN1 KI mice has reduced follicle stimulating hormone (FSH) levels, which is known to cause brain atrophy and bone loss. We found for the first time that Tau, PSEN, APP were expression in the bone of mice, as determined by western blotting. *MAPT* mutation leads to loss of bone as seen on mCT and altered the mechanical properties of the bone mostly in the males. We observed loss of trabecular and cortical properties in FDD Tg+ in both males and females, as further evidenced in increased bone resorption observed in histological assessments using Trap and Von Kossa staining.
Conclusions: Assessing bone chnages in various preclinical models of AD realved gender specific alterations on the bone distinct to various signalling mechnaisms contributing to AD. This provides mechanistic insights of the brain-bone axis during AD to design new therapeutic strategies.

SHIFT 02-147

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4 - 5 April

APOE AND AMYLOID-BETA INTERACTION-MEDIATED DYSFUNCTION IN ALZHEIMER'S DISEASE

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Aims: Apolipoprotein E (ApoE), particularly the E4 isoform, is the predominant genetic risk factor for late-onset Alzheimer's Disease (AD), accounting for over 95% of cases. Carriers of one ApoE4 allele are 2-3 times more likely to develop AD, with the risk increasing 8-12 times for those with two alleles, often leading to an earlier onset and faster progression of the disease. APOE4 carriers exhibit earlier and more substantial amyloid-beta (Aβ) accumulation, correlating with their increased AD risk. Our recent findings demonstrate that apoE co-aggregates with Aβ in the brain, significantly affecting Aβ function and AD progression. Our current research is focused on exploring how different ApoE isoforms influence Aβ mediated dysfunction by co-aggregating with it, aiming to elucidate the underlying mechanisms through which ApoE modulates the risk and progression of AD.
Methods: To investigate the effects of Aβ-apoE interactions, we have developed induced pluripotent stem cell (iPSC)-derived cortical neurons expressing ApoE3 and ApoE4, which we have cultured with astrocyte-derived ApoE3 and ApoE4. This approach will determine whether apoE4 specifically exacerbates Aβ toxicity compared to ApoE3, regardless of the neuronal lines used, or if high-risk ApoE4 neurons are intrinsically more vulnerable to Aβ damage, independent of the isoform of astrocytic apoE.
Results: We use single-molecule and super-resolution imaging to study the aggregation rate and the size, shape, and stoichiometry of the Aβ-apoE complexes formed during aggregation. Neuronal health is assessed by measuring the release of Caspase-3/7, neurite retraction, electrophysiological activity, and synapse number quantification.
Conclusions: Our studies aim to elucidate the structure-function relationships of apoE-Aβ co-aggregates and how they link specific apoE isoforms to the risk of developing AD.

SHIFT 02-157

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
4 - 5 April

AN EPIGENOMIC ASSESSMENT OF CORTICAL METHYLATION PATTERNS IN LEWY BODY DEMENTIA

Joshua Harvey[1], Jennifer Imm[1], Byron Creese[2], Leonidas Chouliaras[3], Emma Dempster[1], Jonathan Mill[1], Clive Ballard[1], John O'Brien[3], Dag Aarsland[4], Lasse Philstrom[5], Ehsan Pishva[6], Katie Lunnon[1]
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Aims: Lewy body diseases (LBD) are a group of neurodegenerative disorders that are characterized by the presence of abnormal protein deposits called α-Synuclein in the brain. α-Synucleinopathies often occur with abnormal accumulation of tau and amyloid-β in the brain. Epigenetic mechanisms—molecular processes that modify gene expression without changing the underlying genetic sequence—represent a potential area of contribution that has been under-researched to date.
Methods: Genome-wide DNA methylation in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) was profiled for a total sample size of 1,251 in three independent cohorts. The UK Brain Bank Cohort (UKBBN, n = 805; 419 donors; PFC and ACC), the Netherlands Brain Bank Cohort (NBB, n = 322; PFC) and the Brain's for Dementia Research Cohort (BDR, n = 124; PFC).
Results: Meta analyses identified three differentially methylated positions (DMPs) with genome wide significant association ($P < 9 \times 10\text{-}8$), including sites annotated to the genes UBASH3B and PTAFR and an intergenic loci cg13847853. A further 20 DMPs were associated at a more lenient false discovery rate (corrected $P < 0.05$). Subsetting meta-analysis to samples with LB pathology in the absence of significant Alzheimer's pathology (Braak NFT stage < 3, n = 798) showed attenuated significance, with only cg13847853 passing multiple testing correction.
Conclusions: We conducted the largest meta-analysis of DNA methylation changes related to LB pathology in brain to date, identifying several DMPs significantly associated with the pathology. We also demonstrated that methylomic signatures associated with LB pathology are independent of Alzheimer's disease co-pathology. Ongoing analyses are (1) comparing epigenetic profiles associated to LB pathology with those associated to AD pathology, and (2) performing cell-type specific DNA methylation analyses in a subset of the cohort to determine the disease-specificity of nominated loci.

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SHIFT 02-158

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
4 - 5 April

PLASMA EPIGENETIC SIGNATURES FOR BIOLOGICAL ALZHEIMER'S DISEASE

Yiyi Ma[1], Dolly Reyes-Dumeyer[2,3], Clifton Dalgard[4], Badri Vardarajan[5,6,7], Richard Mayeux[6,7,8]
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Aims: Epigenetic mechanism is involved in the etiology and progression of the Alzheimer's disease (AD). However, there is no systematic epigenome-wide study on the plasma biomarkers of AD.
Methods: PAXgene blood tubes were collected in the 751 Caribbean Hispanics from the EFIGA cohort. NEBNext Enzymatic Methyl-seq (EM-seq) was used for the identification of genome-wide 5-methylcytosine and 5-hydroxymethylcytosine. 10 ng of DNA went through a two-step conversion of the cytosines. Site and sample level quality control identified 3,789,103 CpG sites in 751 subjects. Association of methylation levels were tested with plasma levels of Aβ40, Aβ42, phosphorylated Tau-181 and 217 (P-tau181 and P-tau217), and total-Tau (T-tau) adjusting for age, sex, total reads, and methylation batch. We further conducted the pathway analysis for those genome-wide significant CpG sites (P<1.0x10^{-9}) by STRINGdb.
Results: 88 CpG sites were genome-wide significant: 26 for Aβ40, 37 for Aβ42, 3 for P-tau181, 8 for P-tau217, and 14 for T-tau. These CpG sites were located within or close to 58 genes, of which14 were previously reported to be associated with AD, including *ROCK2*, *DEK*, *FSD1L*, *WDR5*, *DOCK8*, *DUSP5*, *LCOR*, *CAMKK1*, *RPS27A*, *TRIB3*, *LRPAP1*, *ARHGEF2*, *TYMS*, and *DCHS2*. Among significant genes, we detected five clusters (driven by 25 genes) using STRINGdb's k-means clustering. Cluster 1 contains 16 genes enriched in microtubule cytoskeleton and intracellular non-membrane-bounded organelle pathways. Three genes within the cluster 2 are enriched in tRNA aminoacylation, glutaminyl-tRNAGln biosynthesis via transamination, and translation pathways.
Conclusions: We have identified epigenetic signatures and pathways for the plasma biomarker levels of AD. Replication and validation is underway in independent datasets and tissues.

SHIFT 02-162

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

GLYCOPROTEOMIC NETWORK AND TARGET DISCOVERY FOR ALZHEIMER'S DISEASE

Lian Li, Qi Zhang, Lih-Shen Chin
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Aims: Glycosylation is the most prevalent and complex form of protein modification which produces vastly diverse arrays of glycosylated proteoforms or glycoforms to regulate numerous biological processes, including synaptic function and brain homeostasis. Works from our group and others have implicated a role for altered glycosylation in Alzheimer's disease (AD) pathogenesis. However, current knowledge of system-wide changes in site-specific glycans and glycoforms in AD is still limited. This study aimed to address the gap in knowledge and perform innovative research to identify disease-associated glycoproteomic networks and glyco-targets in AD brain.
Methods: We established a network-based glycoproteomics approach that integrates intact glycopeptide-based quantitative glycoproteomics with network biology for large-scale, in-depth analysis of protein glycoforms and site-specific glycans in complex biospecimens. We used this approach to analyze human brain tissue samples from neuropathologically confirmed AD cases and their age-matched controls to uncover the valuable biological information hidden in the human AD brain glycoproteome.
Results: Our analyses revealed the glycoproteomic landscape of human brain and identified disease signatures of altered glycoproteins, glycoforms, and glycans in AD brain. Our study uncovered glycoform and glycan co-regulation networks and multiple processes and pathways impacted by altered glycosylation in AD, including matrisome function, cell adhesion, synaptic transmission, cell signaling, endocytic trafficking, lysosome function, and neuroinflammation.
Conclusions: The identified glycan modification aberrations and brain glyco-network alterations from this study provide mechanistic insights into AD pathogenesis and pave the way forward for developing glycosylation-based therapies and biomarkers to combat this devastating disease.

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SHIFT 02-163

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

ASSOCIATION BETWEEN BLOOD METABOLITES, DEMENTIA AND REGIONAL BRAIN CHANGES

Yue Liu[1], Asger Wretlind[2], Dorsa Abdolkarimi[1], Sheena Waters[1], Charles Marshall[1], Cristina Legido-Quigley[3], Petroula Proitsi[1]
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Aims: Metabolic dysfunction is increasingly recognized as an early pathobiology of dementia. Our study aimed to combine supervised prediction model with unsupervised co-expression network analysis to identify key dementia-related metabolites and uncover the complex metabolic relationships underlying dementia. We also sought to examine how these key metabolites influence structural brain changes.
Methods: We analysed data from 271,474 participants in the UK Biobank, focusing on 327 circulating metabolites measures, including lipoproteins, ketone bodies, amino acids, and glycolysis-related compounds. We employed Weighted Gene Co-expression Network Analysis (WGCNA) to identify co-expressed metabolite modules and hub metabolites. Cox proportional hazards and linear regression models were used to assess associations between metabolite modules, hub metabolites, and incident dementia. Key metabolites were selected using a Cox proportional hazards elastic-net regression model, to generate metabolomic scores to predict all-cause dementia, vascular dementia (VaD), and Alzheimer's dementia (AD). We further explored the relationship between metabolomic scores, dementia-related metabolite modules, and neuroimaging markers.
Results: WGCNA clustered metabolites into modules primarily consisting of lipoproteins in different sizes and compositions. While AD was only associated with LDL/VLDL cholesterol-related modules, VaD was linked to most of modules. Modules characterized by LDL/VLDL cholesterols, VLDL triglycerides (TG), and lipids in larger HDL were significantly associated with volumes across multiple regions. In contrast to WGCNA, fatty acids, amino acids, glycolysis-related metabolites and ketone bodies were additionally identified in dementia prediction model. VaD metabolomic score was associated with a broader range of brain regions compared to the ACD/AD scores.
Conclusions: Elastic-net prediction model and WGCNA complement each other in identifying key metabolites and elucidating molecular pathways involved in dementia. Blood-based metabolite markers of brain endophenotypes may offer valuable insights into early dementia mechanisms and suggest potential avenues for intervention strategies.

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On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

LONGITUDINAL PROFILING OF IMMUNOLOGICAL DYNAMICS IN PERIPHERAL BLOOD DURING ALZHEIMER'S DISEASE-RELATED COGNITIVE DECLINE USING SCALABLE FLOW CYTOMETRY ANALYSIS

Karola Mai[1,2], Jannis Spintge[3,4], Caterina Carraro[5], Lorenzo Bonaguro[2,4,6], Lisa Holsten[2,6], Karoline Mauer[2,4], Emily Hinkley[2,4], Sophie Müller[2,6,7], Yuanfang Li[2,8], Ioanna Gemünd[2,6,7], Charlotte Kröger[2,6], Tarek Elmzzahi[7,8], Rainer Knoll[2,6], Rebekka Scholz[2,8], Dina Hüsson[2,8], Victoria Isakzai[2], Nico Reusch[2,6], Michael Kraut[9], Heidi Theis[3], Anna Drews[2], Maren Büttner[3,6,10], Delcode Study Group[11], Anna Aschenbrenner[2,6], Elena De Domenico[2,9], Matthias Becker[5,12], Martina Van Uelft[2,6], Joachim Schultze[2,9], Thomas Ulas[2,6,9], Marc Beyer[2,5,8,9]
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Aims: Clinical studies have established a link between peripheral immune dysregulation in AD and cognitive function, as well as disease status. To address this knowledge gap, we aimed to investigate the immune system's involvement in AD development and identify potential blood-based biomarkers for early diagnosis and prediction of disease progression prediction using scalable flow cytometry.
Methods: We performed a comprehensive analysis of peripheral blood mononuclear cells from 70 individuals spanning the AD spectrum using high-throughput flow cytometry. To investigate longitudinal dynamics, we assessed individuals again at follow-up one year later. Additionally, we stimulated B cells from AD patients and healthy controls with lipopolysaccharide to assess their activation potential.
Results: Our findings revealed dynamic alterations in immune cell populations that correlated with cognitive decline preceding AD onset. Notably, we observed significant shifts in monocyte and B cell frequencies, suggesting their potential as early biomarkers for AD. Specifically, individuals with mild AD exhibited decreased B cell frequency and increased classical monocyte frequency compared to healthy controls. Furthermore, B cells from AD patients displayed diminished expression of surface activation markers after LPS stimulation. Our analysis also uncovered changes in the longitudinal dynamics of peripheral immune cells, providing valuable insights for the development of novel therapeutic strategies.
Conclusions: These findings hold promise for advancing personalized diagnostic and prognostic tools,

enhancing our understanding of neurodegenerative diseases, and ultimately improving patient care. By elucidating the immunological mechanisms accompanying AD-related cognitive decline, our study provides new insights which might lead to more effective treatments and interventions for AD patients

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SHIFT 02-165

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

CEREBROSPINAL FLUID PROTEOMIC PROFILING OF DEPRESSION IN OLDER PEOPLE IN THE CONTEXT OF ALZHEIMER'S DISEASE

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Aims: Depressive symptoms are common in older people with cognitive decline and Alzheimer's disease (AD), may occur at early stages, and contribute to clinical progression. Little is known about the underlying pathology. Here, we aim to investigate molecular pathway alterations related to depression in AD.
Methods: We considered individuals with normal cognition (NC), mild cognitive impairment (MCI) or mild AD dementia with available depression scores and untargeted mass spectrometry-based cerebrospinal fluid (CSF) proteomics data from two independent cohorts: the single-centre Amsterdam Dementia Cohort (ADC) and the multi-centre European Medical Information Framework for Alzheimer's disease Multimodal Biomarker Discovery study (EMIF-AD MBD). Depressive symptoms were measured using the Geriatric Depression Scale (GDS). Linear regression models were applied to identify proteomic signatures related to GDS scores in both cohorts, followed by analysis stratified according to amyloid status and clinical diagnosis. Pathway enrichment analysis was applied to identify pathway alterations using the gene ontology database.
Results: In ADC, 450 individuals (164 with NC, 94 with MCI, 192 with AD dementia) and in EMIF-AD MBD 274 subjects (70 with NC, 121 with MCI, 83 with AD dementia) were investigated. The CSF levels of 45 proteins (4.8% of all tested) were associated with higher depression scores in both cohorts, of whose 40 were upregulated and 5 downregulated. These proteins were associated with pathways related to signal transduction, immune system, and synaptic function. Stratified analysis revealed that most of the identified proteins were related to depression independently of amyloid positivity or cognitive impairment.
Conclusions: Using a data-driven approach, we identified distinct pathway alterations related to depression in two independent cohorts. The results suggest specific pathomechanisms underlying depression symptoms, which may represent intervention targets to treat depression in cognitive decline and AD.

SHIFT 02-166

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

A NOVEL INDUCIBLE CRISPRI TOOL (CRISPRI-CRE) TO STUDY NEURON-SPECIFIC PHENOTYPES IN IPSC-DERIVED NEURON MODELS OF ALZHEIMER'S DISEASE

Daniel Ramos[1], Matthew Nelson[1], Elizabeth Calzada[1], Sanjana Krishna[1], Samuel Neuman[1], Cory Weller[1], Nicholas Johnson[1], Erika Lara[1], Andy Qi[1], Marianita Santiana[1], Caroline Pantazis[1], William Skarnes[2], Michael Nalls[1,3], Andrew Singleton[1], Mark Cookson[1,4], Michael Ward[1,5]
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Aims: The iPSC Neurodegenerative Disease Initiative (iNDI) is the largest-ever induced pluripotent stem cell (iPSC) genome engineering project, modeling over 100 ADRD mutations in high-quality isogenic human iPSCs. As part of iNDI, we use unbiased CRISPRi screens as a powerful tool to identify fundamental mechanisms and modifiers of disease. However, current CRISPRi molecular tools are poorly optimized for use in iPSC-derived neurons (iNeurons). Here we develop a Cre-lox inducible CRISPRi system (CRISPRi-Cre), enabling gene knockdown upon Cre delivery to postmitotic iNeurons, and identification of neuron-specific, disease-relevant modifiers.
Methods: We modified a piggybac plasmid carrying a potent Zim3-dCas9 transcriptional repressor to include a strong floxed STOP cassette upstream of the Zim3 start codon. We leveraged HaloTag-TDP43 and HaloTag-FUS iSPCs from the iNDI project paired with flow cytometry to validate leakiness and responsiveness to Cre in iPSCs and iNeurons treated with sgRNAs. We then performed a genome-wide CRISPRi survival screen in iNeurons to demonstrate the broad functionality of this inducible CRISPRi system with over 20,000 sgRNAs. Finally, we use CRISPRi-Cre to identify neuron-specific regulators of neuronal activity in iNeurons.
Results: We demonstrate that in the absence of Cre, dCas9 is inactive. Upon delivery of lentivirus-Cre to post-mitotic D7 iNeurons, dCas9 is robustly activated, resulting in potent gene knockdown. In genome-wide CRISPRi screens, we show that CRISPRi-Cre identifies many of the same hits observed in screens using constitutive-active dCas9, and importantly uncovers novel neuron-specific hits not identified in previous CRISPRi screens.
Conclusions: Here, we developed a robust Cre-inducible CRISPRi system that enables post-mitotic gene knockdown in iPSC-derived neurons. Our CRISPRi screens identify neuron-specific hits, demonstrating the utility of our tool to help uncover disease-relevant mechanisms, modifiers, and potential therapeutic targets in relevant cell types.

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SHIFT 02-167

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β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

DISCOVERY AND VALIDATION OF DEMENTIA SUBTYPE SPECIFIC BIOMARKERS USING UNTARGETED CEREBROSPINAL FLUID DATA-INDEPENDENT ACQUISITION MASS SPECTROMETRY PROTEOMICS

Marijke Stokkel[1], Lisa Vermunt[1], Jaco Knol[2], Sander Piersma[2], Thang Pham[2], Berend Gagestein[2], Richard Goeij-De Haas[2], Afina Lemstra[3], Yolande Pijnenburg[3], Pieter Visser[3], Betty Tijms[3], Charlotte Teunissen[1], Connie Jimenez[2]
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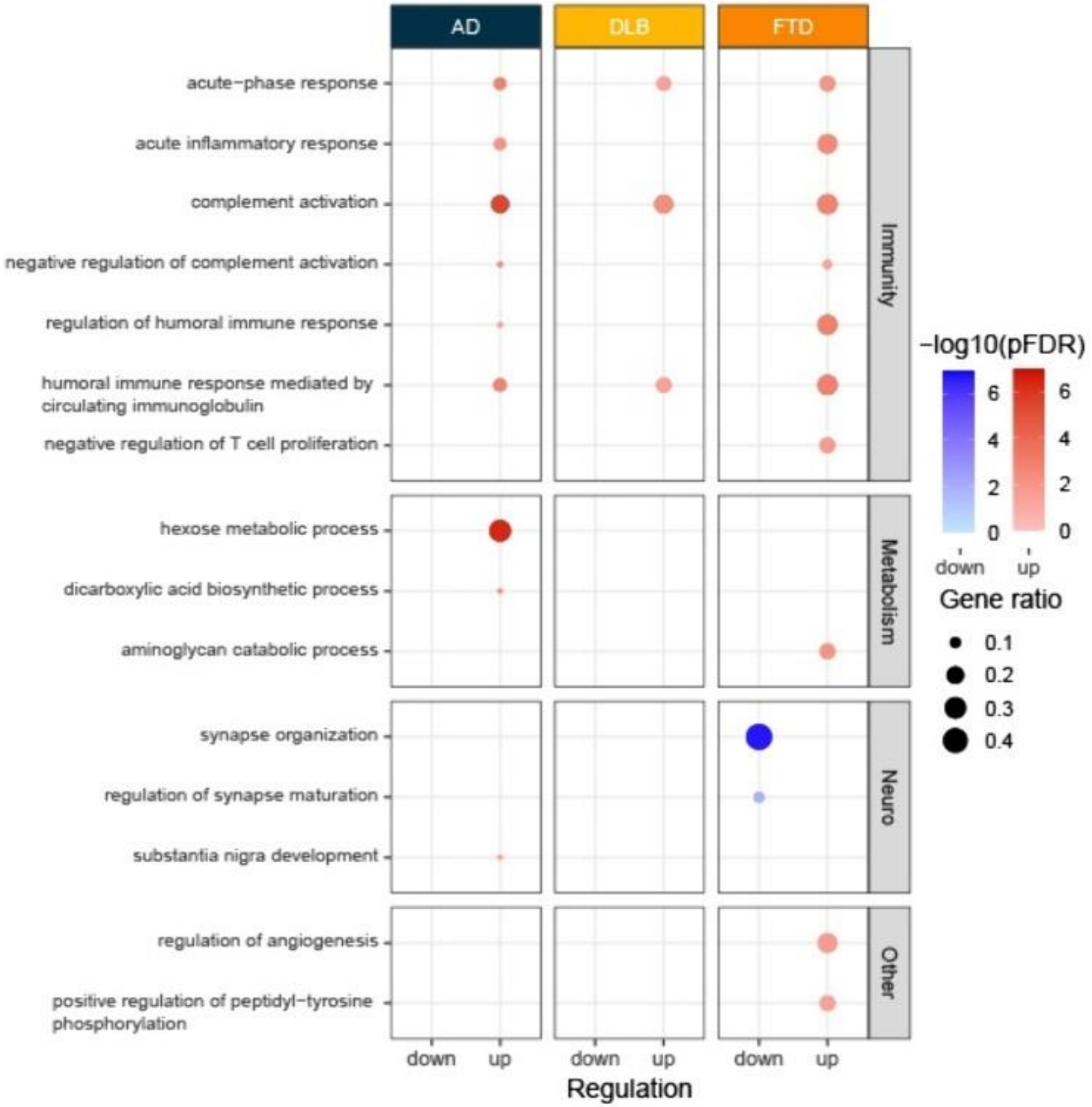
Aims: Dementia can be caused by different pathologies, including Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). Understanding the biological mechanisms underlying these diseases is important in order to guide biomarker and therapy development. Here, we performed proteomics in cerebrospinal fluid (CSF) from patients with AD, DLB and FTD in order to study proteomic changes and identify potential biomarkers.
Methods: Individuals from the discovery (n=80) and validation (n=77) cohort were selected from the Amsterdam Dementia Cohort based on clinical diagnosis and availability of a CSF sample. Single shot nano-LC-MS/MS was performed using a data independent acquisition (DIA) method in a QExactive HF mass spectrometer. For each cohort, protein intensities were log2 transformed, and scaled according to the control group. Next, all groups were compared to each other on the levels for each protein with linear regression models, including age and sex as covariates.
Results: We identified 33, 23, and 31 differentially expressed proteins in AD, DLB and FTD. All three diseases exhibited increased immune related responses, namely acute phase response, complement activation and processes related to humoral immune response. Of the differentially expressed proteins, 11, 3 and 8 also showed significant changes is the validation cohort for AD, DLB and FTD, respectively. Replicating AD proteins correlated positively with CSF tTau and pTau, and negatively with Aβ42. Literature study confirms similar direction of change for 19 of the 22 proteins.



Conclusions: We identified and validated potential biomarkers for AD, DLB and FTD. Some proteins, like SMOC1 for AD, CHI3L1 (YKL-40) for FTD and VGF for DLB have been numerously observed in literature (>2 studies). For proteins identified in fewer studies, we can now provide confirmation.

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SHIFT 02-168

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

ADVANCEMENTS IN NEURODEGENERATION BIOMARKER RESEARCH THROUGH THE GLOBAL NEURODEGENERATION PROTEOMICS CONSORTIUM (GNPC) FOR PREDICTION MODELING

Varsha Krish[1], Jacob Vogel[2], Muhammad Ali[3], Amelia Farinas[4]
[1]Gates Ventures, Seattle, United States of America, [2]Lund University, Department Of Clinical Sciences, Lund, Sweden, [3]Washington University, Department Of Psychiatry, St. Louis, United States of America, [4]Stanford University, School Of Medicine, Stanford, United States of America

Aims: The GNPC is a collaborative effort aimed at advancing the understanding of major neurodegenerative diseases [AD, PD, ALS, and FTD] through comprehensive proteomic analysis. More than 20 distinct cohorts contributed clinical data and samples to create the largest discovery proteomics dataset to date, including ~40,000 samples and ~300 million individual protein measurements. Harmonization of proteomics data and clinical metadata for ~50 variables was completed in June 2024, and the dataset will be shared with the global research community in June 2025. The consortium has established distinct workstreams, each focusing on specific aspects of neurodegeneration research. Preliminary results from the Prediction Modeling Workstream are presented here.
Methods: The GNPC's prediction modeling workstream is dedicated to developing robust models that can predict the onset and progression of neurodegenerative diseases. This workstream is focused on leveraging the GNPC's extensive dataset to create predictive models for various neurodegenerative conditions, using a combination of methods including regression models, machine learning, and deep learning.
Results: The prediction modeling workstream has developed models that can forecast disease diagnosis and prognosis utilizing only proteomic biomarker data and minimal clinical attributes. Initial work shows the accuracy of these models approaching and/or matching that of prior models requiring significantly higher information content. The workstream's efforts are exemplified by projects such as Proteomics Deep Embedding and Plasma Biomarker Identification for ADRD, which aim to use machine learning and network strategies to identify disease-specific biomarkers.
Conclusions: The GNPC's prediction modeling workstream plays a crucial role in the consortium's efforts to advance neurodegenerative disease research. By creating predictive models and identifying biomarkers, the workstream contributes to a better understanding of disease mechanisms and could potentially identify a robust blood-based biomarker to diagnose and predict disease progression.

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SHIFT 02-169

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

CSF AND BLOOD METABOLOMICS REVEALS METABOLIC SIGNATURES AND SUBTYPES OF ALZHEIMER'S DISEASE

Xiaoli Yang[1], Feng Gao[2], Yong Shen[2]
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Aims: The objective is to advance our comprehension of AD-related metabolic disorders, while simultaneously furnishing novel metabolic biomarkers and subtypes of AD for clinical diagnosis and personalised treatment.
Methods: In this study, untargeted metabolomics analysis was conducted on CSF and serum samples from cognitively normal (CN), mild cognitive impairment (MCI), AD, and non-AD dementia (Non-ADD) patients from China Aging and Neurodegenerative Initiative (CANDI) cohort to identify differentially expressed metabolites in AD. Subsequently, an analysis was performed to investigate the association between metabolite changes and key pathological features of AD. Furthermore, the blood-brain barrier (BBB) transport of common metabolites detected in CSF and blood was also investigated. Finally, the ability of metabolites to predict AD pathology was evaluated, and the metabolomic data were used to classify AD patients into different subtypes.
Results: The alterations in both the central and peripheral metabolites, as well as in the blood-brain transportation of metabolites in AD patients were demonstrated. There is a noteworthy correlation between metabolite alterations and AD pathological features, as well as cognitive function. Meanwhile, blood metabolites exhibit a considerable potential for improving the prediction of AD pathology status in patients. Metabolic subtyping of AD patients was also achieved by using metabolomics.
Conclusions: CSF and blood metabolites have been identified as potential biomarkers for AD traits, offering a promising avenue for improving the prediction of AD pathology status. Furthermore, the metabolome could be used to classify AD patients into distinct metabolic subtypes, providing a valuable tool for understanding the heterogeneity of this disease.

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SHIFT 02-177

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4 - 5 April

COMPUTER MODELING OF COGNITIVE AGING THEORIES

Lewis Mehl-Madrona[1], Barbara Mainguy[2]
[1]University of Maine, Philosophy, Orono, United States of America, [2]Coyote Institute, Education, Orono, United States of America

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 and Scaffolding models. We used longitudinal data across the life span of 11 patients to “train” the model to predict cognitive functioning. This data was obtained through life story interviews. Three separate 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 11 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 a major neurocognitive disorder. We defined success as a prediction of the 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 62% of the time compared to 32% 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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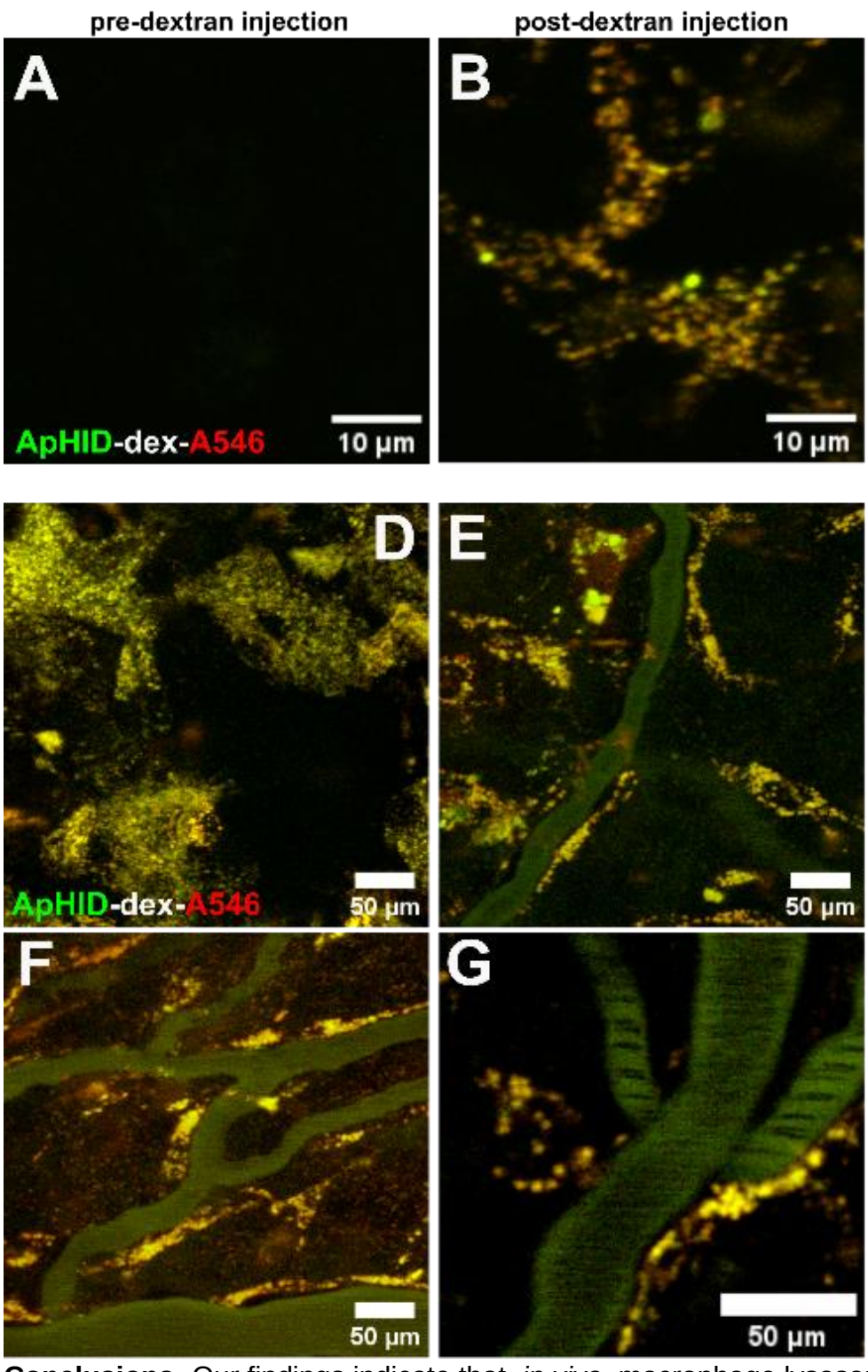
SHIFT 02-178

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4 - 5 April

INTRAVITAL RATIOMETRIC PH IMAGING OF BRAIN MACROPHAGE LYSOSOMES USING THE NOVEL PH-SENSITIVE PROBE APHID

Santiago Sole Domenech, David Warren, Frederick Maxfield
Weill Cornell Medicine, Biochemistry Department, New York, United States of America

Aims: Prior research indicates that perivascular macrophages can degrade Alzheimer's disease (AD) amyloid-beta (Aβ) more efficiently than microglia (Meyer-Luehmann and Prinz, 2015), partly due to more efficient lysosomal acidification (Majumdar et al 2012). We aim to measure and compare, for the first time, lysosomal pH in macrophages and microglia *in vivo*, particularly in relation to AD and aging, using intravital microscopy and the new pH-sensitive probe *ApHID.*
Methods: Mice with implanted cranial windows received subcutaneous injections of 70 KDa dextran polymers labeled with ApHID and Alexa 546 (pH-independent) and were allowed to recover overnight. Dextrans were internalized by brain macrophages, which were imaged ratiometrically. Prior to imaging, brain vasculature was labeled with 500 KDa fluorescein-dextran. Measured cellular ApHID/Alexa 546 ratios were interpolated to pH using a ratio-to-pH calibration prepared in fixed cells.
Results: Prior to labeling brain vasculature, blood vessels appeared free of any fluorescence, indicating that the previously injected 70 KDa dextrans were no longer available for endocytosis. In absence of circulating dextran, endocytosed polymers would be delivered to lysosomes within 1-2 hours. ApHID brightness increases with acidity (Sole-Domenech et al. 2024) and its fluorescence was intense in labeled compartments (Fig. 1A-1C), indicating acidic pH. Leptomeningeal (Fig. 1D) and perivascular (Fig. 1E-1G) macrophages showed robust dextran uptake, with lysosomal pH ranging between 4.5 and 6.0 (Fig. 1H) and a mean of pH 5.5 (Fig. 1I, *n*: 5 mice).



Conclusions: Our findings indicate that, *in vivo*, macrophage lysosomal pH is notably less acidic than the pH 4.7-5.0 reported in cell culture. Our research will further explore differences in lysosomal acidification between macrophages and microglia associated with aging and AD. The results will be expanded and discussed at the ADPD meeting.

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SHIFT 02-179

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4 - 5 April

DIVERGENT HUMAN CYTOSKELETAL GAIN OF FUNCTION DEFINES GENETIC BACKGROUND FOR NEUROPSYCHIATRIC DISEASES

Kinga Szigeti[1], Ivanna Ihnatovych[1], Nicolas Rosas[1], David Bennett[2], Eduardo Cortes Gomez[3], Jianmin Wang[3]
[1]University at Buffalo, Neurology, Buffalo, United States of America, [2]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America, [3]Roswell Park Cancer Institute, Bioinformatics, Buffalo, United States of America

Aims: Objective: Understanding the fundamental differences between the human and pre-human brain is a prerequisite to designing meaningful models and therapies for AD. CHRFAM7A, a human restricted gene is emerging as genetic background for neuropsychiatric diseases. We utilized human brain multiomics and iPSC model to elucidate the molecular mechanism for the genetic background.
Methods: The physiological role of direct and inverted alelles of *CHRFAM7A* in human brain is explored using multiomics approach on 600 post mortem human brain tissue samples (ROSMAP). The emerging pathways and mechanistic hypotheses are validated in an isogenic hiPSC model of *CHRFAM7A* knock-in neurons.
Results: Allele specific cytoskeleton gain of function is uncovered. Mechanistically, the direct allele leads to a hypomorphic a7 nACh receptor, while the inverted structural variant (SV) allele regulates *ULK4* through genetic epistasis. The a7/*CHRFAM7A* receptor modulates intracellular calcium dynamics and an upstream regulator of Rac1. Rac1 activation re-designs the actin cytoskeleton leading to dynamic actin driven remodeling of membrane protrusion and a switch from filopodia to lamellipodia. In the neuronal lineage actin cytoskeleton reorganization shifts dendritic spine differentiation from filopodia towards spines with increased head area to stem diameter ratio resulting in increased synapse clustering (“high quality wellcro”) in neurons. In contrast, the inverted allele infers ULK4 hypermorphism leading to increased a-tubulin acetylation and microtubule cytoskeleton driven neuronal arborization.
Conclusions: Human restricted *CHRFAM7A* alleles define the genetic background for AD pathology through distinct cellular biology affecting the cytoskeleton. The biallelic split forcasts genetic background dependent driver mechanisms.

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SHIFT 02-184

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / SECRETASES
4 - 5 April

CEREBRAL ORGANOID MODELS OF ALZHEIMER'S DISEASE AS A TOOL TO STUDY THE AD-PATHOGENESIS-MODULATING EFFECTS OF BACE2

Aoife Murray[1], Emre Fertan[2], Dorothea Boeken[2], Yee Jie Yeap[3], Gillian Gough[3], Ana Muniz-Garcia[4], Ivan Alic[5], Kah Leong Lim[3], Anne Rovelet-Lecrux[6], David Klenerman[2], Dean Nizetic[4]
[1]Faculty of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom, [2]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [3]Lee Kong Chian School of Medicine, Singapore, Singapore, [4]Faculty of Medicine and Dentistry, Queen Mary University of London, The Blizard Institute, London, United Kingdom, [5]Faculty of Veterinary Medicine, University of Zagreb, Croatian Institute For Brain Research, Zagreb, Croatia, [6]Normandie Univ, UNIROUEN, Inserm U1245, Department Of Genetics And Cnr-maj, Rouen, France

Aims: We recently developed a model displaying reproducible Alzheimers-like pathology in human cerebral organoids grown in vitro from non-invasively sampled strands of hair from 71% of Down syndrome (DS) donors (in a donor–specific manner), secreting Aβ peptides in the picomolar range, and faithfully reproducing proteolytic processing of Aβ detectable in patients' CSF.
Methods: From a trisomy 21 (T21) iPSC line that does not show overt organoid pathology, by CRISPR elimination of a single copy of the chromosome 21-located β-secretase-2 (BACE2), we developed a unique, isogenic T21 iPSC line (T21C5Δ7) that shows an accelerated triad of AD-like pathologies (amyloid plaque-like structures, pathologically conformed intra-neuronal Tau, and neuronal loss) which can be completely prevented by combined chemical β- and γ-secretase inhibition. Our main finding was recently reproduced by others, who grew organoids from non-DS individuals with 2 copies of APP, but only one functional copy of BACE2, and these organoids too developed a similar triad of AD-related pathologies.
Results: We now observe (preliminary, unpublished) up to 20-fold increased production of soluble oligomeric aggregates of Aβ, and >4 fold increased soluble aggregates of pTau and inflammasome ASC-specks in conditioned media of the T21C5Δ7 organoids compared to unedited T21 organoids. Furthermore, we recently generated (unpublished) iPSC lines from a non-DS patient whose EOAD was caused by a de-novo 12kbp intronic deletion in BACE2. We show that amyloid aggregates and hyperphosphorylated Tau in cerebral organoids from this patient (ApoE3,4) are more pronounced than in organoids from his father (no deletion in BACE2, cognitively normal, despite carrying ApoE4,4).
Conclusions: In summary, we present the cerebral organoid system as a viable model in which to study the gene-dose and novel drug effects on the AD-pathogenic process relevant to human brain.

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SHIFT 02-185

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / SECRETASES
4 - 5 April

ALZHEIMER'S DISEASE-ASSOCIATED MUTATIONS INTERFERE WITH PRODOMAIN CLEAVAGE AND MATURATION OF ADAM10

Gözde Ozcelik[1,2], Esther Alvarez Sanchez[1,2], Stefan Lichtenthaler[1,2,3]
[1]Neuroproteomics, School of Medicine and Health, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, [3]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Aims: Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques, and ADAM10, the primary α-secretase, plays a critical role in preventing Aβ formation by processing amyloid precursor protein (APP) through the non-amyloidogenic pathway. Reduced α-secretase activity due to ADAM10 mutations is linked to AD pathology, making ADAM10 a potential therapeutic target. ADAM10 is initially synthesized as an inactive proenzyme and becomes activated upon prodomain cleavage. Recently, numerous rare, coding mutations were discovered in ADAM10. While some were linked to increased AD risk, it remains unclear whether and how they affect ADAM10 activity. This study aims to investigate the impact of AD-associated prodomain mutations in ADAM10, which are linked to AD risk but whose functional effects remain unclear.
Methods: In our study, we characterized selected prodomain mutations in ADAM10 associated with AD. To understand how these mutations affect ADAM10 maturation and activity, we performed overexpression experiments in ADAM10-deficient HEK cells.
Results: While some mutants impaired maturation, prodomain cleavage and activity of ADAM10, others did not induce significant alterations. We also discovered an unidentified potential furin-processing site within the prodomain of ADAM10, required for normal ADAM10 maturation and shedding activity.
Conclusions: This research uncovers the mechanisms by which ADAM10 prodomain mutations affect its maturation and activity, shedding light on their contribution to AD pathology. These findings suggest that restoring ADAM10 function could serve as a therapeutic strategy for AD. Furthermore, the identification of a key furin-processing site in ADAM10 opens new pathways for studying its role in both health and diseases.

SHIFT 02-186

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4 - 5 April

ROLE OF AMYLOID RESPONSOME IN AMYLOID AGGREGATION – FRIENDS OR FOES

Yona Levites, Yong Ran, Xuefei Liu, Mihir Beheray, Cindy Hillah, Kyu Shim, Danny Ryu, Todd Golde
Emory University, Atlanta, United States of America

Aims: Research using proteomic and biomarker approaches reveals the complexity of brain changes as AD develops, affecting all brain cell types and leading to organ failure. Comparing AD brain proteomes with those of Aβ-depositing transgenic mice identified conserved and divergent protein networks, Aβ amyloid responsome. Proteins in the most conserved network (M42) accumulate in plaques, cerebrovascular amyloid (CAA), and/or dystrophic neuronal processes, making them potential therapeutic targets. The "amyloid scaffold" hypothesis suggests that Aβ aggregation may not be sufficiently toxic to induce downstream neurodegeneration unless accompanied by AAP accumulation. We proposed to test effects of a few of the differentially expressed proteins (DEP) on Amyloid pathology.

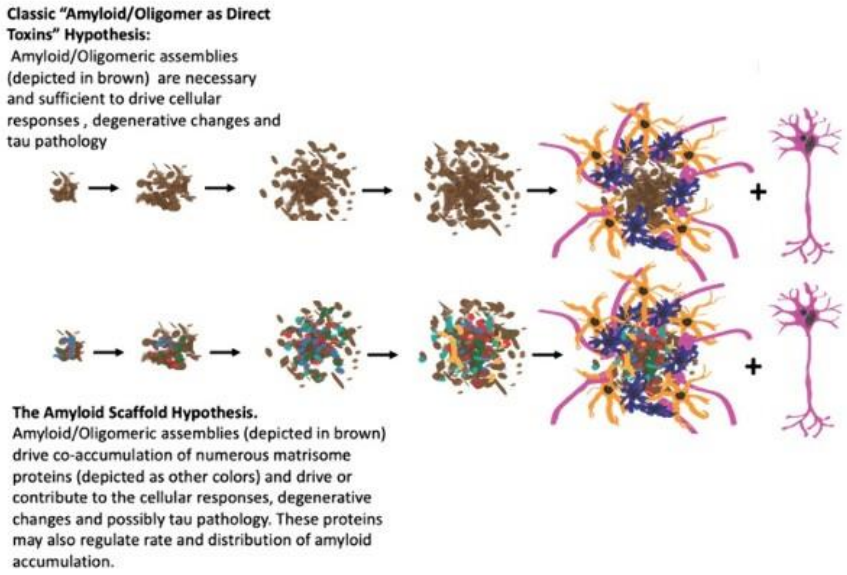

Figure 1. The amyloid scaffold hypothesis

Methods: Proteins in a conserved module, M42, are pathologically related to amyloid deposits. Overexpression of two of M42 proteins, midkine or pleiotrophin, by AAV-mediated delivery, increased amyloid deposition. To further investigate this hypothesis, we set up a continuation study to assess the effects of additional M42+ DEPs on amyloid deposition by overexpressing them in CRND8 mouse brains via AAV delivery. Amyloid burden and soluble and insoluble Aβ levels were compared between various cohorts.
Results: We overexpressed Vtn, Ntn1, Egfl8, Sdc4, Hhipl1, Sfrp3, and Smoc1 by AAV-mediated

delivery to newborn CRND8 mice. AAV-mediated delivery resulted in robust overexpression of these genes in the mouse brain. Preliminary data demonstrated differential effects of DEP overexpression on amyloid pathology, suggesting complex roles of each of these individual proteins in development of Amyloid pathology

Conclusions: These studies provide important insights into the biology of DEP in AD pathogenesis. It is likely that basic mechanisms of DEP binding to amyloid also apply to proteins implicated in peripheral amyloidosis which makes these studies important in the broad field of neurodegenerative disorders.

SHIFT 02-187

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4 - 5 April

ROLE OF PRO-INFLAMMATORY S100A9 PROTEIN IN AMYLOID NEUROINFLAMMATORY CASCADE IN ALZHEIMER'S DISEASE.

Ludmilla Morozova-Roche
Umea University, Medical Biochemistry And Biophysics, Umea, Sweden

Aims: The amyloid cascade and neuroinflammation are central mechanisms involved in neurodegeneration and manifested in numerous diseases, including Alzheimer's and Parkinson's diseases, traumatic brain injury and others. Increasing evidence has accumulated demonstrating critical role of pro-inflammatory S100A9 in the amyloid-neuroinflammatory cascade in these diseases. We have demonstrated that S1009 protein is intrinsically amyloidogenic and able to form amyloids both in vitro and in vivo in cell models and in the brain tissues in neurodegenerative diseases.
Methods: We use innovative charge detection mass spectrometry together with biophysical techniques to provide mechanistic insight into the amyloid aggrgeation and co-aggregation process and differentiate amyloid complexes at a single particle level. We demonstrate that synergy between mass spectrometry, microscopy, kinetic and microfluidic analyses together with immunohistochemistry and cellular technqiues opens new directions in interdisciplinary research.
Results: In Alzheimer's disease, deciphering the interaction between proinflammatory S100A9 protein and Aβ peptide and their co-aggregation mechanisms are particularly important since these lead to amyloid plaques formation and neural cytotoxicity of amyloid oligomers. We revealed that the co-aggregation involves templating of S100A9 fibrils on the surface of Abeta42 amyloids. Kinetic analysis further corroborates that the surfaces available for the Abeta42 secondary nucleation are diminished due to the coating by S100A9 amyloids, the length of Abeta42 fibrils significantly increased, while the stoichiometry of binding of S100A9 to Abeta42 fibrils was validated by a microfluidic assay. Interactions of S100A9 with small molecules as potential regulators of its amyloid aggregation and functions, including interactions with polyoxometalates, oleuropein aglycone and DOPA-derivatives were studied by using the above mentioned technqiues.
Conclusions: The results are discussed in the light of their potential therapeutic applications in preventing amyloid aggergation or mitigating the effect of amyloid aggregates on neuronal cells.

SHIFT 02-188

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4 - 5 April

HOW FRUCTOSE METABOLISM IS AFFECTING AMYLOID PRECURSOR PROTEIN (APP)

Patricia Munoz, Tudor-Fabian Troncea, Michael Rossiter, Ivan Nalvarte
Karolinska Institutet, Nvs, Stockholm, Sweden

Aims: The proposed project **aims to bring new knowledge to the impact of fructose on AD risk**. Specifically, we will study the **neurotoxic role of fructose in the bioenergetics of neuron metabolic , and how this can affect amyloid peptide folding.** This project will provide new knowledge about the early influence of fructose ingestion on brain function and plasticity, and will add to the understanding of the impact of fructose on events that may predispose neurological disorders and propose new innovative therapies to preserve brain energetics.
Methods: For this, we will set up an neuron culture and fructose treatment protocol. A Seahorse extracellular flux analyser will characterize cell metabolic function, and the OC and A11 conformation-selective antibodies will detect mutually exclusive structural epitopes of amyloid-forming proteins with different solubility.
Results: The results indicate that the incubation of SH-SY5Y wild-type cells with fructose at concentrations of 5 mM, 10 mM, 20 mM, and 40 mM increased the secretion of the amyloid-beta 42 fragment after 10 days of incubation. Additionally, western blot analysis of amyloid protein processing showed a higher expression of CTFβ compared to CTFα under the same incubation conditions. Furthermore, qPCR results revealed changes in the relative expression of proteins involved in the amyloidogenic pathway, specifically ADAM10, BACE1, and Presenilin.
Conclusions: We conclude that a 10-day incubation with fructose increases the processing of amyloid-beta protein via the amyloidogenic pathway, affecting the expression of key proteins and promoting uric acid production. These findings correlate with the hypothesis that fructose metabolism plays a significant role in the development of Alzheimer's disease, potentially contributing to early features such as reduced neuronal function, impaired bioenergetics, and elevated uric acid levels.

SHIFT 02-189

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4 - 5 April

DECOMPOSING AMYLOID-BETA KINETICS INTO ITS OLIGOMER AND FIBRIL COMPONENTS USING OLIGOMER-SELECTIVE DYES

Dalton Zona, Tyler Hull, Martin Muschol
University of South Florida, Dept. Of Physics, Isa 2019, Tampa, United States of America

Aims: Given the recent success of antibody therapies preferentially targeting Aβ oligomers, it is critical to elucidate the mechanisms and environmental conditions promoting Aβ oligomer over fibril formation, in vitro and in vivo. Using a kinetics screening assay developed in our lab we have identified fluorescent dyes selective for amyloid-β (Aβ) oligomers over fibrils. Using these oligomer-selective dyes (OSDs) we have investigated the relationship between oligomer growth vs. fibril nucleation and growth during in vitro amyloid assembly.
Methods: We have previously shown that ThT kinetics, upon the onset of oligomer formation in vitro, undergoes a well-defined transition from pure sigmoidal to biphasic kinetics. Using this transition, we have screened fluorescent dyes for preferential responses to only the initial, oligomeric phase of biphasic kinetics. Here we report on several dyes displaying oligomer selectivity. Utilizing these OSDs, we monitored the kinetics of Aβ oligomer formation independently from fibril nucleation and growth.
Results: Using ThT in combination with OSDs, we have separated the kinetics of in vitro Aβ amyloid growth into its separate oligomer and fibril components. Our results indicate that the long-lived Aβ oligomers observed in vitro and in vivo form only under a sub-set of fibril growth conditions, and along an assembly path separate from fibril nucleation and growth. At the same time, oligomers interact with and alter the nucleation and growth kinetics of fibrils.
Conclusions: The identification of OSDs enables studying the conditions promoting the formation of Aβ oligomers vs. fibrils. In addition, they reveal the complex interactions of amyloid oligomers with fibrils. Finally, OSDs represent promising candidates for the development of positron-emission tomography probes to detect Aβ oligomers in vivo. This work was supported, in part, by NIH grants 1R21AG077735 and 1R21AG087910

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SHIFT 02-190

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4 - 5 April

AMYLOIDOGENIC PROPERTIES OF FDA-APPROVED CATIONIC AMPHIPHILIC DRUGS

Javier Pacheco-Quinto[1], Dana Clausen[1,2], Elizabeth Eckman[1]
[1]BRINJ, Cedar Knolls, United States of America, [2]Rutgers School of Graduate Studies, Newark, United States of America

Aims: Cationic amphiphilic drugs (CADs) are a diverse group of molecules that includes commonly prescribed CNS-active compounds. CADs are characterized by having a hydrophobic and hydrophilic region, and an ionizable amine group. Their amphiphilic nature allows them to cross cell membranes. However, in acidic compartments such as endosomes, the amine group becomes protonated, reducing the drug's ability to diffuse back across the membrane, leading to drug accumulation and disruption of endosomal function. Such impairment is known to alter the balance between Aβ production and degradation within endosomes. Using a cell model susceptible to intracellular Aβ fibrillization, we evaluated the amyloidogenic potential of several FDA-approved CADs.
Methods: Endothelin converting enzyme-1 knock-out SH-SY5Y cells overexpressing human APP were treated with chlorpromazine (an antipsychotic), sertraline (a selective serotonin reuptake inhibitor), amiodarone (an antiarrhythmic), nicardipine (a calcium channel blocker) and chloroquine (an antimalarial drug). Levels of secreted and intracellular Aβ42 were measured by ELISA and the formation of Aβ fibrils was evaluated by immunohistochemistry with the OC antibody. Endosomal function was assessed by LC3B staining. To study APP processing, APP-CTFs were analyzed by Western blot.
Results: All tested drugs, at subtoxic levels, disrupted endosomal trafficking and led to the accumulation of LC3B-positive vesicles. Additionally, all CADs increased Aβ production, resulting in significant intracellular Aβ42 accumulation and the formation of OC-positive fibrils.
Conclusions: Our results demonstrate that all tested CADs, despite their diverse pharmacological properties, exhibit strong amyloidogenic potential. These findings may extend to other CADs and warrant further investigation into the long-term effects of this drug class.

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SHIFT 02-198

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4 - 5 April

SERPINE1, BRAIN CELL SENESCENCE, AND ALZHEIMER'S DISEASE

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Aims: Objectives: The etiology and mechanisms underlying the late-onset Alzheimer's disease (LOAD), an aging-related neurodegenerative disease, remains unclear. Cellular senescence, a permanent arrest of cell growth, has been increasingly recognized as an important contributor to aging and aging-related diseases, including LOAD. Our studies focus on the mechanisms and consequence of brain cell senescence during aging and in LOAD.
Methods: Different techniques, including single nuclear RNA sequencing (snRNA-seq), were used to identify senescent cells in the brains of LOAD patients, in aging model mice and LOAD model mice exposed to O_3, an environmental risk factor for LOAD. The mechanisms underlying brain cell senescence and how senescent cells promote AD neuropathology were further studied in primary cells.
Results: snRNAseq and immunostaining data show that different types of cells, including neurons, astrocytes, immune cells etc., express many cell senescence markers in the dorsolateral prefrontal cortex from LOAD patients and in the hippocampus or cortex of O3 exposed old ApoE3 mice and ApoE4 mice, although more in ApoE3 mice. This is associated with an increased oxidative stress responses, neuroinflammation, and memory decline. In vitro studies further show that senescent astrocytes express higher levels of SERPINE1, a serine protease inhibitor. Silencing SERPINE1 significantly reduces H2O2-stimulated p53/p21/p16 expression and senescence-associated beta galactose (SA-b-gal) activity in primary human astrocytes, whereas overexpression of PAI-1 in PAI-1-/- astrocytes along induces p21/p16 and SA-b-gal activity. The secretome from senescent human astrocytes promotes apoptosis in primary human neurons, whereas PAI-1 deficient secretome has significantly reduced effect on neurons.
Conclusions: Our data suggest that cell senescence contributes importantly to neuropathophysiology of AD and that senescent astrocytes can promote neuron apoptosis through secretion of biologically active molecules, including PAI-1.

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SHIFT 02-199

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4 - 5 April

A SINGLE JUVENILE CONCUSSION LEADS TO PROGRESSIVE COGNITIVE DEFICITS AND IS ASSOCIATED WITH LATE-LIFE TISSUE ALTERATIONS REMINISCENT OF ALZHEIMER'S DISEASE

Andre Obenaus[1], Jeong Lee[2], Aurélien Trotier[3], Sylvain Miraux[3], Nicola Marchi[4], Jerome Badaut[5]
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Aims: Concussion/mild traumatic brain injury (TBI) is known to be a risk factor for late-onset neurodegenerative disease accompanied by behavioral and neuropathological decrements. Unknown is whether early in life concussions, during brain development, can lead to evolving pathophysiology late in life sharing landmarks with Alzheimer Disease.
Methods: To address this knowledge gap, we investigated the long-term effects of single concussion in mice at postnatal day 17, with repeated assessments of long-term temporal behavioral and associated tissue-level deficits up to late adulthood (18mo) using clinically relevant in-vivo diffusion magnetic resonance imaging (dMRI). Histological assessments were also conducted at selected time points.
Results: A single concussion led to increased glial fibrillary acidic protein (GFAP) and neurofilament-light (NFL) in blood plasma, impaired spatial learning and memory at 18m of age. Extensive longitudinal dMRI analysis from 1 to 18mo post-injury revealed that jmTBI produced temporally-dependent dynamic tissue level perturbations. Neuroimaging alterations were concentrated at earlier timepoints (1-3mo) and were associated with behavioral deficits at 18mo. White matter regions, such as corpus callosum were investigated in depth.
Conclusions: We demonstrate that a single concussion early in life leads to lasting behavioral impairments later in life and are linked to early tissue level structural deficits. We note that region specific early dMRI alterations preceded the long-term cognitive deficits. Our work not only establishes that juvenile concussion elicits chronic long-lasting effects but provides an unprecedented insight into how an early-in-life concussions may produce adverse effects late in life that are reminiscent of Alzheimer's Disease symptomology. *Financial support:* NeuVasc (ANR; Eranet Neuron); Nanospace (ANR); IRP CNRS INNOVAtion (JB/AO), NIH NINDS R01 NS119605 (AO/JB), RO1NS135556 (AO/VS/DA), 1RF1NS138032 (AO/PT)

SHIFT 02-206

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4 - 5 April

ENDFEET CA2+ SIGNALING IN REACTIVE ASTROCYTES OF FULLY AWAKE MICE WITH BRAIN PARENCHYMAL AMYLOID PATHOLOGY IS UNCOUPLED FROM THE ACTIVITY OF LOCAL CEREBRAL ARTERIOLES.

Christopher Norris[1], Blaine Weiss[2], Christopher Gant[1], Ruei-Lung Lin[2], Susan Kraner[1], Edmund Rucker[1], Yuriko Katsumata[1], Yang Jiang[1], Peter Nelson[1], Donna Wilcock[3], Olivier Thibault[1]
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Aims: Study assessed the fidelity of cortical astrocyte endfeet signaling in conjunction with arteriole dilatory responses in a fully awake mouse model of Alzheimer's disease.
Methods: Two-photon imaging applied to fully awake mice (male/female WT and 5xFAD littermates, 6-8-months-old) was used to assess arteriole dilations in barrel cortex, simultaneously with astrocyte Ca2+ fluctuations (detected with GCaMP8f), evoked by air-puff stimulation of contralateral whiskers. Individual regions of interest were segmented and Ca2+ transeint properties were assessed across multiple cellular compartments (whole cell, processes, and endfeet). A custom application called Localized Analysis of Vascular Astrocytes (LAVA) was used to identify endfeet-vessel pairings and evaluate temporal and proportional relationships between endfeet Ca2+ changes and dilation events in immediately adjacent arterioles.
Results: 5xFAD mice exhibited a significant reduction in evoked arteriole dilations and smaller evoked Ca2+ transients in all cellular compartments. Correlated activity across astrocyte networks was also impaired in 5xFAD mice. No sex differences were observed. Using LAVA, we found that endfeet Ca2+ transients nearly always occured after dilatory events in immediately adjacent arterioles. Ca2+ endfoot transients were smaller and delayed in 5xFAD mice. In WT mice, evoked vessel dilations were followed by astrocyte Ca2+ transients ~80% of the time vs only ~58% of the time for 5xFAD mice. The ampitude of vessel dilations in WT mice strongly predicted the ampltiude of subsequent Ca2+ transients in adjacent endfeet ($r = 0.54$, $p < 0.001$). In contrast, endfeet Ca2+ transient ampitudes in 5xFAD mice were independent of the magnitude of local vessel dilations ($r = 0.012$, $p = 0.37$)
Conclusions: Ca2+ signaling in reactive astrocytes appears to be largely uncoupled from local cerebrovascular changes, possibly shedding new light on the mechanistic underpinnings of brain hypometabolism in Alzheimer's disease.

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SHIFT 02-207

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4 - 5 April

IDENTIFICATION OF SERPINA3HIGH ASTROCYTES SUBTYPES AS A POTENTIAL MODULATOR OF AMYLOID PATHOLOGY IN ALZHEIMER'S DISEASE

Mariko Taga[1], Berke Karaahmet[1], Laurine Duquesne[2], Ya Zhang[1], Alina Sigalov[1], Christina Yung[1], Alexandra Kroshilina[1], David Bennett[3], Caghan Kizil[4], Hans-Ulrich Klein[1]
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Aims: To address the need for identifying specific targets to modulate the progression of Alzheimer's disease pathology (AD), it is essential to characterize genes that are not only expressed by particular cellular subtypes but are also physically associated with the pathology. In this study, we employed various spatial techniques in different systems such as human post-mortem tissue and zebrafish models to identify potential target genes involved in the progression of amyloid pathology.
Methods: Spatial transcriptomics combined with immunofluorescence was performed on the dorsolateral prefrontal cortex of 15 AD and two non-AD subjects to characterize cellular signatures in the neuritic plaque microenvironment. The identified targets were validated at single-cell resolution at the protein level through immunofluorescence staining by segmenting 64,753 astrocytes across 20 AD subjects. Their association with amyloid pathology was further validated in CSF (n= 259 and n=800) and a zebrafish model.
Results: Within the 263 neuritic plaques detected, a total of 182 plaque-associated genes were identified within a 150 µm radius of the neuritic plaques. GFAP and SERPINA3 were both upregulated within the neuritic plaque niche. These findings were validated at the protein level using immunohistochemistry with an automated segmentation pipeline in whole brain sections revealing an increase of $SERPINA3^{High}$ $GFAP^{High}$ astrocytes near the neuritic plaques. Increased SERPINA3 levels were observed in the CSF in individuals with AD diagnosis. Elevated expression of the SERPINA3 ortholog by astrocytes was also detected near amyloid deposits in the zebrafish model.
Conclusions: We identified $SERPINA3^{High}$ $GFAP^{High}$ astrocyte subpopulation as a potential contributor to the formation of the neurotoxic microenvironment using unbiased approaches. Its association with pathology was validated across various systems. This is a crucial step in understanding cellular networks and designing targeted therapeutic approaches.

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SHIFT 02-214

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4 - 5 April

QUANTIFYING MOLECULAR TAU ACCUMULATION RATES AND MECHANISMS FROM AGGREGATE PATTERNS IN PSP BRAINS.

Georg Meisl[1,2], Shih-Huan Huang[3], Tuomas Knowles[2], Timothy Rittman[4], Annelies Quaegebeur[5], James Rowe[6], David Klenerman[2]
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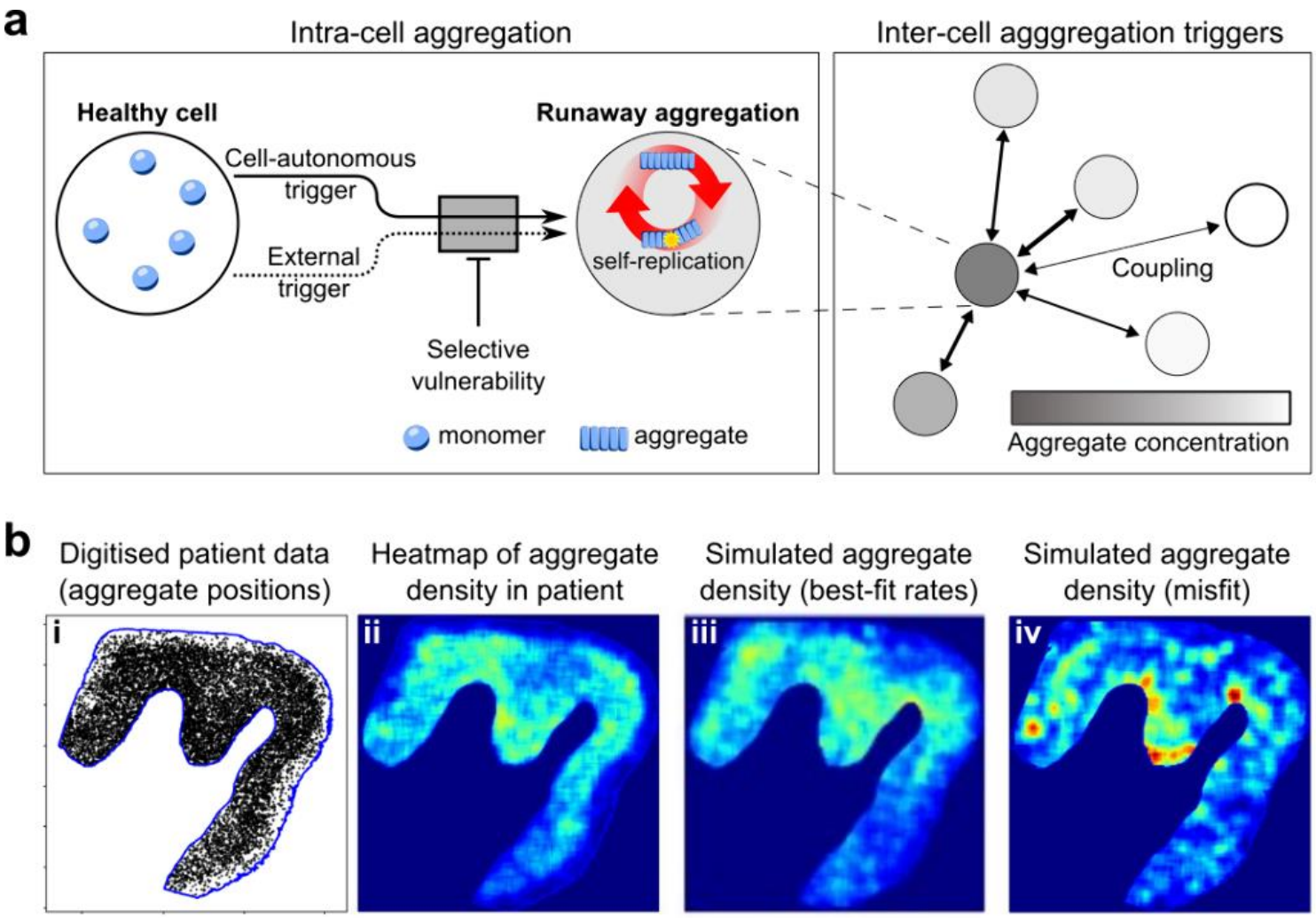
Aims: In vitro experiments have established the formation mechanisms for pathological aggregates under well-controlled conditions. However, the molecular processes that govern their appearance in the brains of patients are still poorly understood. We build a mathematical model of protein aggregation to: 1) predict tissue-level patterns from molecular processes. 2) interpret spatial patterns of aggregates observed in progressive supranuclear palsy (PSP) brain slices mechanistically. 3) predict the effects of potential therapeutic strategies.
Methods: We developed a cell-level mathematical model that combines known protein aggregation mechanisms with ideas from epidemiology to capture the cell-to-cell triggering of aggregation and apparent spreading within brain tissue. Image analysis of histopathological brain slices stained for aggregated tau allows us to determine the spatial patterns of tau aggregates from patient data.
Results: Our model reproduces the spatial patterns of aggregation seen in data from PSP patients (11 individuals, stages 2-6) remarkably well, see figure. We find that the dominant molecular mechanism and rates are conserved across disease stages and brain regions, with cell-to-cell triggering being an important factor that influences spatial patterns. Moreover, we find that there is an increased propensity to aggregate in dense cell regions, a finding which is consistent with cell-to-cell triggering being more pronounced when cells are closer together in space.



Conclusions: We have demonstrated the power of our model on tau aggregation in PSP, but we envision that it will be equally applicable to other aggregation-related diseases. Together with methods that can measure the effects of potential drugs on the aggregation reaction in vitro, we believe that our model can form the basis for the prediction of drug candidate efficacy in patients, a tool that is desperately needed to progress the development of therapies for neurodegeneration.

SHIFT 02-215

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4 - 5 April

DEFECTIVE TAU UNDERLIES MALADAPTIVE NUCLEAR LAMINA STRUCTURE WHICH INDUCES EPIGENETIC AND TRANSCRIPTIONAL ALTERATIONS, DRIVING NEURONAL SENESCENCE PHENOTYPE

Zachary Walton[1], Jose Sarmiento[2], Indra Heckenbach[3], Morten Scheibye-Knudsen[3], Melike Lakadamyali[2], Rakez Kayed[4], Mauro Montalbano[1]
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Aims: The nuclear lamina (NL) is a meshwork of four lamin proteins (Lamins A, B1, B2 and C) along the nuclear margin involved in nuclear structure and chromatin organization. With emerging evidence stipulating that Alzheimer's disease (AD) associated Tau protein aggregation profoundly impacts nuclear processes, we hypothesize that Tau dysfunction misshapes NL structure and affects chromatin organization and drive senescence phenotype in neurodegeneration.
Methods: Using confocal microscopy, we depicted a compelling structural NL and chromatin compaction alterations in neurons and glia cells in human age-matched, non-demented and AD brains. Using Stochastic Optical Reconstruction (STORM) microscopy and live cell imaging we visualized chromatin organization and nuclear morphology rearrangements modulated by soluble Tau oligomers. Moreover, using image-based Nuclear Senescence Predictor (NUSP) we predicted senescence in correlations with lamins in human brains. Finally using single-cell RNA-sequencing (sc-RNAseq) we measured the impact of such defective Tau at the transcriptional level.
Results: Tau dysfunction generated by pathological conditions, such as oligomerization, triggers maladaptive NL structures driving chromatin organization which ultimately altering gene expression of factors involved in preservation of nuclear structure and senescence. Moreover, *In vivo* observations revealed that pathogenic mutants P301S-Tau and Tau-KO exacerbate age-related NL alterations, impacting lamins cellular localization and expression.
Conclusions: Our data, unifying *in vitro*, *in vivo*, and human brain tissues, suggests that loss of function of Tau dysregulates NL and chromatin organization. This triggers nuclear dysfunction in neurodegenerative diseases by exacerbating age-related nuclear features.

SHIFT 02-216

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4 - 5 April

PAK1-MEDIATED ENDOCYTOSIS MODULATES RAB3-DEPENDENT VESICLE FUSION TO REPAIR AMYLOID-BETA INDUCED PLASMA MEMBRANE DAMAGE AND CELL-TO-CELL SPREADING.

Sangeeta Nath[1], Deepak Valappil[1], Priyadarshini V[2], Prakhyath Hegde[1], Jeevan M Gowda[1], Anujith Kumar[1], Nikhil Gandasi[2]
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Aims: The interaction of amyloid-β (Aβ) peptides with the plasma membrane (PM) is a potential trigger that initiates the formation of higher-order aggregates, membrane alterations/damage, and progressive neurotoxicity in Alzheimer's disease (AD). We study how Aβ-oligomers (oAβ) induce damage to plasma membrane (PM), triggering a repair cascade involving rapid and interconnected endocytosis-exocytosis dynamics, and facilitating the formation of tunneling nanotubes (TNTs) like intercellular conduits.
Methods: PM repair was studied in SH-SY5Y neuronal cells in response to oAβ peptides, following endocytosis dynamics using the membrane-impermeable dye TMA-DPH and concurrent Rab3a-vesicle fusion-mediated exocytosis-kinetics using total internal reflection fluorescence microscopy. PM repair is a calcium-dependent process. Therefore, we observe the extent of PM damage by quantifying propidium iodide internalization in the presence of the calcium chelator EDTA. Further, shRNA-mediated Rab3a knockdown cells were used to observe disruption in PM repair-caused neurodegeneration.
Results: We found the aggregation-prone peptide $oA\beta_{1-42}$ significantly boosts phosphorylated p21-activated kinase (pPAK1) dependent endocytosis and Rab3a-mediated exocytosis to aid in PM repair compared to $oA\beta_{1-40}$. The rapid, interconnected endocytosis-exocytosis dynamics and pPAK1-mediated actin remodulation result in formation of TNTs. The oligomers hijack these TNTs and facilitate their spreading from one cell-to-another. IPA-3 is a selective inhibitor of pPAK1 that works without affecting ATP. It helps prevent the internalization of oAβ and PM repair. When the expression of Rab3a is reduced, it inhibits pPAK1 and disrupts PM repair, which can result in neuronal cell death.
Conclusions: This study unveiled the interconnected action of Rab3a and pPAK1 in repairing PM damage by oAβ, along with their potential correlation with TNT-mediated propagation and neurotoxicity.

SHIFT 02-223

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4 - 5 April

GUT MICROBIOME VARIATIONS IN ALZHEIMER'S DISEASE: A UGANDAN STUDY

Kamada Lwere, Haruna Muwonge, Mark Kaddumukasa, Noeline Nakasujja, Hakim Sendagire
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Aims: To investigate the gut microbiome composition and diversity in an urban and rural Ugandan population to identify microbial markers associated with Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitive health.
Methods: We recruited 104 participants aged 60 years and older, categorized into AD, MCI, and control groups based on Montreal Cognitive Assessment (MoCA) scores and ICD-11/DSM-V criteria. DNA was extracted from fecal samples using the QIAamp kit, and sequencing of PCR products was performed using Nanopore technology. Diversity indices, principal coordinate analysis (PCoA), Permutational Multivariate Analysis of Variance (PERMANOVA), and Linear Discriminant Analysis Effect Size (LefSe) were employed to identify significant microbial differences among the groups.
Results: Our findings revealed a significant reduction in gut microbiome diversity, measured by Chao1 and Shannon indices, linked to cognitive decline. The AD group exhibited the lowest diversity, with Chao1 richness significantly lower than the control group ($P < 0.05$) and a significant difference in Shannon diversity ($P < 0.05$). PCoA and CAP analyses demonstrated distinct microbial shifts between the AD and control groups, with the MCI group showing an intermediate profile. Genera such as *Novosphingobium*, *Staphylococcus*, and *Mesorhizobium* were more prevalent in controls, while *Hafnia-Obesumbacterium* and *Dickeya* were more common in AD. Age-related microbial changes were noted, with *Exiguobacterium* and *Carnobacterium* increasing with age, while *Acinetobacter* and *Klebsiella* decreased. Additionally, *Glaciecola* and *Bacillus* correlated with BMI.
Conclusions: This study identified distinct microbial profiles in the AD, MCI, and control groups, suggesting potential microbiome markers of cognitive impairment in the Ugandan population. Further research is needed to clarify the gut microbiome's role in AD and MCI progression.

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SHIFT 02-224

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4 - 5 April

USING HIGH-RESOLUTION SPATIAL TRANSCRIPTOMICS TO CHARACTERIZE CELLULAR RESPONSES AROUND PATHOLOGY IN ALZHEIMER'S DISEASE

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Aims: The amyloid plaque is a pivotal hallmark of Alzheimer's disease. New advances in the field of spatial transcriptomics allowed us to study changes in the cellular neighbourhood around plaques. However, these approaches, such as the CosMx platform, predominantly rely on nuclear stains for cell segmentation, which presents a major limitation for studying cellular processes in the brain, as these cells have complex shapes and processes, such as neuronal dendrites. Here, we have used CosMx data to study cellular changes around the amyloid plaque and developed a novel approach to study cellular processes.
Methods: Using Nanonstring's CosMx platform, we investigated cellular interactions in the *App*$^{NL\text{-}G\text{-}F}$ mouse model of Alzheimer's disease. In addition to the nuclear segmentation, we also analysed cellular processes using a newly developed method that allowed us to average transcriptomic information from cellular processes in existing CosMx datasets.
Results: With the nuclear segmentation, we surveyed highly variable microglial – astrocytic responses across the amyloid plaque micro-environment and provided first insights into how these responses relate to neuronal transcriptomic alterations. Investigating data from cellular processes we found that they contain cell-type specific information that is different to that found in segmented nuclear areas, such as containing synapse-related transcripts in astrocytic processes.
Conclusions: The work highlights that we can differentiate between plaques based on changes in cellular interactions in their neighbourhood, which allows us to map the progression of molecular and cellular changes occurring in this disease. By including dendritic information, we offer a strategy to interrogate subcellular transcript expression and its spatial relationship to pathology in cell types of interest, thereby expanding the questions we can answer with spatial transcriptomics.

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SHIFT 02-225

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4 - 5 April

PRESERVED TRANSCRIPTIONAL IMMUNE NETWORKS ASSOCIATED WITH ALZHEIMER'S AND PARKINSON'S DISEASES ACROSS BRAIN AND BLOOD TISSUES

Joseph Reddy[1], Samantha Strickland[2], Wei Tsai[2], Xuan Chen[2], Yesesri Cherukuri[1], Mariet Allen[2], Zachary Quicksall[1], Xue Wang[1], Kejal Kantarci[3], Minerva Carrasquillo[2], Kwangsik Nho[4], Andrew Saykin[5,6], Ronald Petersen[7], Nilufer Ertekin-Taner[8]
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Aims: Systemic inflammation is a pathological driver of aging and neurodegeneration. Using publicly available data, we sought to elucidate conserved and distinct genes and pathways involved inflammation in aging, Alzheimer's disease (AD) and Parkinson's disease (PD).
Methods: Twelve transcriptomic datasets obtained from brain tissue or peripheral blood of approximately 6000 donors across AD and PD consortia including Accelerating Medicines Partnership (AMP)-AD, AD Neuroimaging Initiative (ADNI), Molecular Mechanisms Of Vascular Etiology of AD (M^2OVE-AD) and AMP-PD were consensus processed using standardized pipelines. Utilizing weighted gene coexpression network analysis, pathways involved in immune response were identified and tested for association with aging and disease. Pathways were evaluated for enrichment of cell types and subsequently for preservation across modalities. Differential gene expression and QTL analysis was performed to identify key drivers of immune perturbations.
Results: Conserved immune signatures were observed in the brain and periphery. Strongest preservation was observed in brain regions of AMP-AD cohorts and across AD and PD blood cohorts. Some preservation was also observed across modalities. All immune modules in brain were associated with aging, while some were associated with AD. Similar associations were also observed across blood modules. While immune modules in the brain were primarily enriched for endothelial and microglial cell types, blood modules were enriched for B-cells and neutrophils. Molecular signatures conserved across all AD and PD datasets as well as those distinct to cohort, tissue or disease were detected.
Conclusions: Preserved transcriptional immune networks were identified across blood and brain and across two neurodegenerative diseases. Expanding gene co-expression network analyses to other diseases and integrating additional omics measures and phenotypes can further strengthen these findings to unravel the immune signatures across complex diseases.

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SHIFT 02-226

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4 - 5 April

THE RELATIONSHIP OF NLRP3 INFLAMMASOME ACTIVATION WITH EXPRESSION AND DNA METHYLATION OF BDNF IS DISRUPTED IN ALZHEIMER'S DISEASE

Hao Tang[1], Helene Fachim[2], Gavin Reynolds[3], Michael Harte[4]
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Aims: Activation of the NLRP3 inflammasome pathway and deficient brain-derived neurotrophic factor (BDNF) activity are implicated in the pathogenesis of Alzheimer's disease (AD). While in vitro and in vivo models support these mechanisms, there is little research investigating their relationship in human brain tissue, and whether this relationship may be abnormal in the AD brain.
Methods: Temporal cortical brain tissue taken post-mortem from AD patients (n=78) and control subjects (n=37) was analysed for expression of genes in the NLRP3 inflammasome pathway (NLRP3, PYCARD, CASP1), the potassium channel THIK1, and pro-inflammatory cytokines (IL-1β, IL-18). Two indicators of BDNF expression were also determined; mRNA, and DNA methylation at four CpG sites in the BDNF exon IV promoter. Rank correlation analyses were conducted between these BDNF measures and NLRP3-related genes.
Results: A significant relationship between BDNF mRNA expression and mean methylation was observed in control subjects but not in AD. In controls, significant correlations with both BDNF expression and mean BDNF methylation were observed for NLRP3, CASP1 and IL-1β. These correlations were lost in the AD group, which also showed a significant correlation of THIK1 with both BDNF measures, not seen in controls.
Conclusions: This study indicates that the relationship between BDNF and NLRP3 activation, as measured by NLRP3 inflammasome components and the proinflammatory product IL-1β, is disrupted in AD. The contrary finding of a correlation emerging in AD with expression of the regulatory THIK1 channel, previously shown to be elevated in AD, indicates the possible relationship of this finding with BDNF dysfunction. These findings enhance our understanding of AD pathophysiology, demonstrating the importance of research to better understand the neuroinflammatory-neurotrophic balance in neurodegenerative processes.

SHIFT 02-227

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4 - 5 April

ELEVATED NEURONAL EXPRESSION OF CCAAT-ENHANCER BINDING PROTEIN BETA IS ASSOCIATED WITH ALZHEIMER'S DISEASE

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Aims: Neuroinflammation plays a significant role in numerous neurodegenerative diseases including Alzheimer's Disease (AD), yet its regulatory mechanisms remain poorly understood. CCAAT-Enhancer Binding Protein beta (CEBPβ) is a transcription factor that mediates the expression of cytokines and other inflammatory mediators. CEBPβ is expressed as 3 isoforms: LAP1, LAP2, and LIP. These isoforms have different subcellular locations depending on celltype and cellular conditions. Prior studies suggest that levels of CEBPβ were elevated in AD and is believed to express mainly in glial cells. Other studies indicate that CEBPβ is also expressed in neuronal cells. Nevertheless, the expression of CEBPβ in aged and diseased brains and its role in neuroinflammation and neurodegeneration is largely unexplored. The objectives of the current study are to examine CEBPβ subcellular and cell type expression and its association with AD.
Methods: 48 FFPE sections of superior middle temporal gyrus (SMTG) obtained from the University of Kentucky Alzheimer's Disease Research Center were subjected to immunohistochemistry (IHC) using various CEBPβ antibodies. Slides were scanned using an Aperio ScanScope and the positive stains digitally analyzed. Additional sections were used for immunoflorescence (IF) study examining the colocalization of CEBPβ with neuron, astrocyte, and microglia markers. Furthermore, freshly collected SMTG were subjected to subcellular fractionation and Western blot analysis to determine the localization of CEBPβ isoforms.
Results: 1) CEBPβ levels were significantly elevated in AD cases; 2) IF studies showed that CEBPβ largely colocalized with neurons; 3) while all 3 isoforms of CEBPβ could be detected in total tissue lysates, LAP was mostly present in the nucleus and LIP in the cytosol.
Conclusions: Our data demonstrated an overall elevation of CEBPβ in neuronal cells in both the nucleus and cytosol of AD brains.

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SHIFT 02-233

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ISYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
4 - 5 April

THE CYCLASE-ASSOCIATED PROTEIN 2: A NOVEL BINDING PARTNER OF ADAM10 IN THE SYNAPSE

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Aims: ADAM10 is a synaptic enzyme relevant for dendritic spine stabilization and for cleaving the amyloid-precursor protein (APP) to prevent Amyloid-β (Aβ) production. A finely balanced membrane level of ADAM10 is an essential prerequisite to control enzyme activity and its functions. Proteins interacting with ADAM10 cytoplasmic tail can control its intracellular trafficking and, thereby, its membrane availability. In light of these considerations, we carried-out a two-hybrid screening using ADAM10 cytoplasmic tail as bait. Among the positive clones we focused our attention on the Cyclase-Associated Protein 2 (CAP2). CAP2 is a postsynaptic actin-binding protein responsible for the translocation of cofilin into spines upon long-term potentiation (LTP) induction. Remarkably, CAP2 is downregulated in Alzheimer's Disease (AD) and, thereby, CAP2/Cofilin pathway is dysregulated in AD hippocampus, suggesting CAP2 involvement in AD synaptic failure.
Methods: We used biochemical and imaging techniques and different in vitro and in vivo models to investigate the role of ADAM10/CAP2 complex in neurons and its alterations in AD.
Results: After confirming ADAM10/CAP2 interaction using biochemical and imaging approaches, we identified the domains responsible for their association. Taking advantage of CAP2 KO mice and CAP2 deletion mutants, we demonstrated that CAP2 is critical for ADAM10 synaptic localization and endocytosis, suggesting that ADAM10/CAP2 association can be important for synaptic function. In line with this hypothesis, we found that LTP modulates the ADAM10/CAP2 complex formation. Furthermore, ADAM10/CAP2 association is altered in AD mice hippocampus and is impaired upon exposure to Aβ oligomers.
Conclusions: Overall, these data show that CAP2 may act as a novel regulator of ADAM10 in synaptic plasticity phenomena and in AD.

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SHIFT 02-234

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING
4 - 5 April

PALMITIC ACID INDUCES DYNAMIC TIME-DEPENDENT ALTERATIONS IN HDACS, NEURONAL CHROMATIN ACETYLATION, AND GENE EXPRESSION.

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Aims: Palmitic acid (PA) is a major component of high-fat diets that have been linked to an increased risk for mild cognitive impairment and even Alzheimer's disease (AD). The aims of this work were to study: 1) the metabolic consequences of neuronal exposure to PA, 2) the association between metabolic alterations and changes in histone deacetylases (class I and III HDACs), 3) the quantity and distribution of H3K9ac and 4) the effects of these changes on the expression of the coding, *BDNF* and non-coding, *LINE-1* genes.
Methods: Human neuroblastoma cells (MSNs) were differentiated to mature neurons using retinoic acid and neuronal growth factor. Cells were exposed to 300 μM PA for 3, 6, 12 or 24 h. Lipid droplets and β-Hydroxybutyrate (β-HB) were quantified using colorimetric assays. Protein quantification was evaluated by Western Blot. Immunocytochemistry and confocal microscopy were used to assess protein localization and distribution, and gene expression by RT-qPCRs.
Results: β-HB and lipid droplets content increased and SIRT1 decreased after 24 h PA treatment, whereas protein levels of HDAC3 and HDAC2 increased only after a 3 or 24 h PA treatment, respectively. Concomitantly, H3K9ac content increased after 3 h and tended to re-localize to one side of the nuclear periphery in a time-dependent manner. Finally, *BDNF* expression was upregulated at 6 h after PA treatment, whereas *LINE1* was downregulated after 3 h and progressively returned to baseline levels after 24 h PA treatment.
Conclusions: Chronic PA exposure is presumed to alter neuronal physiology, affecting neuronal function and plasticity processes. Here we provided evidence on how a PA treatment dysregulates neuronal lipid metabolism and how PA deregulates the expression of coding and non-coding genes, possibly associated by changes in HDACs and H3K9ac content.

SHIFT 02-235

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING
4 - 5 April

UNCOVERING THE ROLE OF AN AFRICAN-SPECIFIC ABCA7 FRAMESHIFT DELETION ON LIPID METABOLISM IN ALZHEIMER'S DISEASE

Younji Nam[1], Juan Young[2], Brooke Derosa[1], Charles Golightly[1], Shaina Simon[2], Aura Ramirez[2], Patrice Whitehead[3], Larry Adams[3], Takiyah Starks[4], Michael Cuccaro[3], Scott Williams[5], Allison Caban-Holt[6], Jonathan Haines[7], Goldie Byrd[6], Farid Rajabli[3], Derek Dykxhoorn[2], Jeffery Vance[3], Margaret Pericak-Vance[3]
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Aims: A 44-base pair deletion in the ATP-binding cassette sub-family A member 7 (*ABCA7*) gene is significantly associated with Alzheimer disease (AD) in African Americans. The deletion produces a truncated protein (p.Arg578Alafs). *ABCA7* is a lipid transporter across cellular membranes. We previously demonstrated that *ABCA7* is highly expressed in iPSC-derived neurons. We studied the effect of the deletion on the lipid metabolism using differentiated neurons derived from isogenic induced pluripotent stem cells (iPSC). This study aims to discover if the *ABCA7*-44bp deletion has an effect on lipid metabolism and transcriptome in neurons.
Methods: We transfected a tagged *ABCA7* gene with and without the deletion into HEK cells to analyze truncated ABCA7 stability and localization. We created isogenic iPSC lines from three AA-control individuals to introduce the *ABCA7* deletion. These were differentiated into neurons. A multi-omics study of the neuronal lines was performed using RNAseq, mass spectrometry-based proteomics and lipidomics
Results: The truncated *ABCA7*-tagged protein appeared stable and localized to the plasma membrane in transfected HEK cells as seen for the WT protein. Transcriptome comparison showed that the *ABCA7* transcripts were expressed at similarly low levels in all isogenic lines. Proteomics analysis failed to detect ABCA7 protein expression in either cell line. However, the lipidomics data showed that the homozygous *ABCA7* deleted neurons show a 2~5-fold increase in diaglycerol, phosphoinositol, phosphoethanolamine, cholesterol ester, and triacylglycerol in comparison to their isogenic controls.
Conclusions: The *ABCA7* deletion alters lipid content within neurons. Our data suggest that the AA-specific deletion in *ABCA7* generates a transcript that escapes nonsense-mediated decay and can influence *ABCA7* function. Studies into why some individuals appear to escape this mutation's effect may highlight compensational mechanisms in lipid metabolism.

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SHIFT 02-248

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4 - 5 April

AGE-DEPENDENT INCREASE OF SENESCENT MARKERS IN MICROGLIA OF APPNL-G-F MICE: IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Aims: Cellular senescence, a state of irreversible cell cycle arrest, has increasingly been implicated in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD). This project aims to investigate the contribution of senescent microglia to AD progression in the *App*$^{NL-G-F}$ mouse model, focusing on the age-dependent expression of senescence markers p16INK4, p21, and p53, as well as their impact on amyloid plaque formation.
Methods: The presence of senescent was evaluated in female *App*$^{NL-G-F}$ mice at 4, 12, and 24 months of age. Levels of senescence markers p16INK4, p21, and p53 were evaluated using Western blot analysis, while immunofluorescence analysis was performed to localize and quantify these proteins specifically in microglia. Additionally, gene expression levels of the corresponding markers were analyzed to evaluate their regulation. To provide a comprehensive overview of senescence, SA-β-GAL activity was also measured.
Results: Senescence levels in microglia varied significantly across the three-time points studied. Immunofluorescence analysis indicated no differences in p16INK4 and p21 levels between wild-type (WT) and *App*$^{NL-G-F}$ mice at 4 months of age. However, by 12 months, Western blot analysis revealed a significant increase in both p16INK4 and p21 levels and SA-β-GAL activity in *App*$^{NL-G-F}$ mice compared to WT mice. This increase was supported by elevated gene expression levels in the *App*$^{NL-G-F}$ mice. At 24 months of age, the results were similar to those observed at 12 months, showing significantly elevated levels of p16INK4 and p21 in *App*$^{NL-G-F}$ mice.
Conclusions: This study demonstrates the age-dependent accumulation of senescent microglia in the *App*$^{NL-G-F}$ mouse model of AD at 12 and 24 months of age. These findings underline the necessity of further exploring senotherapeutics as a therapeutic strategy to reduce the impact of microglial senescence on the progression of AD.

SHIFT 02-249

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4 - 5 April

ROLE OF MICROGLIA RETROMER COMPLEX ON PATHOLOGIC TAU AND NEUROINFLAMMATORY RESPONSES IN A MOUSE MODEL OF HUMAN TAUOPATHY

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Aims: Retromer complex system dysfunction is associated with neurodegenerative disorders including Alzheimer's disease (AD). Reduction of its main recognition core component, Vps35, has been reported in AD brains. Retromer can influence the microglial activation response, which has emerged as a major hallmark of neurodegenerative pathology. In the current study, we aim to delineate the relationship between microglial retromer function and pathophysiologic changes in a mouse model of human tauopathy.
Methods: We generated mice lacking Vps35 in microglia of a mouse model of human tauopathy overexpressing human P301S mutant tau. A battery of behavioral assessments, total tau, its phosphorylated isoforms and an array of neuroinflammatory mediators were assessed in these mice at 3 ate 6 months of age and compared with controls.
Results: Downregulation of microglial Vps35 enhanced accumulation of insoluble tau and phospho-epitopes of tau and was associated with a significantly dysregulated neuroinflammatory response in the central nervous system of P301S transgenic mice.
Conclusions: Our findings shed new light on the role of microglial Vps35 in the development of tauopathy and further support the concept that targeting the retromer is a viable therapeutic strategy for neurodegenerative diseases.

SHIFT 02-250

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4 - 5 April

ELEVATED LINE-1 TRANSPOSABLE ELEMENT ACTIVITY IN MICROGLIA TRIGGERS DYSREGULATION IN LATE-ONSET ALZHEIMER'S DISEASE

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Aims: Background: Aberrant activity of the retrotransposable element long interspersed nuclear element-1 (LINE-1) is hypothesized to contribute to cellular dysfunction in age-related disorders, including late-onset Alzheimer's disease (LOAD). However, the specific expression patterns of LINE-1 across different cell types in the LOAD brain and their contribution to disease pathology remain unclear. Objective: To investigate the differential expression of LINE-1 across neurons, astrocytes, oligodendrocytes, and microglia in the prefrontal cortex of LOAD patients, and to explore the functional impact of LINE-1 upregulation in microglia
Methods: We assessed LINE-1 expression in human postmortem prefrontal cortex tissue from LOAD patients and age-matched cognitively normal controls. Immunoreactivity of the open reading frame 1 protein (ORF1p), encoded by LINE-1, was quantified across cell types. We further utilized human iPSC-derived microglia (iMG) to perform CRISPR-mediated transcriptional activation of LINE-1, assessing morphological changes, cytokine secretion, amyloid beta (Aβ) phagocytosis, and transcriptomic alterations through RNA sequencing.
Results: LINE-1 ORF1p expression was significantly elevated in microglia from LOAD patients compared to controls, with a positive correlation to disease-associated microglial morphology. In iMG, transcriptional activation of LINE-1 resulted in altered microglial morphology, increased pro-inflammatory cytokine secretion, impaired Aβ phagocytosis, and significant transcriptomic changes in genes related to antigen presentation, lipid metabolism, and several AD-relevant pathways.
Conclusions: Our findings suggest that heightened LINE-1 expression in microglia contributes to microglial dysfunction in LOAD, potentially driving disease pathogenesis. These results highlight a novel role for LINE-1 in the regulation of microglial behavior and present LINE-1 activity as a potential target for therapeutic intervention in Alzheimer's disease.

SHIFT 02-269

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4 - 5 April

USP11 AS A NOVEL THERAPEUTIC TARGET FOR TAU AGGREGATION IN ALZHEIMER'S DISEASE

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Aims: USP11 removes ubiquitin from tau, exposing sites to acetylation and driving elevated tau aggregation. We hypothesise that inhibiting USP11 may be therapeutically beneficial in AD and tauopathies, by enhancing ubiquitination and degradation of tau. We aim to validate USP11 as a tractable therapeutic target and develop a HTS to identify USP11 inhibitors that inhibit tau deubiquitination and suppress tau aggregation.
Methods: USP11 was modulated genetically or pharmacologically in iHEK-tau^{P301L} lines and levels of tau were assessed. To investigate USP11 modulation in a neuronal system we used CRISPR to knockout USP11 in NGN2-Tau^{P301L} cortical neurons. We have developed and optimised a USP11 activity assay in a 1536-well format with a Z' of 0.75 and used it to screen 179,280 compounds.
Results: An 80% knockdown of USP11 reduced tau levels in iHEK-tau^{P301L} lines by 60%, treatment with the USP11 inhibitor Mitoxantrone also dose-dependently suppressed tau levels, demonstrating pharmacological inhibition of USP11 can mimic a genetic knockdown. USP11 knockout also suppresses tau aggregation in iPSC cortical neurons. Our HTS had a hit rate of 0.5%, 60% of which confirmed in CRC and were clean in a counterscreen. Confirmed hits have a potency range of 1-20 μM and cluster into four distinct chemotypes with promising SAR. Potent hits will be validated our iHEK-tau^{P301L} assays and assessed for efficacy in our iPSC models.
Conclusions: We have designed a screening and target validation workflow allowing us to identify and validate novel USP11 inhibitors as potential therapeutics to address tau aggregation in AD. Our initial target validation confirms that USP11 inhibition prevents tau aggregation and our HTS has yielded good starting points for medicinal chemistry.

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SHIFT 02-270

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
4 - 5 April

INTEGRATED HYPOMETHYLATION OF N6-METHYLADENOSINE-MODIFIED SITES AND TRANSCRIPTS IMPLICATES GABA HOMEOSTASIS IN ALZHEIMER'S DISEASE

Jenna Libera[1], Tuyet-Anh Nguyen[2], Junming Hu[1], Zihan Wang[1], Sophie Van Der Spek[1], Kamryn Schult[1], Luke Dorrian[3], Jordan Majka[4], Sambhavi Puri[1], Alexander Knyshov[1], Peter Nelson[5], Kate Meyer[6], Lei Hou[1], Xiaoling Zhang[1], Benjamin Wolozin[1]
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Aims: N6-methyladenosine (m6A) modifications regulate RNA fate and can be therapeutically targeted for Alzheimer's disease (AD). Published studies investigating m6A in AD quantify m6A as a signal across peaks rather than as modifications at nucleotides, are limited by small sample sizes, and are mostly restricted to animal models. To overcome this, we applied "Deamination Adjacent to RNA Targets" followed by sequencing (DART-seq) on n=38 human AD and control brains. Our objective is to uncover key differential m6A modifications linked to AD pathophysiology and explore genetic tools as potential mechanisms for therapeutic intervention.
Methods: We extracted RNA from the prefrontal cortices of n=19 AD and n=19 control subjects and incubated the RNA with DART enzyme to induce cytosine deamination adjacent to m6A-modified adenosines. RNA was then repurified, converted into cDNA libraries, and sequenced. Count matrices were generated to identify cytosine deamination events (C>T edits; m6A sites). After merging count matrices between cases and controls, we performed differential analysis at the site, gene-domain, and gene level to determine significant methylation differences in AD.
Results: We observed broad hypomethylation in AD and discovered that an age-dependent increase in m6A sites, notably in the 3'UTR, in controls is absent in AD. KEGG and GSEA analyses of 3'UTR m6A sites revealed "GABAergic synapse" as the top affected pathway and that many GABAergic genes interact with hypomethylated glutamatergic and astrocytic genes. Additionally, we validated reduction of GABRA1 transcript and protein in AD synaptosomes, associated with loss of m6A-driven synaptic localization of GABRA1.
Conclusions: We have discovered a pattern of aberrant, hypomethylated m6A-modified nucleotides in AD that might exacerbate tripartite synaptic excitotoxicity by reducing inhibitory GABA signaling. Correcting these changes through site-directed RNA editing could be a therapeutic modality for AD.

SHIFT 02-280

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
4 - 5 April

NEURALCIM® AN ATTRACTIVE, EFFECTIVE AND SAFE OPTION FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

Leslie Perez Ruiz[1], Saily Sosa[2], Nelky Urrutia[2], Carmen Valenzuela[3], Carmen Viada[1], Patricia Lorenzo-Luaces[1], Tania Crombet[1], Kalet León[1], Teresita Rodríguez[1]
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Aims: To assess the effectiveness and safety of NeuralCIM® for a long period of time (real world evidence).
Methods: NeuralCIM® 0.5 mg was administered three times a week nasally in a cohort member during long period of time, after ATHENEA trial. They were compared with a cohort of controls. The primary outcome was change in the 11-item cognitive subscale of the AD Assessment Scale (ADAS-Cog11) score (range, 0 to 70; higher scores indicate greater impairment) from baseline to last evaluation (1, 2, 3 or 4 years). Secondary outcomes included CIBIC+, GDS, MoCA, NPI, IADL and adverse events
Results: After the clinical trial, the participants who continue to be treated with NeuralCIM® or began to be treated with the drug at some point during the evaluated period, stabilized the disease (decrease in -4.0, -5.0, -8.0 and -7.0 points in ADAS-Cog11 score at 1, 2, 3 and 4 years of treatment). On the other hand, the subjects who did not continue or abandoned the treatment with NeuralCIM® plus at some point during the evaluated period, presented a cognitive impairment characteristic of the progression of the disease (increase in 4.0, 3.0, 7.0 and 29.0 points in ADAS-Cog11 score at 1, 2, 3 and 4 years, respectively). No serious adverse events related with NeuralCIM® were reported.
Conclusions: NeuralCIM® treatment, stabilized the progression of Alzheimer's clinical syndrome, with a good safety profile. These efficacy and safety results, together with the easy administration of the drug, make NeuralCIM® an attractive treatment option to consider for use in AD patient

SHIFT 02-281

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
4 - 5 April

MITOCHONDRIA AS A THERAPEUTIC TARGET FOR NEUROGENERATIVE DISEASES

Eugenia Trushina
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Aims: Mitochondria are signaling organelles that mediate multiple cellular functions, including energy homeostasis, inflammation, adaptive stress responses, and epigenetic landscape. We have found that mild inhibition of mitochondrial complex I results in the activation of multiple neuroprotective mechanisms leading to the restoration of synaptic and cognitive function, and health and life extension in multiple mouse models of Alzheimer's Disease, Huntington's Disease, and chronologically aged mice. Studies using mild complex I inhibition reveled rejuvenating effect on brain transcriptome, resulting in an improvement of multiple mechanisms associated with aging, and an increase in lifespan and healthspan in males and females.
Methods: The development of new small molecules partial mitochondrial complex I inhibitors was done using drug discovery funnel with assays specifically catered to address safety, efficacy and target engagement using in vitro and in vivo models, and assays to evaluate drug-like properties. Efficacy of new small molecules was evaluated in mouse models of familial AD, HD and aged mice using a cohort of behavior tests, biochemistry techniques, and systems biology approaches.
Results: In mouse models of AD and HD, significant improvement in mitochondrial function, reduced proteostasis, inflammation and oxidative stress were consistent with improved cognitive and behavior functions. Aged mice demonstrated enhanced health and lifespan. Cross-validation of RNAseq data between compound treated AD mice and patients with Ad demonstrated that treatment improved gene expression in key pathways related to human disease, including inflammation and cognitive function.
Conclusions: Our data suggest that adaptive stress response activated via mild inhibition of mitochondrial complex I could promote healthy aging delaying the onset of age-related disease. This strategy could also serve as disease-modifying approach for AD and HD.

SHIFT 02-286

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4 - 5 April

PHOTOBIOMODULATION: A MULTI-TARGETED APPROACH TO ALZHEIMER'S DISEASE – FROM PATHOPHYSIOLOGY TO CLINICAL OUTCOMES

Lew Lim
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Aims: To elucidate the complex pathophysiology of Alzheimer's disease (AD) beyond amyloid plaques and evaluate photobiomodulation (PBM), which delivers near-infrared light to the brain, as a novel device-based non-pharmacological intervention.
Methods: We conducted a comprehensive review of AD pathophysiology modifiable with PBM. A novel, layered model of AD progression was developed, incorporating pathogenetic factors, biomarkers, precursors, expression of AD symptoms, and networks and waveform expressions. This model was analyzed based on current literature and clinical studies, focusing on PBM's potential to modulate various pathophysiological factors.
Results: Our model revealed that genetic factors significantly contribute to mitochondrial dysfunction, leading to amyloid and tau pathology and other biomarkers such as energy deficit, oxidative stress, calcium overload, and inflammation. Additional pathogenetic factors include blood-brain barrier disruptions, gut-brain microbiota, glymphatic flow, and metabolic syndrome. These lead to loss in synaptic connections, volume, and growth factors, resulting in memory and cognitive decline expressed in aberrated networks and waveforms (Figure 1). PBM demonstrated remarkable potential to address multiple aspects of this complex pathophysiology in a single intervention, significantly reducing these biomarkers. Human clinical studies (1-57 subjects) showed PBM's capacity to improve cognitive and memory functions without adverse events. Parameters such as LED power density and pulsing frequency affect outcomes, but more studies are needed for specificity.

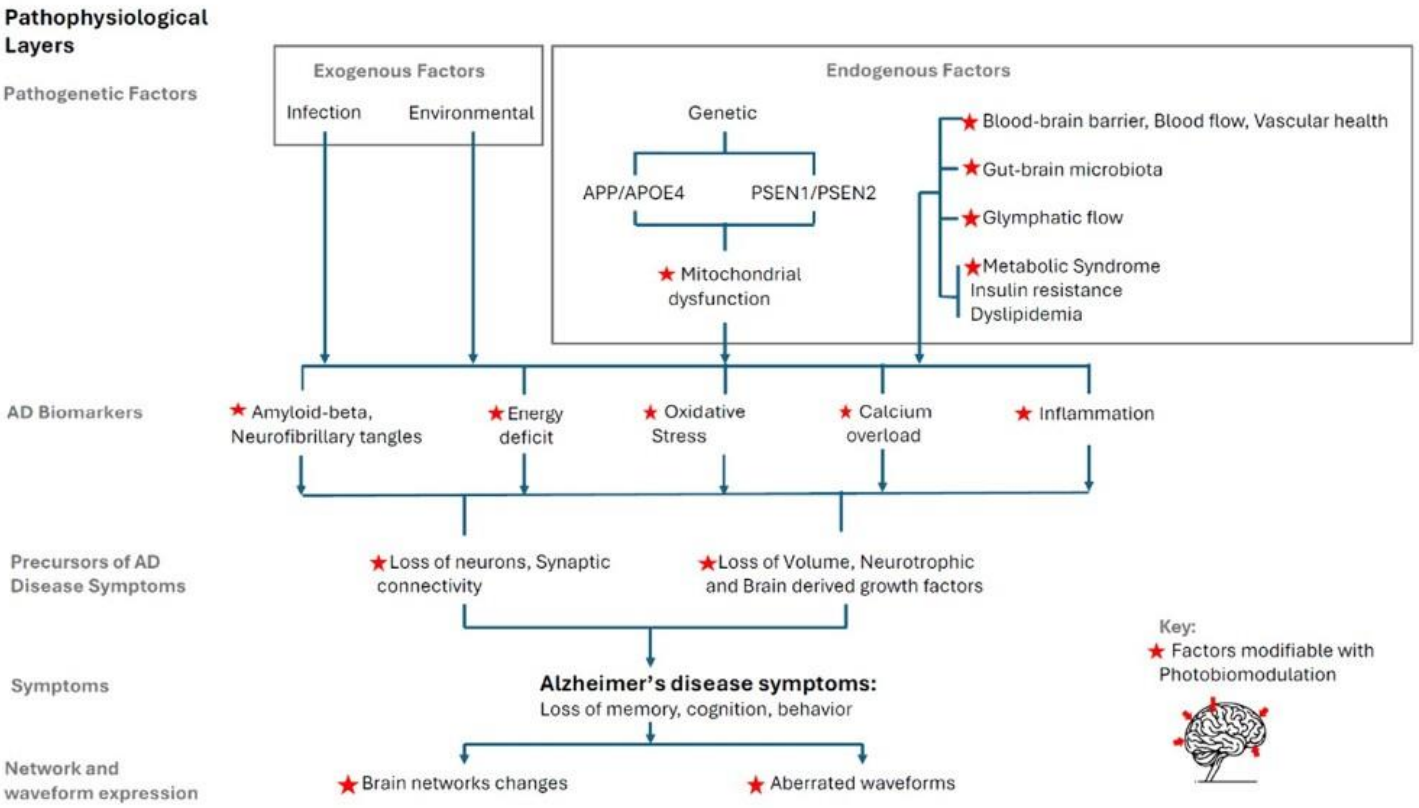

Figure 1: Comprehensive layered model of Alzheimer's disease pathophysiology and photobiomodulation intervention points

Conclusions: PBM emerges as a credible, device-based non-pharmacological intervention for AD, uniquely addressing its multifaceted pathophysiology. This approach could potentially shift AD treatment strategies by simultaneously targeting multiple modifiable factors. Given the promising preliminary results, large-scale controlled clinical trials are warranted to establish PBM's efficacy in modifying AD progression and validate its potential for this disease.

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SHIFT 02-292

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / PERSONALIZED MEDICINES, SEX / RACE, AI, AND COMBINATION THERAPY
4 - 5 April

THE ROAD TO HOPE: COMBINATION OF CIPROFLOXACIN & CELECOXIB AS A NOVEL THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE

Shiran Zimri[1], Daphna Laifenfeld[2], David Pattison[2], Nitai Kerem[1], Diana Shtossel[1], Vered Sasson[1], Eidan Loushi[1], Niva Russek-Blum[1], Rafi Hadad[3], Nataliya Yarovinsky[3], Iris Heller[3], Judith Aharon Peretz[3], Ferenc Tracik[1], Rachel Ben-Hayun[3]
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Aims: Alzheimer's disease (AD) involves multiple pathways, including neuroinflammation, impaired recycling, and autophagy, with dysregulated miRNA and dicer activity affecting brain size, behavior, and longevity. This complexity calls for a multi-targeted therapeutic approach. PrimeC, a combination of ciprofloxacin (a miRNA regulator and an iron chelator) and celecoxib (a COX-2 inhibitor), has shown synergistic effects in ALS by enhancing neuroprotection, microglial function, and clinical outcomes. Its potential in AD is supported by significant biomarker effects in neuron-derived exosomes from people living with AD, suggesting PrimeC's multi-targeted approach as a promising therapeutic option. The safety and tolerability of PrimeC in people with AD were assessed, alongside clinical outcomes and AD biomarkers from plasma and CSF. An AI-driven platform using patient-derived neurons from induced pluripotent stem cells (iPSCs) was also employed to refine the candidate profile, integrating traditional biomarkers with innovative cellular models for a comprehensive evaluation.
Methods: Twenty mild-to-moderate non-familial AD patients will be recruited for a Phase 2 randomized, double-blind, placebo-controlled study. Participants will receive PrimeC or Placebo in a 1:1 ratio BID for 12 months. Extensive plasma and CSF biomarkers, along with clinical outcomes, will be monitored. An iPSC study will use AI and stem cell technologies to predict treatment responses to PrimeC.
Results: Patient derived neurons differentiated from human iPSCs exhibited strong cortical neuron markers, confirming the technology's feasibility for AD drug development. Preliminary findings suggest that this proprietary iPSC platform aids in mechanistic insights, patient stratification, and biomarker identification. PrimeC's effects on neuronal plasticity are under assessment. The study is currently ongoing, with four patients already enrolled.
Conclusions: This study could potentially reveal a new therapeutic approach for halting AD progression through a multi-targeted strategy, and identify novel biomarkers for target engagement.

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SHIFT 02-293

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
4 - 5 April

THE INTERNATIONAL REGISTRY FOR ALZHEIMER'S DISEASE (INRAD): A PRACTICE-BASED MINIMUM DATASET FOR HARMONIZED DATA COLLECTION IN THE REAL WORLD

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Aims: To gain consensus for and introduce an international minimum dataset (MDS) for clinical practice, enabling assessment of Alzheimer's disease treatments and their long-term impact. The MDS, together with an extended dataset (EDS), forms the basis of the InRAD data dictionary. Collaboration with existing registries aligning with the MDS and data dictionary will be key in execution of international real-world studies.
Methods: During the 2023 Alzheimer's Association International Conference, experts agreed on the need for an MDS for real-world evidence. The InRAD working group developed the initial draft based on Ellison et al. (Alzheimers Dement 2023; 19(6)2707-2729), reviewed by an International Steering Committee (ISC). A survey was sent to 143 stakeholders, respondents included: 72 clinicians/academics from 27 countries, 4 pharmaceutical companies, and 4 patient representative groups. The results were discussed and final datasets were approved in August 2024. Consensus required > 75% agreement among clinicians/academics for inclusion in the MDS. Items with ≤50% agreement went into the EDS, while those with 51% to 74% agreement were further discussed by the ISC including context from pharmaceutical companies and patient groups.
Results: The domains of relevance to AD and prioritised outcomes identified[1] included in the MDS are: demographics, disease history, current conditions, effectiveness and key safety, while the EDS encompasses additional data, tests, functional and patient reported outcomes to ensure standardisation of data collected beyond the MDS.
Conclusions: The principle is to ensure the MDS is consistent with practice and requires minimal additional time to collect in clinic; the EDS is optional and adds richness to the data. The MDS and EDS enable systematic outcomes and codified and relevant safety data recording in a way designed to evaluate treated and untreated patient cohorts.

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SHIFT 02-295

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / AGING
4 - 5 April

MEDICATION USE, HEALTH CONDITIONS, AND BIOMARKERS TEN YEARS PRECEDING A DIAGNOSIS OF ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND AMYOTROPHIC LATERAL SCLEROSIS

Dang Wei[1], Anna Freydenzon[2], Octave Guinebretiere[3], Karim Zaidi[3], Fen Yang[1], Weimin Ye[4], Niklas Hammar[1], Karin Modig[1], Naomi Wray[2], Maria Feychting[1], Nadine Hamieh[3], Bruno Ventelou[5], Beranger Lekens[6], Laurene Gantzer[6], Stanley Durrelman[7], Allan Mcrae[2], Baptiste Couvy-Duchesne[2], Fang Fang[8], Thomas Nedelec[3]
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Aims: Many studies have investigated early predictors for Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). However, evidence is sparse regarding specific and common prodromal factors for these diseases. We aimed to identify medication use, health conditions, and blood biomarkers associated with the risk of AD, PD, and ALS 5-10 years later.
Methods: We conducted population-based nested case-control studies of AD, PD, and ALS across France, the UK, Sweden, and Australia. We retrieved data on medication use, diagnosed health conditions, and measured blood biomarkers from electronic medical records or biomedical cohorts. Conditional logistic regression and meta-analysis were applied to assess the associations between these prodromal factors and the risk of receiving a diagnosis of AD, PD, or ALS.
Results: We included a total of 149,642 AD cases (mean age: 79.1-81.2 years), 252,696 PD cases (73.2-75.9 years), and 27,533 ALS cases (64.4-69.6 years). The prescription of psychoanaleptics and nasal preparations was consistently associated with an increased risk of AD, PD, and ALS 5-10 years later. Constipation and use of related medications were associated with an increased risk of AD and PD, while diabetes and use of antidiabetics were associated with a reduced risk of ALS. A higher level of triglycerides was associated with a lower risk of AD, whereas a higher level of Apolipoprotein B was associated with a lower risk of PD, 5-10 years later.
Conclusions: Psychoanaleptics and nasal preparations may serve as common predictors for diagnosis of AD, PD, and ALS 5-10 years later. Conversely, the increased prevalence of constipation is specific to AD and PD, while the decreased prevalence of diabetes and use of antidiabetics are specific to ALS.

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SHIFT 02-300

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
4 - 5 April

THE ROLE OF EDUCATIONAL ATTAINMENT AND APOE E4 IN ALZHEIMER DISEASE AMONG PUERTO RICANS: DISPARITY IN RESILIENCE

Farid Rajabli[1], Azizi Seixas[2], Dingtian Cai[1], Kara Hamilton-Nelson[1], Larry Adams[1], Pedro Mena[1], Carolina Scaramutti[2], Katrina Celis[1], Vanessa Rodriguez[1], Jose Javier-Sanchez[1], Glenies Valladares[1], Patrice Whitehead[1], Michael Prough[1], Heriberto Acosta[3], Katalina Mcinerney[4], Anthony Griswold[1], Briseida Feliciano[5], Jeffery Vance[1], Michael Cuccaro[1], Margaret Pericak-Vance[1]
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Aims: Cognitive reserve research in African Americans shows that higher educational attainment (EA) can mitigate Alzheimer disease pathology (ADP), though this effect is less pronounced in APOEε4 carriers, suggesting resilience disparities influenced by the interplay of educational and genetic factors. Our study examines whether similar patterns exist in Puerto Ricans (PR), a population with distinct social and ancestral backgrounds. We aim to explore education as a modifiable risk factor in AD among PRs and to determine whether the APOEε4 allele affects resilience between carriers and non-carriers.
Methods: We analyzed 732 PRs, focusing on their education years, plasma pTau181 levels, and *APOE* genotypes. We derived a composite functional score, CDR-FUNC (0–12), by summing the non-memory components of the Cognitive Dementia Rating scale. EA was classified as low (≤9 years) and high (>9 years). Plasma pTau181, used as a proxy for ADP, identified advanced pathology if $\log_{10}$(pTau181) was >mean+1SD. We used the Mann-Whitney U test to assess associations between EA and CDR-FUNC in those with advanced pTau181 levels and the *APOE*ε4 allele.
Results: We found a significant association between EA and functional difficulties in participants with high pTau181 levels. Individuals with high EA showed better functional ability than those with low EA($pv=3.2\times10^{-4}$). Additionally, ε4 carriers with low EA had worse functional outcomes compared to non-carriers ($p = 0.045$). No difference was observed in functional outcomes among individuals with high EA.
Conclusions: Our study demonstrates that education functions as a modifiable risk factor for AD in PRs, contributing to resilience against ADP.Notably, APOEε4 carriers with low EA had worse functional outcomes than non-carriers. Understanding the combined influence of education, genetics, and functional resilience in PRs is essential for creating targeted interventions to improve health outcomes in this distinct population.

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SHIFT 02-305

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

ELUCIDATING ANCESTRAL DIFFERENCES IN EXPRESSION QUANTITATIVE TRAIT LOCI ARCHITECTURE RELATIVE TO ALZHEIMER'S DISEASE STATUS

Makaela Mews[1], Yousef Mustafa[1], Nicholas Wheeler[2], Tianjie Gu[3], Lissette Gomez[3], Larry Adams[3], Takiyah Starks[4], Mario Cornejo-Olivas[5], Maryenela Illanes-Manrique[5], Concepcion Silva[6], Briseida Feliciano-Astacio[7], Goldie Byrd[8], Margaret Pericak-Vance[3,9], Jonathan Haines[2], Anthony Griswold[3,9], William Bush[2]
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Aims: The genetic architecture of Alzheimer's Disease (AD) is different across ancestries, and the disease process likely induces changes to gene expression in important and poorly understood ways. To address this gap, we examined how genetic variants alter whole-blood gene expression in the context of AD within a diverse cohort of African American (AA; N=224), Caribbean Hispanic (CH; N=209), Peruvian (PER; N=83), and Non-Hispanic White (NHW; N=235) AD cases and controls.
Methods: RNAseq data alongside TOPMed imputed genotype data was processed using the Alzheimer's Disease Sequencing Project (ADSP) FunGen-xQTL protocol. We performed expression quantitative trait loci (eQTL) analysis stratified by population, examining AD status as an effect modifier, adjusting for sex, age at exam, population substructure (PC1-3), 14 cell-type proportions calculated (CIBERSORTx), and additional experimental factors.
Results: We identified 68 genes which harbor significant interaction eQTLs (ieQTLs), shared amongst at least two populations. Notably, we identified *CACNG6*, which encodes a voltage gated calcium channel, shared among NHW, AA, and PER populations. We observed an enrichment for genes regulated by the ZFHX3 and ELF2 transcription factors, which may point to specific immune regulatory mechanisms altered by the Alzheimer's disease process. Our population-specific analyses identified 4,733 significant ieQTLs in AA, 4,322 in NHW, 3,084 in CH, and 1,436 in PER populations. All ieQTLs were population-specific at a variant-level, with 20-30% overlapping known AD loci.
Conclusions: Our eQTL analysis revealed substantial diversity in whole blood gene expression regulation across ancestries, with many population-specific ieQTL effects. These findings underscore how genetic variation across populations interacts with the disease process to drive changes in the peripheral immune system. This insight may pave the way for developing more inclusive and effective therapeutic approaches that account for genetic diversity.

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SHIFT 02-306

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

EXPLORING RACIAL DIFFERENCES IN THE ASSOCIATION OF PLASMA BIOMARKERS AND APOE4 GENOTYPE IN A LARGE MEMORY CLINIC COHORT

Xuemei Zeng[1], Rebecca Deek[2], Michel Nafash[1], Jeremy Gu[1], Lamia Choity[1], Tara Lafferty[1], Marissa Farinas[1], Shayna Brodman[1], Anuradha Sehrawat[1], Annie Bedison[3], Rocco Mercurio[4], Cristy Matan[5], Alexandra Gogola[5], Julia Kofler[6], Dana Tudorascu[1], C. Elizabeth Shaaban[7], Jennifer Lingler[8], Tharick Pascoal[9], William Klunk[1], Victor Villemagne[10], Sarah Berman[9], Robert Sweet[4], Beth Snitz[4], Ann Cohen[10], Ilyas Kamboh[3], Oscar Lopez[9], Thomas Karikari[1]
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Aims: The *APOE4* is a major genetic risk factor for Alzheimer's disease (AD) and has been shown to impact plasma AD biomarker levels. We utilized a large memory clinic cohort to assess potential differences in this association race.
Methods: Participants at the University of Pittsburgh Alzheimer's Disease Research Center (Pitt-ADRC) underwent baseline blood collection and cognitive function assessment using the Clinical Dementia Rating (CDR) scale, followed by annual CDR assessments for a median of 3.0 year (IQR 1.9-5.9). *APOE* genotyping was determined using TaqMan assays. Plasma p-tau181, p-tau217, brain-derived tau (BD-tau), GFAP and NfL, were measured using SIMOA assays. Cohen's d and Kaplan-Meier analysis were employed for statistical inference.
Results: This study included 4,073 participants (59.9% female; 90.2% self-identified non-Hispanic White [NHW]), aged 71.9 ± 9.8 years. Both *APOE4* genotype and race were significantly associated with cognitive decline. Black/African American (B/AA) *APOE4* non-carriers had the most stable cognition over time, with a median stability of 11.3 years, followed by 7.2 years for B/AA carriers. Importantly, NHW showed more cognitive decline than B/AA regardless of *APOE4* carriage, with median stability times of 4.9 and 6.0 years for *APOE4* carriers and non-carriers, respectively. All biomarkers, except NfL, showed significant *APOE4*-dependent levels, with effect sizes (carriers/non-carriers) of 0.176 for p-tau181, 0.361 for p-tau217, 0.118 for BD-tau, and 0.215 for GFAP. The *APOE4* effect on BD-tau was insignificant in B/AA, but p-tau217 had a larger effect size in B/AA (0.50) than NHW (0.35). The p-tau217/BD-tau ratio further highlighted differences between racial groups, with effect sizes of 0.39 for B/AA and 0.07 for NHW.
Conclusions: Racial identity may significantly influence the associations between *APOE4* genotype and plasma biomarkers. This should be considered when applying these biomarkers in diverse populations.

SHIFT 02-307

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

INVESTIGATING GENETIC ASSOCIATIONS BETWEEN MEDICATION USE AND ALZHEIMER'S DISEASE

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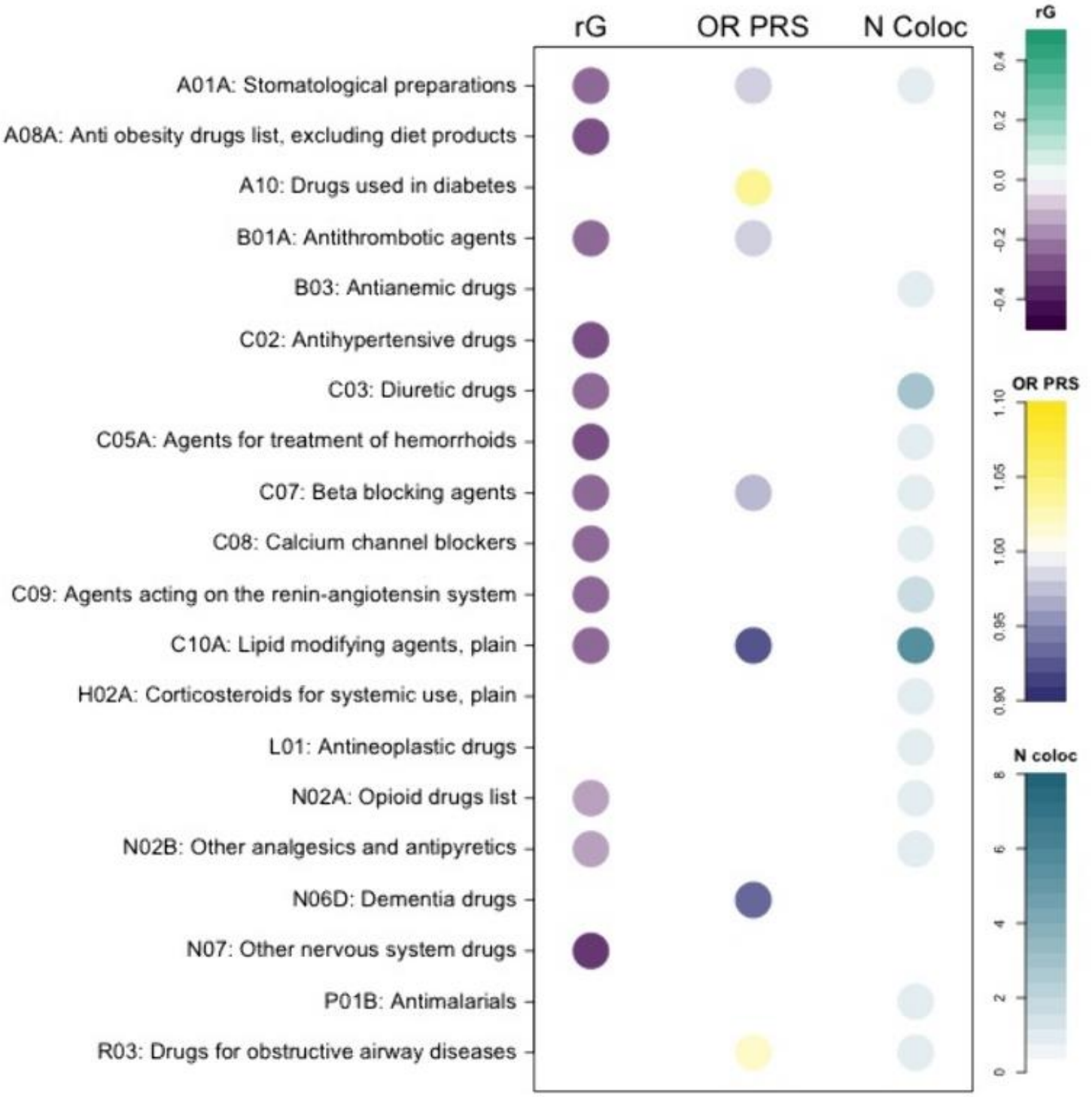
Aims: Our study aimed to explore the genetic associations between medication use and Alzheimer's disease (AD). Some medications have been associated to AD diagnoses 5 to 10 years after the prescription, in a previous study from our consortium.
Methods: We conducted genome-wide association studies (GWAS) on 86 self-reported medication classes from the UK Biobank (~502,356 individuals; 8,807,037 SNPs). We estimated the genetic correlations (rg) between each medication use and AD using GWAS summary statistics. In addition, we tested if a polygenic risk score (PRS) for AD was associated with medication use. Thirdly, we performed colocalization analyses to identify shared genetic loci between medication use and AD. Lastly, we used Mendelian randomization (MR) to investigate the causal direction of the identified associations.
Results: We identified 20 medications associated with AD in at least one genetic analysis, including two that were previously identified in our previous epidemiological findings (A08, C05). Three medication classes showed a consistent association with AD across all three methods: they were FDR-significant for both rg and PRS analyses, and had at least one genetic variant with a posterior probability of colocalization with AD greater than 0.9 (Figure 1). Notably, all three demonstrated a negative relationship with AD risk. These included A01A (Stomatological preparations) with rg= -0.21(95%CI:-0.30,-0.12), ORprs= 0.98(0.97,0.99), Ncoloc=1 ; C07 (Beta blocking agents) rg=-0.25(-0.34 ,-0.16),ORprs= 0.98 (0.97,0.99),Ncoloc=1; and C10A(Lipid modifying agents) rg=-0.24(-0.37 ,-0.11),ORprs=0.92 (0.92,0.93),Ncoloc=6. Additionally, MR analysis suggested that A01A (β(medication→AD)=-1.15,SE=0.55,p= 0.03) and C07 (β(medication→AD)=-0.66,SE= 0.29,p= 0.03) have a causal protective effect on AD risk.



Conclusions: Our analyses suggest that genetics mediate the relationship between medication use and AD. We identified two candidate drugs with a potential causal protective effect on AD, providing a basis for future intervention studies.

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β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

LONG READ SEQUENCING ENABLES STRUCTURAL VARIANT DISCOVERY AND IDENTIFICATION IN HAPTOGLOBIN, A MODIFIER OF APOE RISK

Yuchen Yang[1], Anthony Griswold[2], Takiyah Starks[3], Goldie Byrd[4], Larry Adams[2], Eden Martin[2], Margaret Pericak-Vance[2], Jonathan Haines[5], William Bush[6]
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Aims: Haptoglobin (HP) structural variants (SVs) have been associated with many diseases including cardiovascular and neurological disorders. HP contains a tandem two-exon repeat, where exons 3 and 4 are sequence-similar to exons 5 and 6, leading to alleles containing 1 (HP1) or 2 (HP2) copies of this exon pair. This SV interacts with APOE to affect AD risk by modifying both the protective effect of APOE e2 and the deleterious effect of APOE e4, but past studies have relied on array-based imputation methods limited to European-descent. We used long-read (LR) and short read whole genome sequencing (WGS) to build improved imputation panels for haptoglobin in African-descent populations, potentially discovering novel alleles and improving SV calling accuracy.
Methods: We analyzed long-read and WGS data from 32 participants from the African/African American cohort of the Alzheimer's Disease Sequencing Project. Haptoglobin genotypes were called by manual inspection of aligned long-reads. We used the TOPMed server to phase WGS variants and Minimac4 to build a reference imputation panel for calling HP1/HP2. Imputation accuracy was evaluated via leave-one-out cross-validation. Hard calling for imputed HP alleles was done with a threshold of >0.9. We also used an independent dataset to verify our results, using the read count of the exon 4 & 5 junction unique to HP2 in RNA-sequenced samples.
Results: We were able to impute *HP* status from multi-SNP haplotypes in the surrounding region with high accuracy ($r2 > 0.95$). We achieved higher accuracy with WGS compared to array-based SNP sets, but the array-based panel maintained accuracy comparable to existing panels.
Conclusions: Long read sequencing successfully reveals previously unrecognized complex structural variants. We demonstrate that LR can complement other sequencing methods in building imputation panels for variant detection.

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β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4 - 5 April

PLASMA BIOMARKERS MODULATE APOE4 GENOTYPE RISK IN COGNITIVE DECLINE: INSIGHTS FROM A LARGE MEMORY CLINIC COHORT

Xuemei Zeng[1], Rebecca Deek[2], Michel Nafash[1], Jeremy Gu[1], Lamia Choity[1], Tara Lafferty[1], Marissa Farinas[1], Shayna Brodman[1], Annie Bedison[3], Rocco Mercurio[4], Cristy Matan[5], Alexandra Gogola[5], Julia Kofler[6], Dana Tudorascu[7], C. Elizabeth Shaaban[8], Jennifer Lingler[9], Tharick Pascoal[10], William Klunk[1], Victor Villemagne[7], Sarah Berman[10], Robert Sweet[4], Beth Snitz[4], Ann Cohen[7], Ilyas Kamboh[3], Oscar Lopez[4], Thomas Karikari[1]
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Aims: The apolipoprotein E (*APOE*) 4 genotype is a major genetic risk factor of late-onset Alzheimer's disease (AD). We examined the link between *APOE4* carriage, cognitive decline and AD plasma biomarkers in a large memory clinic cohort with annual assessments spanning up to three decades.
Methods: Participants at the University of Pittsburgh Alzheimer's Disease Research Center (Pitt-ADRC) underwent baseline blood collection and cognitive function assessment using the Clinical Dementia Rating (CDR) Sum of Boxes, followed by annual CDR assessments for a median follow-up of 3.0 years (IQR 1.9-5.9). *APOE* genotyping was determined using TaqMan assays. Plasma p-tau181, p-tau217, brain-derived tau (BD-tau), GFAP and NfL, were measured using SIMOA assays. Linear regression and Kaplan-Meier analysis were employed for statistical inference.
Results: This study included 4,073 participants (59.9% female; 90.2% non-Hispanic White), aged 71.9 ± 9.8 years, with 2160 being non-demented (CDR≤0.5) at baseline. *APOE4*, but not *APOE2*, carrier status was significantly associated with worse (higher) CDR scores ($p<0.001$) and higher levels of p-tau181, p-tau217, BD-tau, and GFAP (all $p < 0.001$), but not NfL. The significance of these associations was not influenced by the number of *APOE4* alleles. *APOE4* carriers experienced a faster decline in cognitive function, with a median cognitive stable time of 5.0 years compared to 6.1 years for non-carriers (log-rank $p<0.001$). However, this *APOE4*-dependent cognitive decline was only apparent in participants with <=median plasma biomarker concentrations but disappeared in individuals with >median biomarker levels.
Conclusions: This study shows that the *APOE4* genotype exerts a significant, biomarker-dependent risk on cognitive decline. These findings can guide personalized risk assessment and improve clinical management of AD.

SHIFT 02-315

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
4 - 5 April

CARDIOMETABOLIC MULTIMORBIDITY IS ASSOCIATED WITH ALZHEIMER'S PLASMA BIOMARKERS: ETHNIC DISPARITIES IN THE HABS-HD STUDY

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Aims: To investigate the relationship between cardiometabolic multimorbidity (CMM) and Alzheimer's disease (AD) plasma biomarkers, and how these associations differ among cognitively normal Hispanic Americans (HA) and non-Hispanic White (NHW) in the HABS-HD study.
Methods: Data from 1,194 cognitively normal participants (mean age 66.17 ± 8.5 years) were analyzed, including HA (n = 590, 69.0% female) and NHW (n = 604, 64.7% female). CMM included hypertension, dyslipidemia, diabetes, kidney disease, cardiovascular disease, and stroke and was categorized into three levels: 0-1 conditions, 2-3 conditions, and 4+ conditions. Regression models were used to assess the associations between CMM and AD plasma biomarkers (Aβ40, Aβ42, Aβ42/40 ratio, NfL, t-tau, and pTau181), adjusting for age, sex, education, APOE4 status, and lifestyle factors. Analyses were stratified by ethnicity.
Results: Among HA, there were significant positive trends in Aβ40 ($p<.001$), Aβ42 ($p<.001$), t-Tau ($p=.02$), pTau181 ($p<.001$), and NfL ($p<.001$) levels across CMM groups. Having 2-3 conditions increased Aβ40, pTau181, and NfL, with 4+ conditions additionally elevating Aβ42, t-Tau, pTau181, and NfL (Tables 1 and 2). In NHW, positive trends were observed for Aβ40 ($p<.001$), Aβ42 ($p<.001$), and t-Tau ($p=.02$), with 2-3 conditions increasing these biomarkers and 4+ conditions further elevating them (Tables 1 and 2). However, there were no significant trends for pTau181 or NfL in NHW. No significant trends were observed between CMM groups and the Aβ42/40 ratio in either ethnic group.

Table 1: Association between number of chronic conditions and plasma amyloid biomarkers by ethnicity.

Number of Chronic Conditions	Aβ40		Aβ42	
	β (SE)	P-value	β (SE)	P-value
Hispanic Americans (n=604)				
0-1 (Reference)	1.00	--	1.00	--
2-3	12.18(4.74)	**0.01**	0.27(0.24)	.25
4+	64.06 (10.24)	**<0.001**	3.18(0.51)	**<0.001**
Non-Hispanic Whites (n=590)				
0-1 (Reference)	1.00	--	1.00	--
2-3	10.85(4.25)	**0.01**	0.63(0.23)	**0.006**
4+	56.19	**<0.001**	2.19(0.52)	**<0.001**

Adjusted for: Age, sex, education, APOE4 positivity, current smoking, alcohol use, and physical activity.
P-values < 0.05 indicate statistical significance (bolded).

Table 2: Association between number of chronic conditions and tau and NfL plasma biomarkers by ethnicity.

Number of Chronic Conditions	t-Tau		pTau181		NfL	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
Hispanics Americans (n=604)						
0-1 (Reference)	1.00	--	1.00	--	1.00	--
2-3	0.10(0.07)	0.15	0.20 (0.10)	**0.04**	2.56(.900)	**0.005**
4+	0.36(0.15)	**0.02**	0.83(0.21)	**<0.001**	6.85(1.95)	**<0.001**
Non-Hispanic Whites (n=590)						
0-1 (Reference)	1.00	--	1.00	--		
2-3	0.14(0.05)	**0.04**	0.02(0.09)	0.80	0.87(1.10)	0.43
4+	0.36(.16)	**0.02**	0.36(0.21)	0.08	4.46(2.52)	0.08

Adjusted for: Age, sex, education, APOE4 positivity, current smoking, alcohol use, and physical activity.
P-values < 0.05 indicate statistical significance (bolded).

Conclusions: HA demonstrate stronger and more consistent associations between high CMM and plasma biomarkers compared to NHW. Neither group showed significant associations with the Aβ42/40 ratio, suggesting that this ratio may be less sensitive to changes in CMM than other biomarkers. These findings underscore the importance of considering CMM by ethnicity when interpreting AD plasma biomarkers.

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SHIFT 02-316

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
4 - 5 April

APOE4 MODIFES THE RELATIONSHIP BETWEEN CARDIOMETABOLIC MULTIMORBIDITY AND ALZHEIMER'S DISEASE PLASMA BIOMARKERS: THE HABS-HD STUDY

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Aims: To investigate whether APOE4 status influences the relationship between cardiometabolic multimorbidity (CMM) and Alzheimer's disease (AD) plasma biomarkers in cognitively normal Hispanic Americans (HA) and non-Hispanic Whites (NHW) in the HABS-HD study.
Methods: Data from 1,194 cognitively normal participants (mean age 66.17 ± 8.5 years) were analyzed, including HA (n = 590, 69.0% female) and NHW (n = 604, 64.7% female). CMM included hypertension, dyslipidemia, diabetes, kidney disease, cardiovascular disease, and stroke, and was categorized into three levels: 0-1 conditions, 2-3 conditions, and 4+ conditions. Multivariate linear regression models were used to examine associations between CMM and AD biomarkers (Aβ40, Aβ42, Aβ42/40 ratio, NfL, total tau, and pTau181), adjusting for age, sex, education, and lifestyle factors. Analyses were stratified by APOE4 status and ethnicity.
Results: Among HA, APOE4-negative individuals exhibited significant positive trends for Aβ40 ($p<.001$), Aβ42 ($p<.001$), t-Tau ($p=.03$), pTau181 ($p<.001$), and NfL ($p<.001$) across chronic condition groups, while no trends were observed in APOE4-positive HA. In NHW, positive trends were seen for Aβ40 ($p<.001$), Aβ42 ($p<.001$), and NfL ($p=.03$) in APOE4-negative individuals, though t-Tau and pTau181 were not significantly associated. In APOE4-positive NHW, only Aβ40 showed a positive trend (Tables 1 and 2). No significant trends were found for the Aβ42/40 ratio in either group.

Table 1: Association between number of chronic conditions and plasma amyloid biomarkers by APOE4 status.

Number of Chronic Conditions	AB40		AB42	
	β (SE)	P-value	β (SE)	P-value
APOE4 Negative and Hispanic American (n=483)				
0-1 (Reference)	1.00	--	1.00	--
2-3	11.75(5.26)	**0.03**	.20(0.27)	0.46
4+	73.81(11.31)	**0.000**	3.59(0.58)	**<0.001**
APOE4 Negative and Non-Hispanic Whites (n=439)				
0-1 (Reference)	1.00	--	1.00	--
2-3	12.68(5.02)	**0.012**	0.58(.27)	**0.03**
4+	51.90(12.02)	**0.000**	2.25(0.64)	**<0.001**
APOE4 Positive and Hispanic American (n=107)				
0-1 (Reference)	1.00	--	1.00	--
2-3	13.22(10.89)	0.228	0.57(.46)	0.21
4+	8.85(24.47)	0.718	1.12 (1.02)	0.28
APOE4 Positive and Non-Hispanic Whites (n=165)				
0-1 (Reference)	1.00	--	1.00	--
2-3	4.03(8.18)	0.623	0.58(0.45)	0.20
4+	65.60(17.12)	**0.000**	1.87(.0.95)	0.05

Adjusted for: Age, sex, education, APOE4 positivity, current smoking, alcohol use, and physical activity.
P-values < 0.05 indicate statistical significance (bolded).

Table 2: Association between number of chronic conditions and tau and NfL plasma biomarkers by APOE4 status.

Number of Chronic Conditions	t-Tau		pTau181		NfL	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
APOE4 Negative and Hispanic American (n=483)						
0-1 (Reference)	1.00	--	1.00	--	1.00	--
2-3	0.11(0.08)	0.16	0.20(0.11)	0.06	2.80(1.04)	**0.007**
4+	0.36(0.17)	**0.03**	0.95(0.24)	**<0.001**	8.41(2.23)	**<0.001**
APOE4 Negative and Non-Hispanic Whites (n=439)						
0-1 (Reference)	1.00	--	1.00	--	1.00	--
2-3	0.15(0.08)	0.065	0.09 (0.11)	0.40	1.76(1.09)	0.11

Conclusions: APOE4-negative individuals exhibited stronger and more consistent associations across biomarkers, while APOE4-positive individuals, particularly HA, showed weaker or no significant associations. This suggests that APOE4 modifies the relationship between CMM and AD-related plasma biomarkers, altering the impact of chronic conditions based on genotype.

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SHIFT 02-318

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4 - 5 April

SYSTEMATIC EVIDENCE BASED TIER METHOD FOR IDENTIFYING ALZHEIMER'S DISEASE GENES AND LOCI IN GENETIC STUDIES

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Aims: Many publications report genetic evidence linking certain genes or signals to Alzheimer's Disease (AD) or dementia, though the quality of evidence varies. Retrospective analyses show that therapeutic targets supported by genetic evidence are 2-3 times more likely to succeed. Thus, gene discovery for AD is crucial for identifying valid therapeutic targets. To clarify which loci are valid versus potential false positives, the Alzheimer's Disease Sequencing Project's Gene Verification Committee (GVC) was formed to review evidence for published genome-wide association study (GWAS) loci, as most genetic signals do not clearly identify the causal gene.
Methods: The GVC conducted a literature review and developed a tier system (1–7) to assess evidence quality, considering factors like population differences, sample sizes, and study methods. Tier 1 represents the strongest evidence.
Results: We reviewed >330 association results from single-variant or variant set analyses across 29 publications (2015-2022) and identified 97 high-confidence loci, 12 of which were genes, including *APOE* region, *PSEN1/PSEN2*. About 47% of the loci were supported by multiple studies, with 84% of results conducted on non-Hispanic white subjects and the rest on Asian, African, Hispanic/Latino subjects or in a multi-ancestry manner. Only 29 loci were true AD loci, with the rest classified as associated with AD+dementia. We further annotated these loci with published functional support via cell type specific epigenetics, transcriptomics and proteomics data. We also compared our gene list against those from AMP-AD AGORA and Opentargets platform. 75 of our loci were also reported as AD genes in gene lists from these resources. Yet, our GVC genes were enriched in AD-associated pathways but not necessarily reflected in other lists.
Conclusions: The GVC list will be publicly available soon.

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SHIFT 02-319

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4 - 5 April

MORE THAN SURVIVAL - IS CANCER A PROTECTIVE FACTOR FOR DEMENTIA?

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Aims: Previous studies suggested an inverse association between cancer and subsequent dementia risk. Here, we assessed associations of cancer diagnoses with subsequent risk of dementia and neuropathology of Alzheimer's disease (AD) and related dementias.
Methods: We conducted a case-control and a clinico-pathological observation study. The case-control study included 1,664,608 patients with incident dementia and 3,329,216 matched controls from German health insurance claims data. Exposure included 17 cancer categories according to the German Cancer Registry. We compared the prevalence trajectories of cancer categories between dementia cases and controls over a period of 10 years before the index date. For the clinico-pathological observation study, we retrieved 2,288 cases from the National Alzheimer Coordinating Center cohort. We used Bayesian ordinal regression to assess associations of neuropathological scores with pre-existing or incident cancer diagnoses.
Results: In the case-control study, we identified four different types of trajectories of cancer-associated dementia risk over ten years. Survivors of cancers with poor prognosis showed a particularly strong decline in dementia risk four to three years before the index date. In the clincio-pathologial study, we found extreme evidence that pre-existing and incident cancer diagnoses were associated with better global cognition (Bayes factor (BF) > 2000). We found strong evidence for an effect of preexisting cancer diagnosis on TDP-43 pathology (BF=26) and moderate evidence for an effect on Lewy body pathology (BF=3.2), with lower neuropathology scores in cases with a cancer diagnosis.
Conclusions: Our data suggest that a mixture of causes contributes to the inverse association of cancer and dementia risk. These include selective survival, underdiagnosis of dementia after cancer and of cancer in dementia, but also shared biological factors that are not only related to AD but also to comorbid pathologies.

SHIFT 02-324

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
4 - 5 April

THE DAWN ALZHEIMER'S RESEARCH STUDY: EXPANDING DIVERSITY IN THE ALZHEIMER'S DISEASE SEQUENCING PROJECT (ADSP)

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Aims: The DAWN Alzheimer's Research Study is an international multi-site initiative to expand representation of African ancestry and Hispanic populations for genetic studies of Alzheimer's disease. The DAWN study will include 4000 African-Americans and 4000 Latinos from four US sites and 5000 Africans from nine countries in the African Dementia Consortium (AfDC). This resource of 13,000 individuals will be deeply phenotyped with accompanying whole genome sequence, CVD and plasma biomarker data as well as data on social determinants of health (SDOH).
Methods: Participants are ascertained from clinical and community settings and administered a standard protocol including clinical and family history, neuropsychological assessments, dementia staging, functional assessments, neurobehavioral measures, and SDOH tools. All measures were developed to support subsequent harmonization with ADSP cohorts. All clinical data are collected and compiled in REDCap where it undergoes rigorous quality control processing. Different workflows are in place for our US and African sites but aligned to a standard set of diagnostic criteria.
Results: In our first two years we ascertained 1606 African individuals (57% Female, mean age = 74.5 years, mean education=7.6 years), 1161 African-American individuals (81% Female, mean age=71.3 years, mean education=14.1 years), and 1163 Hispanics (74% Female, mean age=72.3 years, mean education=11.2 years). Resulting clinical data were processed using a combination of decision tree-based algorithms and reviewer-based adjudication to determine clinical status (AD, Non-cognitively impaired and mild cognitive impairment). To facilitate adjudication a computer-based algorithm was developed and tested in US participants reducing reviewer-based primary adjudication by 21% in US participants.
Conclusions: To date the project has ascertained, enrolled, and processed nearly 4,000 participants. This collaborative project will serve as a catalyst for identifying and understanding genetic risk for diverse populations.

SHIFT 02-325

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
4 - 5 April

DECODING RARE VARIANT ASSOCIATIONS IN ALZHEIMER'S DISEASE GENOMES WITH DEEP LEARNING

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Aims: Investigating the role of rare genetic variants in Alzheimer's disease (AD) is complex due to limited specificity in functional predictions for brain cell types. To address this, we developed non-coding variant prediction scores, including splicing and enhancer/promoter effects, tailored to brain cell types. We also introduced a novel rare variant testing method, *gruyere*, and applied these tools to the Alzheimer's Disease whole-genome sequencing (WGS) data.
Methods: We trained deep learning models using RNA-seq data from microglia to predict the splicing and gene regulation effects of variants. Additionally, we devised a novel modifier score (SMS) to improve the prediction of fine-mapped sQTL variants. *Gruyere* is a Bayesian probabilistic model designed to enhance variant prioritization by learning global, trait-specific weights for functional annotations. *Gruyere* was applied to WGS data from the Alzheimer's Disease Sequencing Project (7,966 cases and 13,412 controls) to identify novel AD-associated genes and annotations.
Results: Our models surpassed baseline models in predicting microglia splicing, achieving a PR-AUC of 0.853. The delta scores accurately predicted fine-mapped sQTL variants with a ROC-AUC of 0.656. We validated some of the fine-mapped AD variants using MPRA in iPSC-derived microglia. With *Gruyere, we* identified 10 significant genetic associations (including *TREM2*) not detected by other rare variant methods, with splicing annotations showing the highest enrichment for AD-associated non-coding RVs.
Conclusions: Our study introduces an advanced framework that integrates functional annotations, splicing and enhancer/promoter variants, along with brain cell-type-specific non-coding rare variants. This approach provides a novel method for genome-wide association tests, enabling the identification of AD-relevant genes and annotations with greater specificity. Additionally, our method uncovers numerous novel rare variant associations with AD, offering valuable targets for future validation studies.

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SHIFT 02-326

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4 - 5 April

ASSOCIATIONS BETWEEN DIGITAL SPEECH FEATURES AND THE TRAJECTORY OF REGIONAL BRAIN ATROPHY AND COGNITIVE DECLINE IN EARLY-STAGE ALZHEIMER'S DISEASE

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Aims: Timely screening approaches are crucial for early intervention and treatment of Alzheimer's Disease (AD). Digital speech-based features extracted from automated telephone-based neurocognitive tests, including semantic verbal fluency (SVF), verbal learning and delayed recall tasks (VLT), show promise in this context, by correlating with brain volume changes and traditional cognitive scores. This study further investigated their associations with longitudinal patterns of brain atrophy and cognitive decline in early-stage AD.
Methods: Within the Prospect-AD study, we examined 84 participants from the German DZNE

longitudinal cohorts DELCODE and DESCRIBE (23 healthy elderly, 56 with subjective cognitive decline and 5 with mild cognitive impairment, age = 68±6 years, 67.9% female, follow-up 1-8 years). We automatically extracted global digital cognition score, task correct counts and semantic and acoustic speech features from telephone recordings. These features were compared with task-relative brain regions of interest (ROIs) and cognitive changes before the phone-based tests. Cognitive abilities were assessed using the traditional MMSE, PACC5, SVF, and VLT recall scores. Analyses were performed using linear mixed-effects models in R.

Results: Digital VLT recall and SVF correct counts were associated with hippocampal atrophy rates. Higher SVF correct counts were linked to slower atrophy in the parahippocampal gyrus and anterior cingulate cortex (Figure 1) and associated with slower cognitive decline, as reflected by MMSE, PACC5, SVF, and VLT recall scores (β_{std} for the time-SVF correct count interaction ranged from 0.08 to 0.12, p_{FDR} from 0.002 to 0.040). Global cognition score, semantic and acoustic features were correlated with certain cognitive trajectories but did not show associations with regional brain atrophy rates.

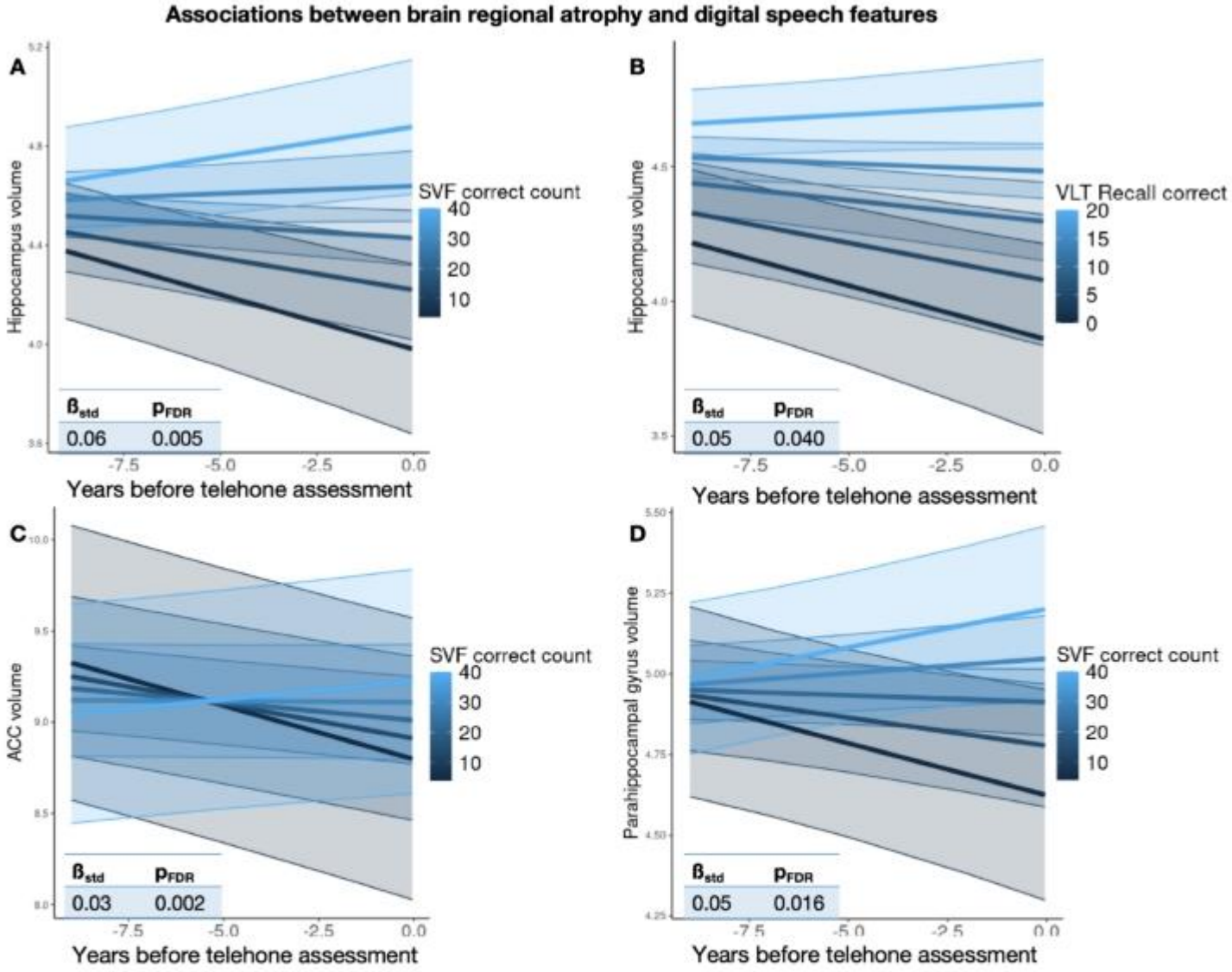

Figure 1 Longitudinal atrophy rates of brain regions before telephone assessment, depending on different digital speech features.

Predicted ROI volumes were derived from mixed-effects regression models, which included covariates for age, sex, years of education, diagnosis, and the interaction between time and digital speech features, with random intercepts and slopes to account for repeated measurements. The ribbons around the regression lines represented 95% confidence intervals (CI) for the predicted values, and the digital speech feature values were depicted on a continuous color bar.

A. A higher digital SVF correct count was associated with a slower atrophy rate in the bilateral hippocampus before the speech assessment
B. A higher digital VLT recall correct count was associated with a slower atrophy rate in the bilateral hippocampus before the speech assessment
C. A higher digital SVF correct count was associated with a slower atrophy rate in the bilateral anterior cingulate cortex before the speech assessment
D. A higher digital SVF correct count was associated with a slower atrophy rate in the bilateral parahippocampal gyrus before the speech assessment

Conclusions: Findings highlight the value of digital speech features for tracking longitudinal changes across the AD spectrum, enhancing their potential clinical utility beyond early diagnosis.

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SHIFT 02-327

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4 - 5 April

LEVERAGING REMOTE DIGITAL HEALTH TECHNOLOGIES FOR RAPID RECRUITMENT AND EFFECTIVE ASSESSMENT IN DECENTRALIZED CLINICAL TRIALS: AN MCI CASE STUDY

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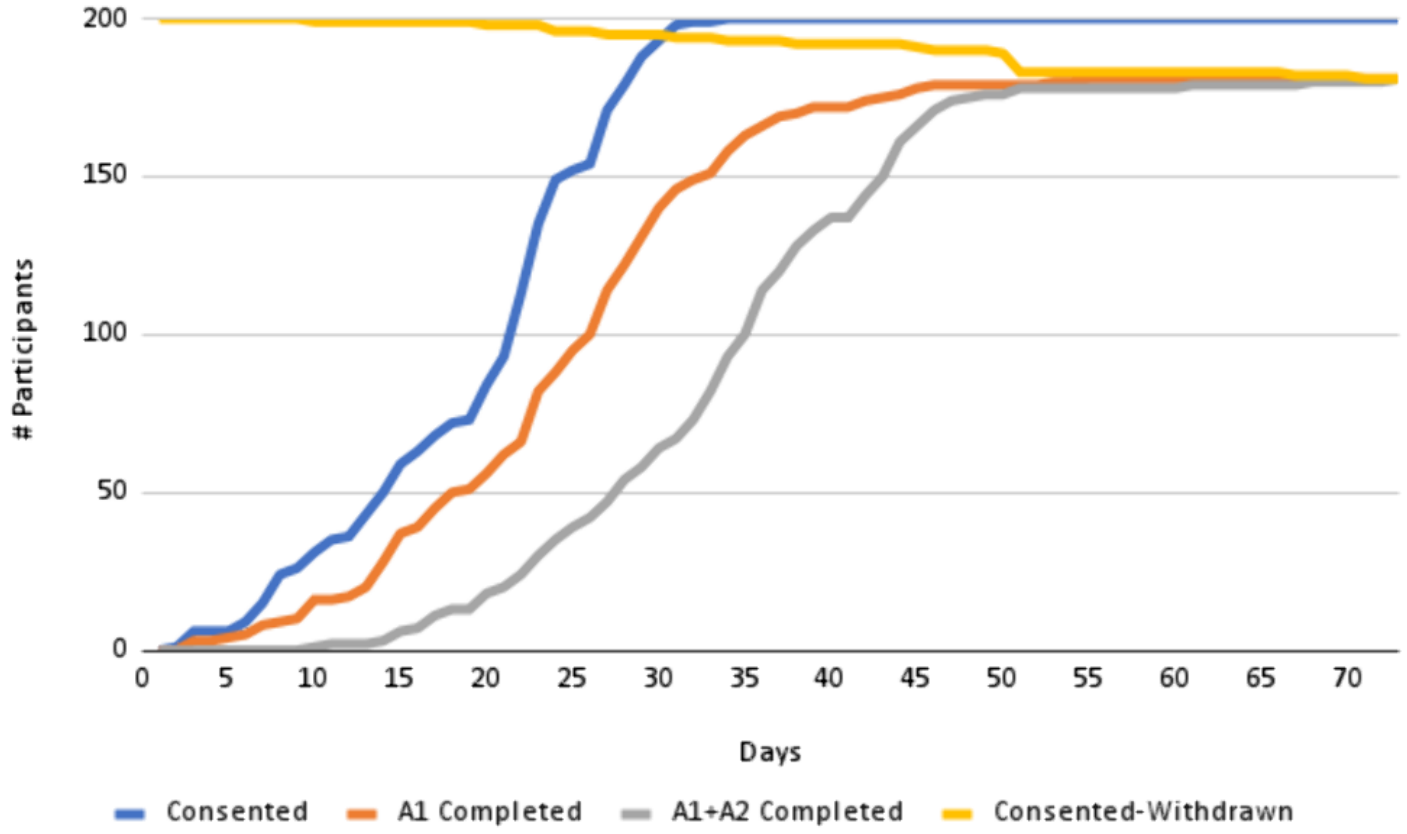
Aims: To demonstrate the feasibility of rapid recruitment and high retention using a remote assessment platform that collects multimodal digital biomarkers from participants.
Methods: Participant recruitment and retention are major bottlenecks in clinical trials, often leading to delays of >1-6 months and accounting for over 10% of the total drug development cost. 11% of sites fail to recruit a single participant and 37% of sites under-recruit, while only 30% of participants who sign up for a study actually complete it. Multimodal digital health technologies (DHTs) that can recruit and assess patients remotely offer an excellent solution to this problem. Therefore, we investigated how quickly we could recruit 200 participants to do two remote assessments of Mild Cognitive Impairment (MCI) using the Modality platform (each one week apart). Recruitment was done via the U.S. Department of Veterans Affairs (VA). First, the number of eligible MCI patients and healthy controls was obtained by querying the VA data warehouse. Second, recruitment emails were sent to all 7,231 potential MCI participants (up to four times) and age and sex matched healthy controls. Third, interested participants were sent a DocuSign consent form link via email. After consent, they were sent the link to their remote Modality assessment. Finally, they were sent reminders before their second assessments.
Results: 100 MCI patients and 100 healthy controls were recruited within 5 weeks of whom 181 completed both assessments, leading to a retention rate of over 90%.



Furthermore, speech and facial biomarkers extracted during the assessment effectively distinguished between MCI patients and healthy controls.

Conclusions: The use of remote DHTs such as Modality allow for rapid participant recruitment and high participant retention, with multimodal biomarkers serving as effective, sensitive endpoints for assessment.

SHIFT 02-340

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

PLASMA NFL, GFAP, AB40/42, PTAU181, AND PTAU217 FAIL TO DETECT LEWY BODY PATHOLOGY IN COGNITIVELY IMPAIRED INDIVIDUALS

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Aims: Differential diagnosis of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) remains a challenge, but is essential as care and treatment differ between these two pathologies. Approximately 20% of AD patients are thought to have biomarkers of DLB, and this co-pathology may lead to disease worsening or a reduced response to treatment. The aims of this study, conducted within the prospective, multicenter ALZAN cohort of patients consulting memory clinics, are: - To evaluate the prevalence of Lewy body pathology in this population using synuclein RT-QuIC in CSF. - To compare RT-QuIC-positive and RT-QuIC-negative patients in terms of plasma and CSF biomarkers.
Methods: Routine CSF analysis and plasma pTau217 were performed using Fujirebio Lumipulse assays. Plasma Aβ40/42, pTau181, NfL and GFAP analyses were performed using Elecsys Roche assays. Synuclein seed amplification assay (RT-QuIC) was performed on FLUOstar Omega using standard protocols and recombinant human synuclein produced in the laboratory.
Results: A total of 242 patients were included, with 17.8% testing positive for RT-QuIC. After adjusting for age, no significant differences were observed between RT-QuIC positive and negative patients in terms of CSF biomarkers (Aβ40/42, total tau, pTau181) or plasma biomarkers (Aβ40/42, pTau181, pTau217, NfL, GFAP). This finding remained consistent when patients were stratified based on the presence or absence of cerebral amyloidosis or according to their diagnosis (with or without AD).
Conclusions: The inability of plasma amyloid, tau, or neurodegeneration markers to detect Lewy body pathology confirms the crucial role of the CSF RT-QuIC approach. It also raises questions about the pathological processes associated with synuclein and highlights the need to identify new blood-based markers for this pathology.

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SHIFT 02-341

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

NOVEL CSF ASTROCYTE BIOMARKERS FOR ALZHEIMER'S DISEASE

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Aims: Astrocytes are highly involved in Alzheimer's disease (AD) pathophysiology. GFAP, an astrocyte-enriched protein, increases in response to amyloid (Aβ) pathology, but it does not fully reflect the astrocytic dynamics in response to the disease. Thus, we aimed to identify novel astrocyte biomarkers in CSF that contribute to the understanding of pathological changes in AD.
Methods: We analyzed CSF proteomic data of 663 individuals from the ADNI cohort (SomaLogic). A pre-defined list of 30 astrocyte-enriched genes was contrasted with the available ADNI CSF proteomic data, resulting in 7 proteins of interest (Fig.1). Spearman rank tested their correlations with AD fluid and imaging biomarkers (Fig.2a). Then, GPC5 and NCAN were selected for further investigation in cognitively unimpaired (CU) and impaired (CI) individuals who were also categorized according to their Aβ status (ptau181/Aβ42 ratio cut-off=0.028). Voxelwise models assessed associations between the selected proteins and [18F]AV45-PET in a subset of the individuals, and CU and CI individuals separately. Models also included age and sex, and RFT was used for multiple comparisons correction in the imaging analyses.
Results: CSF GPC5 and NCAN were significantly elevated in CI+ individuals compared to CI- (Fig.2b). GPC5 levels were also higher in CI+ compared to CU- individuals. Positive associations were observed between CSF GPC5, NCAN, and GFAP and [18F]AV45-PET, with GPC5 and GFAP showing more widespread associations in cortical gray matter than NCAN (Fig.2c). GPC5 and NCAN were associated with amyloid-PET in CI but not CU individuals (Fig.2d).
Conclusions: This study identified CSF GPC5 and NCAN as astrocyte biomarkers altered across the AD continuum and highlighted their association with brain Aβ deposition. Further validation will be performed in an external cohort.

A. List of astrocyte-enriched genes

Gene abbreviation	Gene name
NCAN	Neurocan
NTSR2	Neurotensin receptor 2
SLC7A10	Solute carrier family 7 member 10
ADGRV1	Adhesion G protein-coupled receptor V1
PSD2	Pleckstrin and Sec7 domain containing 2
SLC1A2	Solute carrier family 1 member 2
GABRG1	Gamma-aminobutyric acid type A receptor subunit gamma1
GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
MLC1	Modulator of VRAC current 1
ACSBG1	Acyl-CoA synthetase bubblegum family member 1
SLCO1C1	Solute carrier organic anion transporter family member 1C1
PHKA1	Phosphorylase kinase regulatory subunit alpha 1
BMPR1B	Bone morphogenetic protein receptor type 1B
CACHD1	Cache domain containing 1
COL5A3	Collagen type V alpha 3 chain
EYA1	EYA transcriptional coactivator and phosphatase 1
GLI3	GLI family zinc finger 3
GLIS3	GLIS family zinc finger 3
GPC5	Glypican 5
HPSE2	Heparanase 2 (inactive)
LRIG1	Leucine rich repeats and immunoglobulin like domains 1
NHSL1	NHS like 1
PAMR1	Peptidase domain containing associated with muscle regeneration 1
PIRT	Phosphoinositide interacting regulator of transient receptor potential channels
PRDM16	PR/SET domain 16
PRODH	Proline dehydrogenase 1
RANBP3L	RAN binding protein 3 like
RNF182	Ring finger protein 182
RYR3	Ryanodine receptor 3
ZNRF3	Zinc and ring finger 3

B. Venn diagram of overlapping genes from list of interest and proteins from ADNI dataset

C. List of CSF proteins investigated in this study

Protein abbreviation	Protein name
NCAN	Neurocan
PHKA1	Phosphorylase kinase regulatory subunit alpha 1
BMPR1B	Bone morphogenetic protein receptor type 1B
GPC5	Glypican 5
LRIG1	Leucine rich repeats and immunoglobulin like domains 1
PSD2	Pleckstrin and Sec7 domain containing 2
ZNRF3	Zinc and ring finger 3

Figure 1. List of astrocyte-enriched genes compiled for this study **(a)**. Venn diagram of overlapping genes from the astrocyte-enriched genes list and their respective proteins present in ADNI CSF proteomics data **(b)**. List of CSF proteins of interest investigated in this study **(c)**.

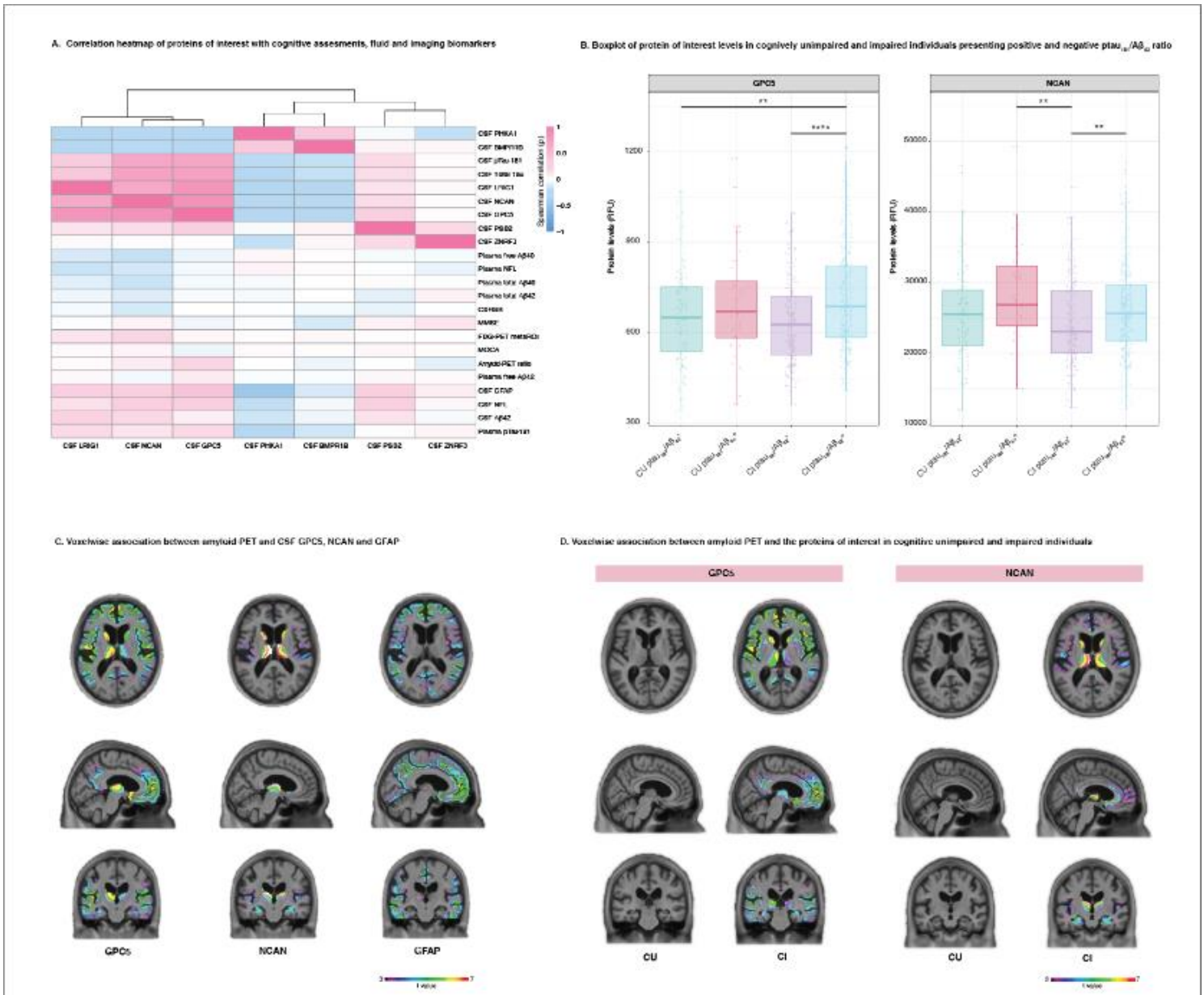

Figure 2: Correlation matrix displaying the positive and negative associations between the proteins of interest (NCAN, PHKA1, BMPR1B, GPC5, LRIG1, PSD2, ZNRF3) and themselves, fluid biomarkers (CSF GFAP, NFL, pTau-181, total tau, and Aβ42, and Plasma NFL, pTau 181, free Aβ40, total Aβ40, total Aβ42, and free Aβ42), imaging biomarkers ([18F]FDG-PET metaROI and [18F]AV45-PET cortical gray matter/cerebellum ratio), and cognitive assessments (CDRSB, MMSE, and MOCA) used for AD diagnosis **(a)**. Boxplot showing differences between cognitively unimpaired (CU) and impaired (CI) individuals, categorized by ptau181/Aβ42 ratio positivity **(b)**. Group differences were analyzed using ANCOVA and Tukey's method, and were adjusted for age and sex (*–p<0.05, **–p<0.01, ***–p<0.001, ****–p<0.0001, n = 663). Images showing voxelwise associations between [18F]AV45-PET and CSF GPC5, NCAN and GFAP (c, t-value>3.1, p<0.001, n = 421). Voxelwise association images, in CU (t-value>3.2, p<0.001, n = 96) and CI individuals (t-value>3.1, p<0.001, n = 325), between [18F]AV45-PET and CSF GPC5 and CSF NCAN **(d)**. The imaging models included age and sex as covariates and RFT was used to correct for multiple comparisons. Only gray matter associations are shown in the voxelwise results, and images are presented on top of the ADNI standard MRI image.

SHIFT 02-342

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

A COMPREHENSIVE HEAD-TO-HEAD CLINICAL AND ANALYTICAL VALIDATION OF TWO NOVEL PLASMA PTAU217 IMMUNOASSAYS IN A CLINICAL DIAGNOSTIC LABORATORY

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Aims: Plasma pTau 217 is a robust biomarker for AD diagnosis. We assessed the clinical and analytical performance of two novel laboratory-developed pTau217 immunoassays currently used for clinical testing: the ALZpath pTau217 and the Fujirebio pTau217 assays.
Methods: Plasma pTau217 levels were measured using ALZpath pTau217 assay on the Quanterix HD-X Simoa platform and LUMIPULSE plasma pTau217 on the Lumipulse G1200 platform. ALZpath and Lumipulse pTau 217 assays were validated based on CLSI guidelines at Neurocode USA & BC Neuroimmunology involving an analytical and clinical validation study using 1100 samples from a USA memory clinic with confirmed Amyloid PET, 400 samples of amyloid PET-negative healthy subjects aged 55 to 95 from the AIBL cohort, and 115 autopsy confirmed cases participants referred to the UBC Clinic for Alzheimer's Disease and Related Disorders.
Results: The plasma pTau217 concentrations ranged from 0.041 to 3.19 pg/mL for the Fujirebio and 0.11 to 3.50 pg/mL for the ALZpath. The intra-laboratory coefficient of variation for the Fujirebio assay, were 12.1%, 12.2%, and 5.3%, and for ALZpath assay were 10.4%, 10.4%, and 9.9%. Sample stability and interference were similar between assays. Moderate heterophilic antibody interference and reduced frozen sample stability at -20ºC observed for the Fujirebio assay. Both assays demonstrated excellent clinical performance for amyloid (ALZpath: AUC 0.95 and Fujirebio: AUC 0.94).
Conclusions: The analytical performance of the assays was comparable in the two labs. The reference range curve could be plotted with high certainty using the data from the 400 AIBL samples. The clinical separation between the healthy controls and those with Amyloid pathology was nearly complete for Alzpath with an AUC of 0.95. The Fujirebio assay had an AUC of 0.90. Similar data was obtained in the two labs.

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On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

BRAIN-DERIVED TAU AS A MARKER FOR ALZHEIMER'S DISEASE-RELATED NEURODEGENERATION IN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES

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Aims: Objectives: Blood-based assays of total tau-protein concentrations usually correlate poorly with cerebrospinal fluid (CSF) tau concentrations. In contrast, the novel blood-based brain-derived tau (BD-tau) correlates well with CSF tau and is a promising biomarker for the intensity of Alzheimer's disease (AD) neurodegeneration. Alzheimer pathology is common in dementia with Lewy bodies (DLB) and has important clinical impact. We wanted to determine, for the first time, the serum concentration of BD-tau in DLB.
Methods: Methods: 90 patients with AD and 56 patients with DLB were included from the longitudinal DemWest cohort study. Controls were cognitively normal individuals without AD pathology (CSF profile A – T – N –) from the Dementia Disease Initiation cohort. Serum samples were analyzed on a Simoa HD-X platform with an in-house assay at Sahlgrenska University Hospital. As BD-tau concentrations were not normally distributed, non-parametric statistical tests were used (Mann-Whitney, Kruskal-Wallis).
Results: Results: BD-tau values were significantly higher in AD (mean 0.293 pg/ml, median 0.26 pg/ml, SD 0.147, interquartile range 0.16 pg/ml) and DLB (mean 0.297 pg/ml, median 0.26 pg/ml, SD 0.148, interquartile range 0.20 pg/ml) than healthy controls (0.206 pg/ml, median 0.19 pg/ml, SD 0.052, interquartile range 0.06 pg/ml) ($p < 0.001$), however concentrations were similar In AD and DLB ($p=0.64$).
Conclusions: Conclusions: Future analyses of the correlation between BD-tau and p-tau217 in this cohort and analyses of the available autopsy material from DemWest might clarify if our findings of similar BD-tau concentrations in AD and DLB is caused by comorbid AD pathology or reflect non-AD neurodegeneration in DLB. Further, we will explore the effect of BD-tau on cognitive decline in AD and DLB, and these results will be presented at the conference.

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SHIFT 02-344

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

SINGLE-CENTER REAL-WORLD PERFORMANCE OF BLOOD BIOMARKERS OF ALZHEIMER'S DISEASE AT DIFFERENT CUT-OFFS

Federico Emanuele Pozzi[1], Elisa Conti[2], Chiara Paola Zoia[2], Giulia Remoli[1], Nicolò Dell'Orto[2], Simona Andreoni[2], Fulvio Da Re[1], Gessica Sala[2], Luca Cuffaro[1], Carlo Ferrarese[1], Ildebrando Appollonio[1], Lucio Tremolizzo[1]
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Aims: The new Alzheimer's disease (AD) criteria allow the use of core blood-base biomarkers (BBAD) in clinical practice, provided they show sufficient accuracy and robustness in the intended population. Recent consensus recommended a two cut-off approach for BBAD for ruling in and out AD pathology. We sought to assess the performance of BBAD in predicting amyloid positivity in a clinical setting.
Methods: We retrospectively analyzed data from 102 consecutive patients undergoing a lumbar puncture for cognitive impairment at our memory clinic in the last three years. Core AD biomarkers were measured in CSF, and Aβ42/Aβ40, pTau217, pTau181, and NfL (Lumipulse®) were analyzed in plasma. Amyloid positivity (A+), as defined with CSF Aβ42/Aβ40<0.069, was 67%. Logistic regression and Receiver Operating Characteristic (ROC) analysis were used to assess biomarker performance. Sensitivity, specificity, positive (PPV), and negative predictive values (NPV) were calculated at different cut-offs.
Results: Plasma pTau217 demonstrated the highest accuracy (AUC=0.91), followed by pTau181 (AUC=0.87) and Aβ42/40 (AUC=0.80). pTau217 and pTau181 performance proved robust up to a coefficient of variation of 0.20, contrary to Aβ42/40 (Figure 1). Using the Youden's index cut-off, pTau217 showed NPV=0.97 and PPV=0.74 (Table 1). A 95%-specificity cut-off resulted in high PPVs (0.97 and 0.96 for pTau217 and pTau181, respectively), while the 95%-sensitivity cut-off showed sub-optimal NPV (Figure 2). Sensitivity analyses using CSF Aβ42/pTau ratio to define AD pathology confirmed the results.

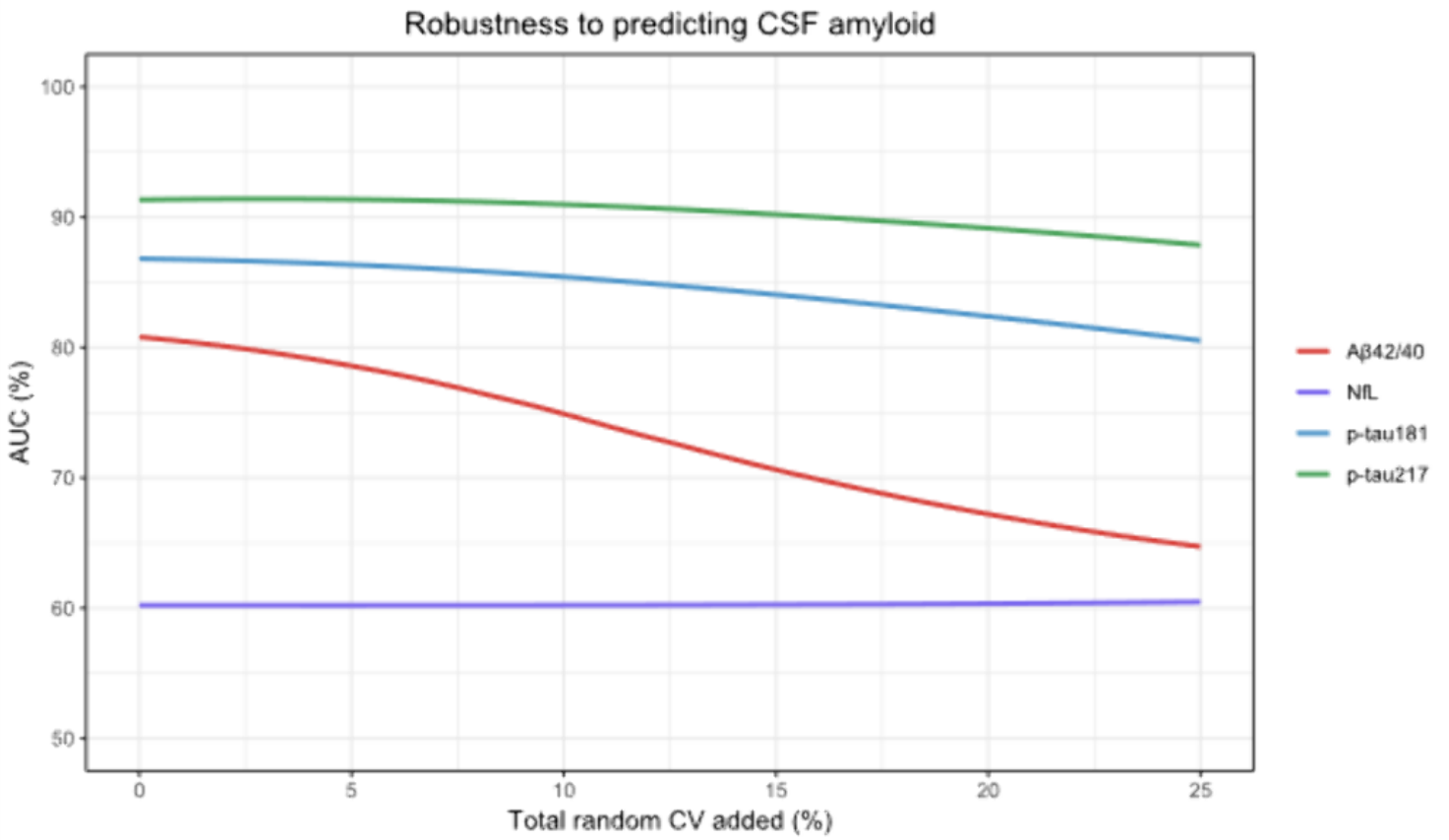
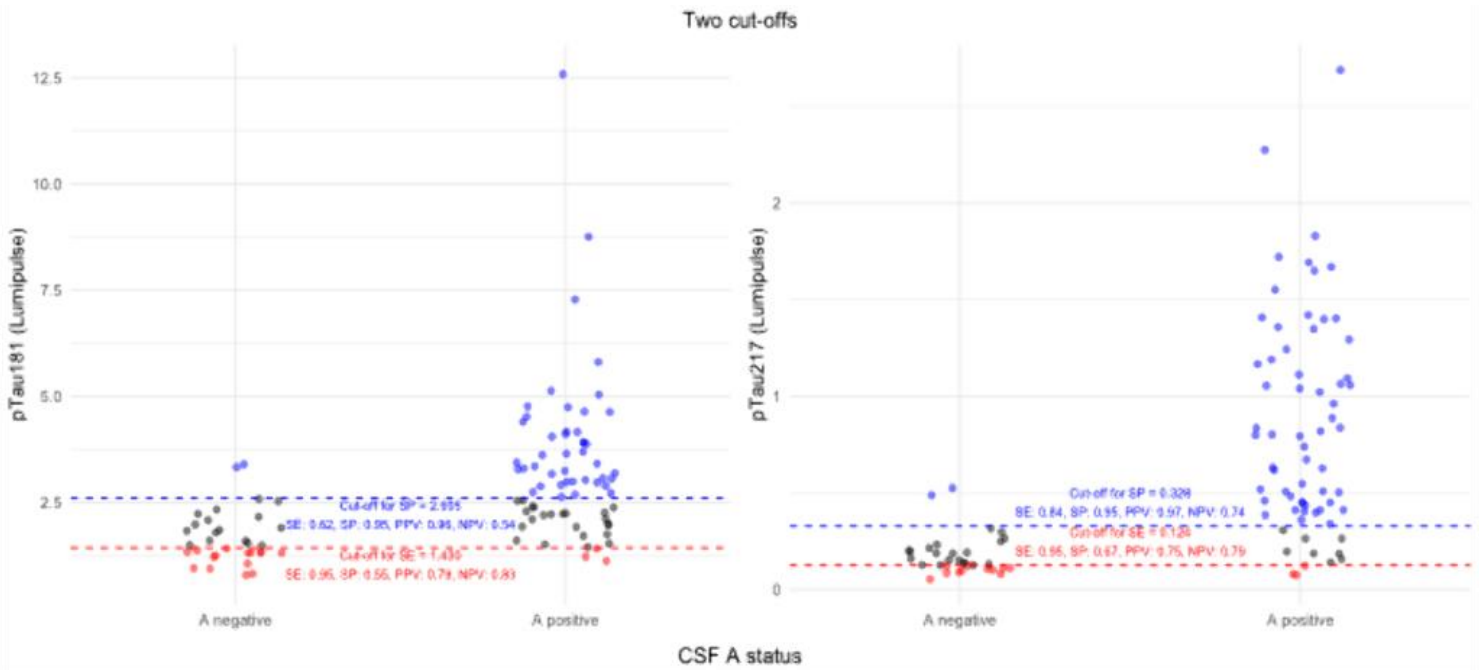


Table 1. Logistic model and diagnostic performances of BBAD to predict amyloid pathology.

BBAD	St. coefficient	p	Cut-off (pg/ml)	AUC [95% CI]	SE	SP	PPV	NPV
Aβ42	-1.37	<0.001	30.836	0.781 [0.684, 0.877]	0.881	0.576	0.81	0.68
Aβ40	-0.44	0,072	195.978	0.602 [0.486, 0.717]	0.224	1.000	1.00	0.38
pTau181	3.16	<0.001	2.180	0.869 [0.796, 0.942]	0.791	0.818	0.90	0.64
pTau217	5.37	<0.001	0.327	0.911 [0.853, 0.969]	0.836	0.939	0.97	0.74
Aβ42/40	-0.01	0.947	0.081	0.802 [0.713, 0.892]	0.746	0.818	0.89	0.61
NfL	-0.42	0.065	44.840	0.609 [0.484, 0.734]	0.866	0.424	0.75	0.61



Conclusions: Lumipulse® plasma pTau217 is a robust and accurate BBAD for detecting amyloid pathology in a memory clinic setting. The high prevalence of A+ in our cohort results in higher PPV than NPV, making pTau217 more useful for ruling-in pathology.

SHIFT 02-345

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

EVALUATING FUTURE IVD PLASMA P-TAU181 AND APOE4 IMMUNOASSAYS FOR RULE OUT OF AMYLOID PATHOLOGY IN A MULTI-CENTER STUDY REFLECTIVE OF ROUTINE CLINICAL PRACTICE

Imke Kirste[1], Sayuri Hortsch[2], Sheila Baez-Torres[3], Mercè Boada[4], Monica Crane[5], Kristian Frederiksen[6], Kevin Hanson[7], Jonathan Liss[8], Jeffrey Norton[9], Marc Suárez-Calvet[10], Craig Ritchie[11], Stephanie Rutrick[12], David Watson[13], Kelley Yokum[14], Clara Quijano-Rubio[1]
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Aims: Early detection of amyloid pathology using blood-based biomarkers have emerged as powerful tools in the AD patient journey. This study investigates the clinical performance of plasma pTau181 in combination with plasma ApoE4 as a potential IVD to detect amyloid pathology from a broad population as seen in routine clinical practice.
Methods: In this prospective multicenter study, we enrolled 604 patients aged 55-80 with SCD, MCI, or mild dementia being evaluated for AD or other causes of cognitive decline. Plasma samples from eligible patients were analyzed using Elecsys® pTau181 and ApoE4 plasma assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The discriminative ability of pTau181 alone, or in combination with ApoE4 with respect to amyloid PET visual read status and to CSF ratio of the Elecsys Phospho-Tau (181P) and Elecsys Amyloid (1-42) II CSF was evaluated.
Results: The study population was heterogeneous regarding sex, race, and comorbidities, reflective of a real-world setting. The AUC of a combination of pTau181 and ApoE4 was 0.896, while for pTau181 alone was 0.873. Based on an amyloid positivity prevalence of 23.0% (based on amyloid PET), the negative predictive value (NPV) was 96.5%, paired with a positive predictive value of 49.8% (sensitivity: 91.3%, specificity: 72.5%). The performance was only minimally impacted by age, sex, body mass index or impaired kidney function. The rule-out performance of pTau181 alone was similar (NPV: 97.3%, PPV: 43.5%). However, the combination with ApoE4 made the clinical performance more robust towards analytical variability.
Conclusions: The observed clinical performance in this study highlights the potential of plasma pTau181 with the combination of ApoE4 as robust and accurate tools for ruling out individuals with a low likelihood of amyloid pathology in the early stages of the AD continuum.

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SHIFT 02-346

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

N-GLYCANS – EARLY PROGNOSTIC BIOMARKERS FOR COGNITIVE DECLINE IN ALZHEIMER DISEASE

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Aims: Several biomarkers for amyloid and p-Tau (A and T status) can be used for detecting Alzheimer disease (AD). Still, biomarkers that can predict cognitive decline and classify AD subgroups are needed. N-glycans decorate most AD-related proteins. We have shown that N-glycans containing bisecting GlcNAc are increased in CSF in AD and correlate with t-Tau and p-Tau. Here, we investigated how protein glycosylation relates to disease stage, A and T status, and cognitive decline.
Methods: N-glycans containing bisecting GlcNAc were quantified in several clinical and population-based cross-sectional and longitudinal cohorts by a sensitive multiwell-plate assay. For detailed structural information, we optimized a glycomics approach enabling high throughput analysis for simultaneous identification and quantification of over 60 N-glycans in blood. Briefly, glycans from each sample were enzymatically released, purified and injected onto an Orbitrap LC-MS/MS system. The N-glycans were quantified from MS peaks and identified based on MS/MS fragments and retention time.
Results: Increased bisecting GlcNAc in CSF predicted faster cognitive decline already before A and T positivity could be detected. A longitudinal population-based study showed that baseline Tau/bisecting GlcNAc ratio in blood combined with MMSE and ApoE4 status could predict dementia within an 18-years follow-up period with 80% sensitivity and specificity. Using the LC-MS/MS glycomics method, we showed that low blood levels of a group of 14 N-glycans were associated with clinical AD and cognitive decline. Moreover, in early stages of the disease, low levels of the same group of N-glycans was associated with future cognitive decline.
Conclusions: N-glycan analysis in CSF and blood are valuable complements to existing diagnostic methods for AD, especially for predicting cognitive decline at very early stages of the disease. Such analysis may be used for subgrouping of disease.

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SHIFT 02-347

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

ATOMIC FORCE MICROSCOPY REVEALS DISTINCT PROTEIN AGGREGATION PATTERNS IN CSF IN ALZHEIMER'S DISEASE

Thomas Schneider[1], Lily Henry[2], Justus Bürgi[3], Peter Nirmalraj[2], Ansgar Felbecker[1]
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Aims: Atomic force microscopy (AFM) can resolve and quantify protein aggregates in cerebrospinal fluid (CSF). We previously identified an inverse correlation between CSF fibril length and the amyloid beta (Aβ) 42/40 ratio. This study expands the analysis to investigate Alzheimer's disease (AD)-specific protein morphologies in a larger memory clinic cohort.
Methods: We applied liquid-based AFM to measure fibril length, diameter, and sphere size in CSF samples from 100 patients grouped by cognitive status (SCD: subjective cognitive decline, MCI: mild cognitive impairment, and D: dementia) and amyloid pathology (A−/A+). The groups were SCD/other A− (n = 20), MCI/D A− (n = 36), MCI A+ (n = 14), and D A+ (n = 30). Statistical comparisons were conducted using Kruskal-Wallis and Dunn's post-hoc tests, while linear regression assessed correlations with the Aβ 42/40 ratio and p-tau levels.
Results: Spherical proteins were highly prevalent in amyloid-negative patients (SCD/other A−: 95.0%, MCI/D A−: 97.2%) but less frequent in amyloid-positive patients (MCI A+: 57.1%, D A+: 83.3%). Spheres were larger in amyloid-negative patients ($p < 0.001$). Protofibrils were also more common in amyloid-negative patients (SCD/other A−: 45.0%, MCI/D A−: 63.9%) compared to amyloid-positive (MCI A+: 7.1%, D A+: 16.7%). Fibrils were rare in amyloid-negative groups but longer and more prevalent in amyloid-positive patients ($p < 0.001$). Fibril length inversely correlated with the Aβ 42/40 ratio ($r = −0.657$), while sphere size showed a positive correlation ($r = 0.571$).
Conclusions: AFM identified distinct protein aggregate patterns in AD, with longer fibrils and smaller spheres in amyloid-positive patients. These findings suggest that protein morphologies could be used as biomarkers for AD diagnosis.

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On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

ESTABLISHING DIAGNOSTIC CUTOFFS AND EVALUATING PERFORMANCE OF PLASMA P-TAU217 IMMUNOASSAYS

Joel Simren[1,2], Nicholas Ashton[1,3,4], Burak Arslan[1], Hanna Huber[1], Lana Grötschel[1], Anna Dittrich[5], Shorena Janelidze[6], Erik Stomrud[7,8], Niklas Mattsson-Carlgren[7,9,10], Sebastian Palmqvist[7,8], Henrik Zetterberg[1,2,11,12,13,14], Silke Kern[5,15], Oskar Hansson[8,16], Kaj Blennow[1,2,17,18]
[1]Institute of Neuroscience and Physiology, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [2]Clinical neurochemistry laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [3]Banner Alzheimer's Institute and University of Arizona, Phoenix, United States of America, [4]Banner Sun Health Research Institute, Sun City, United States of America, [5]University of Gothenburg, Neuropsychiatric Epidemiology Unit, Department Of Psychiatry And Neurochemistry, Sahlgrenska Academy, Gothenburg, Sweden, [6]Lund University, Department Of Clinical Sciences Malmö, Clinical Memory Research Unit, Lund, Sweden, [7]Clinical Memory Research Unit, Lund University, Department Of Clinical Sciences Malmo,, Lund, Sweden, [8]Skåne University Hospital, Memory Clinic, Malmö, Malmö, Sweden, [9]Skåne University Hospital, Department Of Neurology, Lund, Sweden, [10]Lund University, Wallenberg Center For Molecular Medicine, Lund, Sweden, [11]UCL Institute of Neurology Queen Square, Department Of Neurodegenerative Disease, London, United Kingdom, [12]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong PRC, [13]University of Wisconsin - Madison, Wisconsin Alzheimer's Disease Research Center And Department Of Medicine, School Of Medicine And Public Health, Madison, United States of America, [14]UK Dementia Research Institute at UCL, London, United Kingdom, [15]Department of Neuropsychiatry, Sahlgrenska University Hospital, Region Västra Götaland, Sweden, [16]Clinical Memory Research Unit, Department Of Clinical Sciences, Malmö, Sweden, [17]Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France, [18]Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC, Neurodegenerative Disorder Research Center, Division Of Life Sciences And Medicine, And Department Of Neurology, Hefei, China

Aims: Establishing cutoffs remains a challenge for clinical implementation of plasma phosphorylated tau 217 (p-tau217). This study aimed to establish and validate cutoffs for p-tau217 immunoassays.
Methods: We included Aβ-positive and -negative individuals with subjective cognitive decline, mild cognitive impairment, and dementia from the Swedish H70 and BioFINDER cohorts. Cerebrospinal fluid Aβ42/40<0.072 on the Lumipulse platform defined Aβ-positivity (reference). Plasma p-tau217 was measured using Lumipulse and MesoScale Discovery (MSD) kits. In H70, Aβ-positivity cutoffs were determined using two approaches: 1) a single cutoff with 90% specificity (1-cutoff) and 2) a dual cutoff with 95% sensitivity and specificity, generating an intermediate range (2-cutoff). These cutoffs were tested in BioFINDER, with performance evaluated by positive predictive value (PPV), negative predictive value (NPV), and accuracy.
Results: We included 165 individuals in H70 and 299 in BioFINDER (51% and 46% females), with median (IQR) ages of 67 (61-72) and 75 (69-79) years, respectively. Aβ-positivity prevalence was 62% in H70 and 54% in BioFINDER. The 1-cutoff method (with 90% specificity) in H70 gave 94% PPV, 81% NPV, and 88% accuracy for both assays. When applied in BioFINDER, Lumipulse had 85% PPV, 86% NPV, and 85% accuracy; MSD showed 82% PPV, 94% NPV, and 86% accuracy. Using the 2-cutoff

method (95% sensitivity and specificity), excluding intermediates, Lumipulse and MSD demonstrated 96% PPV, 92% NPV, and 94% accuracy in H70 (18% and 15% intermediates). In BioFINDER, Lumipulse showed 92% PPV, 94% NPV, and 93% accuracy (24% intermediate); MSD had 82% PPV, 98% NPV, and 90% accuracy (20% intermediate).

Conclusions: We established accurate cutoffs for two p-tau217 assays, supporting their clinical use. The 2-cutoff approach provided high NPVs, aiding in the exclusion of Alzheimer's disease. Further assays will be included for ADPD.

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On-Demand Oral Poster on Board - Shift 02
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4 - 5 April

HIGH-THROUGHPUT, FULLY AUTOMATED IMMUNOASSAY FOR DETECTING ZYGOSITY OF APOLIPOPROTEIN E4 (APOE E4) IN EDTA PLASMA

Brian Engel, Miklos Szabo, Katie Hoffmann, Ben Schlichtmann, Kara Curtis, Laura Mediger, Corey Carlson, James Mendoza, Mikaela Nichkova-Doseva
Beckman Coulter, Inc, Chaska, United States of America

Aims: Apolipoprotein E (APOE) and its isoforms (APOE2/3/4) shuttle lipids between cellular compartments and organs. The APOE4 isoform is associated with increased risk of Alzheimer's disease (AD), with higher risk for homozygous APOE $\varepsilon4^{+/+}$ individuals. Availability of high-throughput assays to determine APOE ε4 zygosity would enable reliable and widespread use by researchers. We describe the performance of a prototype high-throughput APOE ε4 zygosity assay on the DxI 9000 and Access 2 Immunoassay Analyzers.
Methods: The prototype APOE ε4 assay is a multiplex of 2 two-step sandwich assays using paramagnetic particles coated with anti-PanAPOE monoclonal antibody (MAb) APOE and complementary anti-PanAPOE MAb/alkaline phosphatase conjugate or anti-APOE4 MAb/alkaline phosphatase conjugate. Sample and reactants are incubated and washed, then a chemiluminescent substrate is added. The light generated is processed through an algorithm that indicates the APOE ε4 zygosity of the sample. EDTA plasma samples were evaluated for imprecision and interferences (n=43), as well as concordance with PCR genotyping and a commercially available research-use only (RUO) APOE ε4 immunoassay (n=300).
Results: The prototype APOE ε4 assay demonstrated intra-assay coefficient of variation of ≤9% on both analyzers. Cross-reactivity of the APOE4-specific assay to APOE2 and APOE3 isoforms was negligible. Minimal interference was observed from other AD biomarkers, AD drugs, and endogenous interferents. Comparison of the DxI 9000 and Access 2 analyzer prototype assays against a commercially available APOE ε4 RUO assay had correlations of r=0.95 and 0.90 (n=43), respectively. Concordance with PCR genotype data was 99.3% (n=300).
Conclusions: This prototype RUO APOE ε4 assay currently in development provided fast and precise results in an automated immunoassay on the Beckman Coulter DxI 9000 and Access analyzers. The assay had excellent concordance with PCR genotyping and a commercially available RUO immunoassay.

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4 - 5 April

THE ISSUE OF PLASMA BIOMARKER CUTOFF VALUES IN ALZHEIMER'S DISEASE: A MACHINE LEARNING AND CLUSTERING APPROACH

Edoardo Guido Torrigiani[1], Giovanni Bellomo[2], Lorenzo Gaetani[2], Davide Cianca[3], Igor Neri[4], Luca Gammaitoni[4], Lucilla Parnetti[2]
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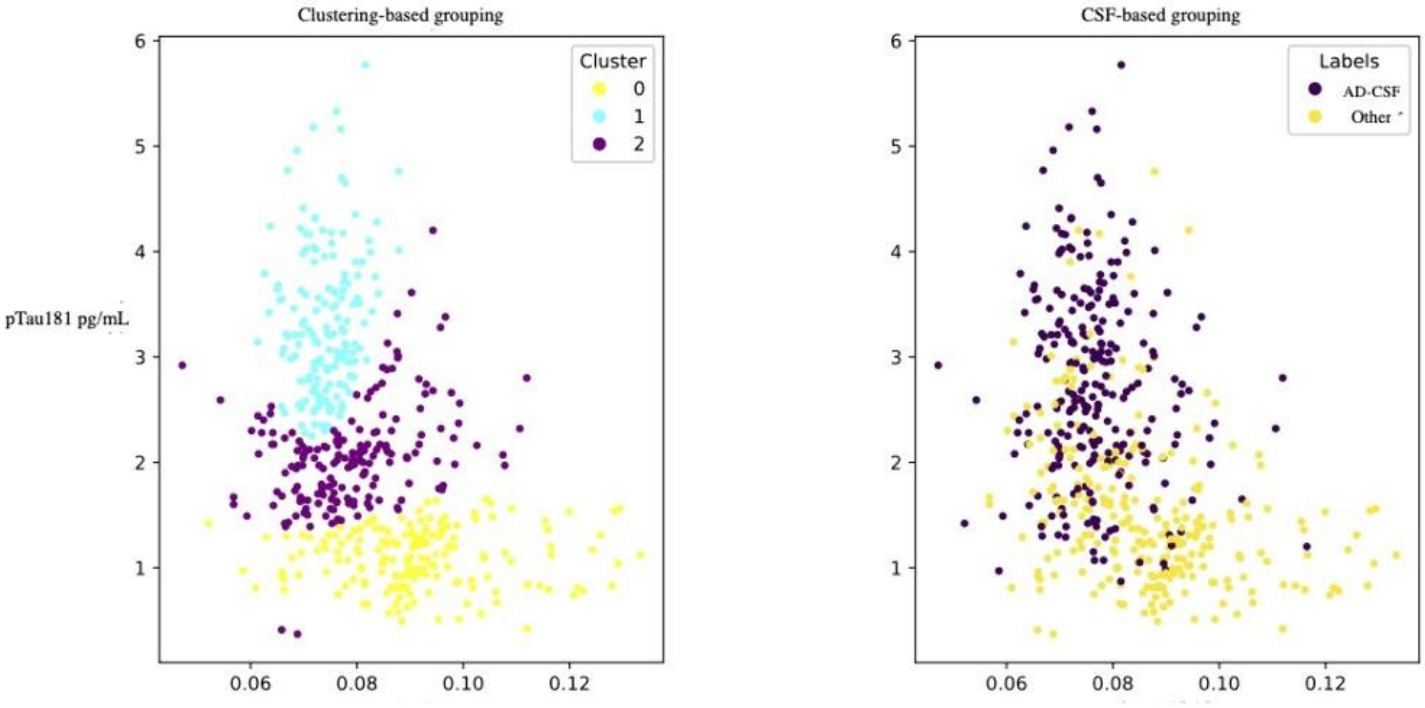
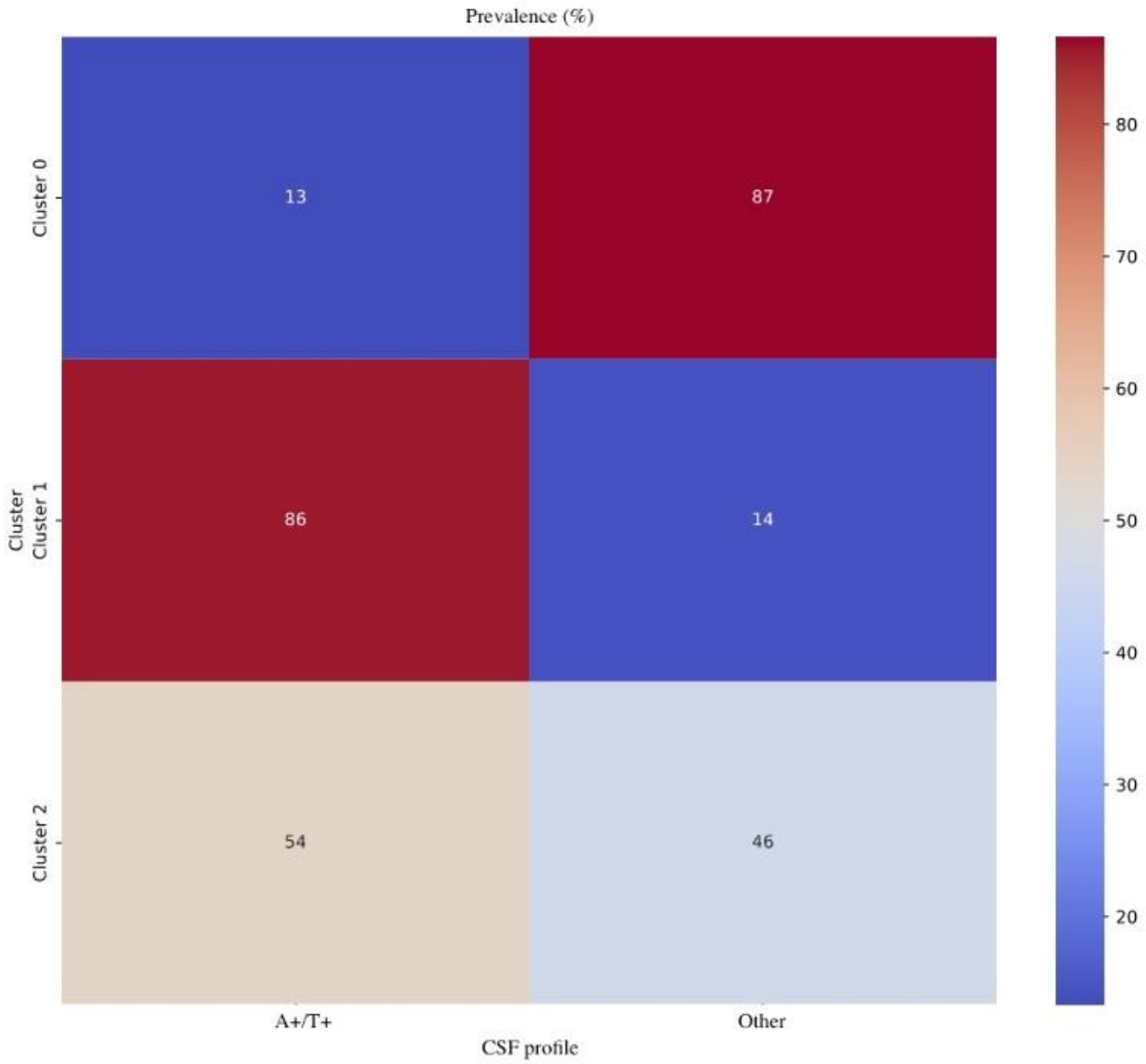
Aims: To develop an algorithm to determine cutoff values of plasma biomarkers in the absence of CSF biomarker profiles and evaluate their concordance with CSF AD profile
Methods: 579 consecutive patients with heterogeneous neurological conditions from the Neurology Section of the University of Perugia were included. Each patient underwent lumbar puncture, blood sampling and neuropsychological evaluation. Plasma and CSF Aß42/40 and pTau181 values were measured with a fully automated CLEIA platform. A Gaussian mixture model (GMM) coupled with ROC analysis was used to determine cutoff values of plasma Aß42/40 and pTau181. Cutoff values and clustering results' concordance with CSF profile was then evaluated. Machine learning algorithms, including support vector machines (SVM) and XGBoost, were also tested as an alternative classification system.
Results: GMM identified three clusters (C0, C1, C2) based on plasma biomarkers. C2 showed an equal prevalence of patients with an A+/T+ CSF profile and controls. C1 reflected an A+/T+ CSF profile, and C0 other CSF profiles, with an accuracy of ~85% with respect to clinical diagnosis of AD, which showed a ~30% disagreement to CSF-assisted diagnosis. The application of SVM and XGBoost showed a good classification accuracy (~80%).


Clustering-based grouping
CSF-based grouping
Cluster
0
1
2
Labels
AD-CSF
Other
pTau181 pg/mL
Plasma Aβ42/40
1
2
3
4
5
6
0.06
0.08
0.10
0.12



Conclusions: The clustering-based algorithm reliably determines cutoffs of plasma biomarkers, aligning with CSF-based values. The presence of three clusters aligns with evidence in favor of a two folded cutoff for plasma biomarkers' use in clinical settings where CSF analysis is scarcely available. As a proof of concept, the analysis was conducted for plasma Aß42/40 and pTau181, but it can be extended to other biomarkers. Machine learning-based classification with SVM and XGBoost, as an alternative to "traditional" ROC analysis, can guarantee a good diagnostic accuracy.

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4 - 5 April

AN IMPROVED, PLATE-BASED ULTRASENSITIVE IMMUNOASSAY THAT QUANTIFIES SOLUBLE AB OLIGOMERS IN HUMAN CSF, PLASMA, AND BRAIN

Ting Yang[1], Yi Ran Xu[1], Shanxue Jin[1], Nagendran Ramalingam[1], Jean-Pierre Bellier[1], Lei Liu[1], Hyun-Sik Yang[2], Jasmeer Chhatwal[2], Trebor Lawton[3], Dennis Selkoe[1]
[1]Brigham and Women's Hospital and Harvard Medical School, Ann Romney Center For Neurologic Diseases, Boston, United States of America, [2]Massachusetts General and Brigham & Women's Hospitals, Harvard Medical School, Department Of Neurology, Boston, United States of America, [3]Abyssinia Biologics, Inc., Durham, United States of America

Aims: Soluble amyloid β-protein oligomers (oAβ) may produce synaptic dysfunction and microglial inflammation in Alzheimer's disease (AD). However, very few immunoassays are reported to detect and quantify this hydrophobic, aggregation-prone analyte in CSF and plasma. Here, we evaluate the ability of the oAβ-preferring antibody 71A1 to detect these species in an optimized assay platform and correlate their levels with certain AD biomarkers.
Methods: We improved our initial oAβ immunoassay (Liu *et al*, *Alz Dem,* 2021) by transitioning from a bead-based to a plate-based format. The assay uses the 71A1 monoclonal raised to a cyclized mid-domain Aβ dimeric peptide for capture and the Asp1-specific N-terminal monoclonal 3D6 for detection. Numerous technical steps led to a well-validated assay.
Results: By surface plasmon resonance, 71A1 had a K_D of 49.5 ± 34.5 nM on synthetic Aβ dimers and no detectable binding to monomers. 71A1 effectively immunopurified neuroactive oAβ species from aqueous AD brain extracts that potently inhibited hippocampal synaptic plasticity. The 71A1/3D6 assay exhibited good reproducibility, oligomer specificity, and dilution linearity, with minimal matrix effects impacting analyte detection in human CSF and plasma. Analysis of >100 CSFs from cognitively impaired patients with positive AD biomarkers revealed a weak, insignificant correlation between oAβ and Aβ42 monomer levels but highly significant correlations with p-tau ($r=0.68$, $p<0.0001$) and t-tau ($r=0.65$, $p<0.0001$) levels.
Conclusions: This plate-based assay provides reliable measurements of oligomeric Aβ species in human biofluids and soluble brain extracts with high throughput and low cost. The approach is suitable for clinical studies tracking this critical pathogenic analyte in CSF and plasma. Its oAβ-neutralizing activity suggests 71A1 as a potential therapeutic candidate, and a current treatment trial in APP NL-G-F knock-in mice will be reviewed.

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4 - 5 April

COMPARISON OF CEREBROSPINAL FLUID PTAU, PTAU/AB38, AB42/40, AND AB42/38 IN PREDICTING AMYLOID-PET POSITIVITY

Yansheng Zheng[1], Joseph Therriault[1], Arthur Macedo[1], Yi-Ting Wang[1], Nesrine Rahmouni[1], Brandon Hall[1], Seyyed Ali Hosseini[1], Stijn Servaes[1], Etienne Aumont[1], Gleb Bezgin[1], Tevy Chan[1], Jenna Stevenson[1], Jaime Fernandez-Arias[1], Lydia Trudel[1], Kely Quispialaya-Socualaya[1], Lujia Wan[1], Thomas Karikari[2], Tharick Pascoal[3], Andrea Benedet[4], Nicholas Ashton[5], Kaj Blennow[6], Henrik Zetterberg[5], Paolo Vitali[1], Gerhard Multhaup[7], Pedro Rosa-Neto[1], Serge Gauthier[8]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]Department of Psychiatr, University of Pittsburgh, Pittsburgh, United States of America, [3]University of Pittsburgh, Pittsburgh, United States of America, [4]University of Gothenburg, Gothenburg, Sweden, [5]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, [6]Gothenburg University, Göteborg, Sweden, [7]Mcgill University, Pharmacology And Therapeutics, Montreal, Canada, [8]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: This study compares the ability of CSF ptau181, 217, and 231/Aβ38 ratios to predict amyloid-PET positivity with CSF ptau (181, 217 and 231), CSF Aβ42/40 and Aβ42/38.
Methods: A total of 291 individuals from the translational biomarkers in aging and dementia (TRIAD) cohort were recruited, including 31 young, 137 cognitively unimpaired (CU), 64 with mild cognitive impairment (MCI), 39 with AD, and 20 with non-AD dementia. CSF Aβ38, Aβ40, Aβ42, ptau181, ptau217, and ptau231 were quantified using an in-house nucleic acid linked Immuno-sandwich assay (NULISA). Amyloid-β was indexed by positron emission tomography (PET) using 18F-AZD-4694. Spearman's rank correlation was used to assess the relationships between CSF ptau (181, 217, and 231), ptau (181, 217, and 231)/Aβ38 ratios and CSF Aβ42/40, Aβ42/38, as well as their correlation with neocortical 18F-AZD-4694 standardized uptake value ratio (SUVR). Receiver operating characteristic (ROC) curves evaluated the ability of these biomarkers to predict Aβ positivity.
Results: CSF ptau181/Aβ38, ptau217/Aβ38, ptau231/Aβ38 levels were negatively correlated with CSF Aβ42/40 levels (Fig1), as well as CSF Aβ42/38 levels (Fig1), and CSF ptau181, 217, and 231(Fig2). CSF ptau181/Aβ38, ptau217/Aβ38, ptau231/Aβ38 levels were positively correlated with amyloid-PET (Fig3), as well as CSF ptau181, 217 and 231 (Fig4), while CSF 42/40 and Aβ42/38 were negatively correlated (Fig3). Furthermore, CSF ptau181/Aβ38, ptau217/Aβ38, ptau231/Aβ38 showed superior ability in predicting amyloid-PET positivity compared to Aβ42/40 and Aβ42/38 (Fig5). However, identical prediction could be found in CSF ptau181, 217 and 231 (Fig6).

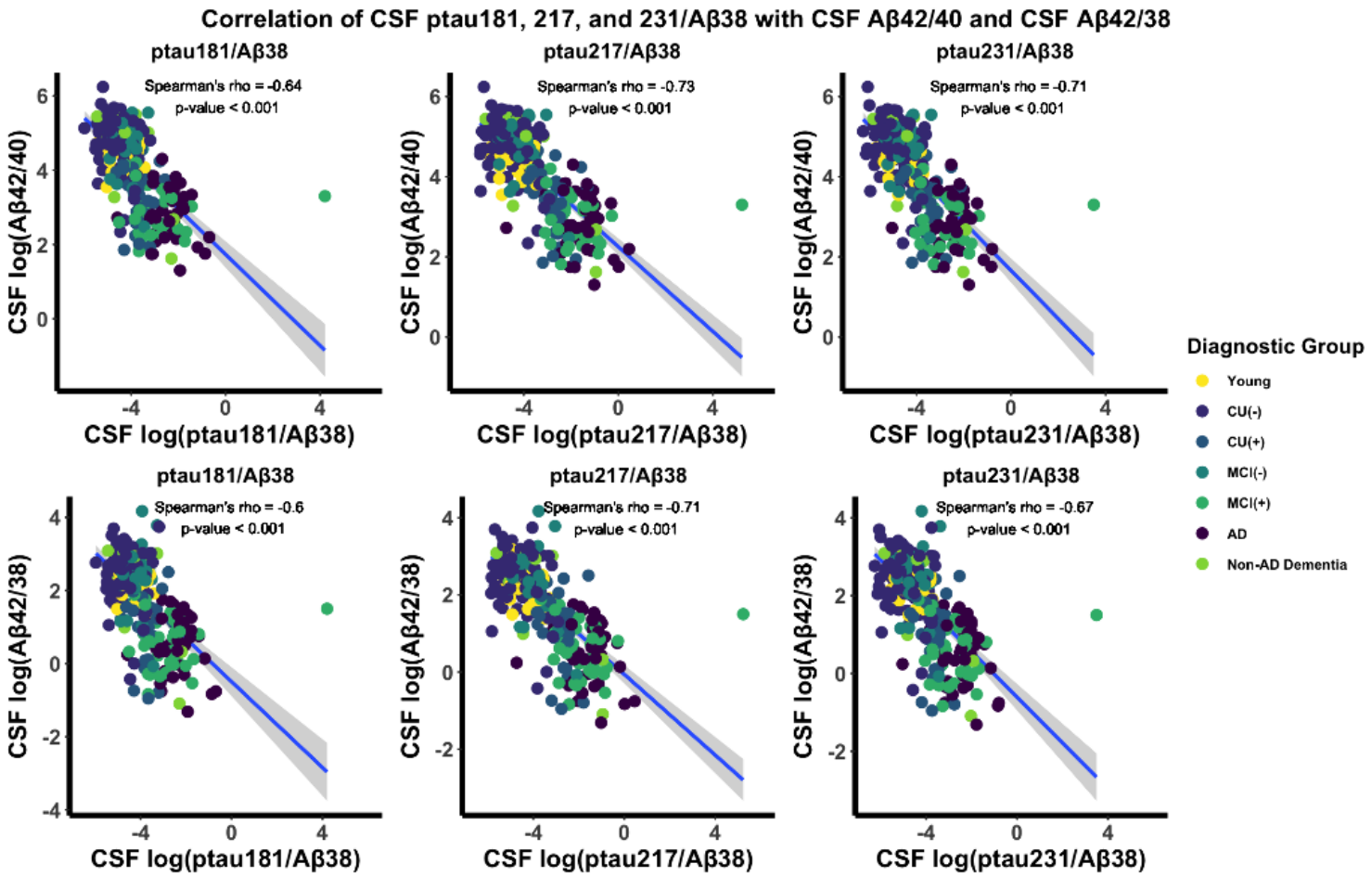
Correlation of CSF ptau181, 217, and 231/Aβ38 with CSF Aβ42/40 and CSF Aβ42/38
ptau181/Aβ38
Spearman's rho = -0.64
p-value < 0.001
ptau217/Aβ38
Spearman's rho = -0.73
p-value < 0.001
ptau231/Aβ38
Spearman's rho = -0.71
p-value < 0.001
CSF log(Aβ42/40)
CSF log(ptau181/Aβ38)
CSF log(ptau217/Aβ38)
CSF log(ptau231/Aβ38)
ptau181/Aβ38
Spearman's rho = -0.6
p-value < 0.001
ptau217/Aβ38
Spearman's rho = -0.71
p-value < 0.001
ptau231/Aβ38
Spearman's rho = -0.67
p-value < 0.001
CSF log(Aβ42/38)
CSF log(ptau181/Aβ38)
CSF log(ptau217/Aβ38)
CSF log(ptau231/Aβ38)
Diagnostic Group
Young
CU(-)
CU(+)
MCI(-)
MCI(+)
AD
Non-AD Dementia

Fig1

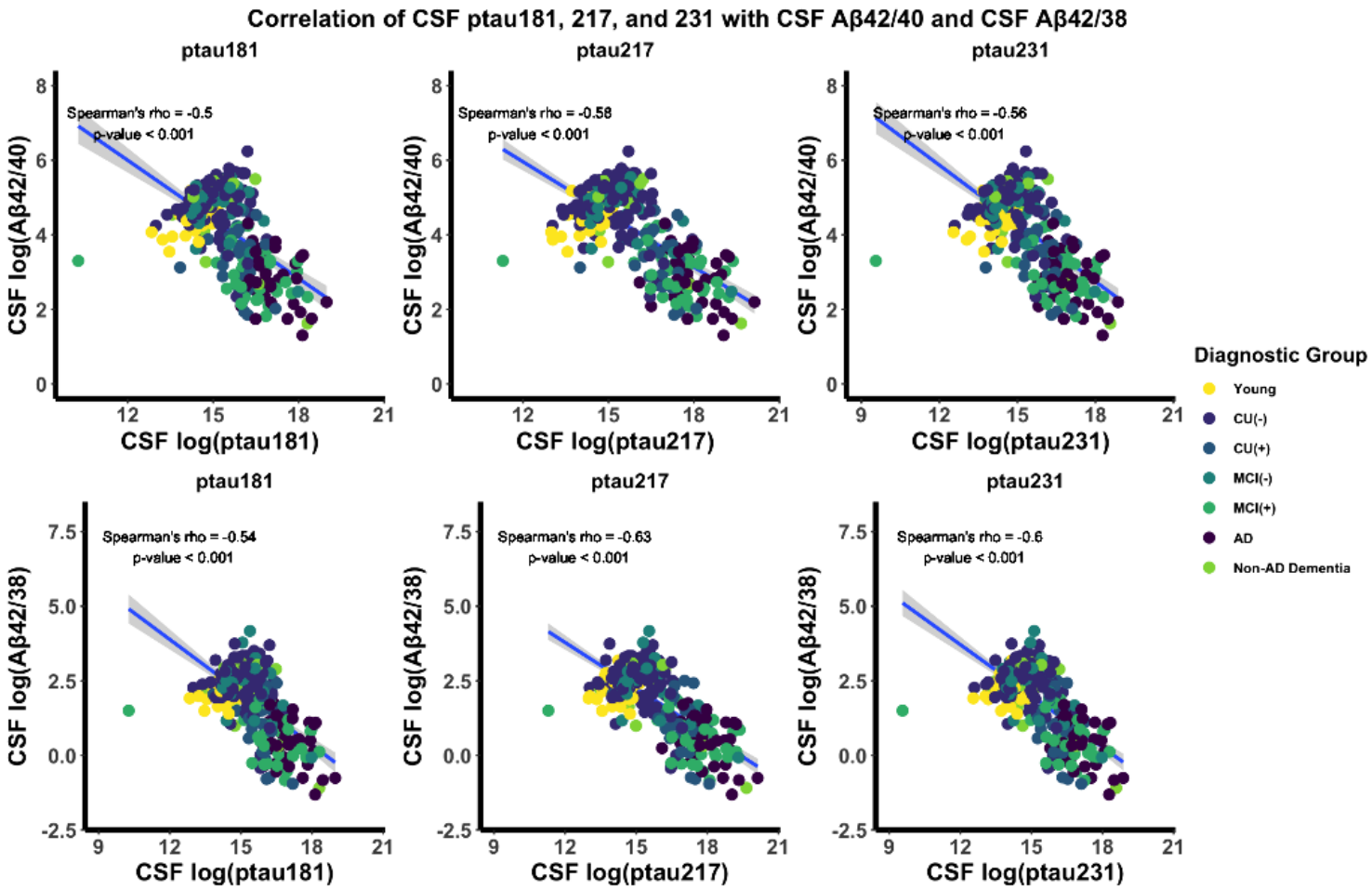
Correlation of CSF ptau181, 217, and 231 with CSF Aβ42/40 and CSF Aβ42/38
ptau181
ptau217
ptau231
Spearman's rho = -0.5
p-value < 0.001
Spearman's rho = -0.58
p-value < 0.001
Spearman's rho = -0.56
p-value < 0.001
CSF log(Aβ42/40)
CSF log(ptau181)
CSF log(ptau217)
CSF log(ptau231)
Spearman's rho = -0.54
p-value < 0.001
Spearman's rho = -0.63
p-value < 0.001
Spearman's rho = -0.6
p-value < 0.001
CSF log(Aβ42/38)
Diagnostic Group
Young
CU(-)
CU(+)
MCI(-)
MCI(+)
AD
Non-AD Dementia

Fig2

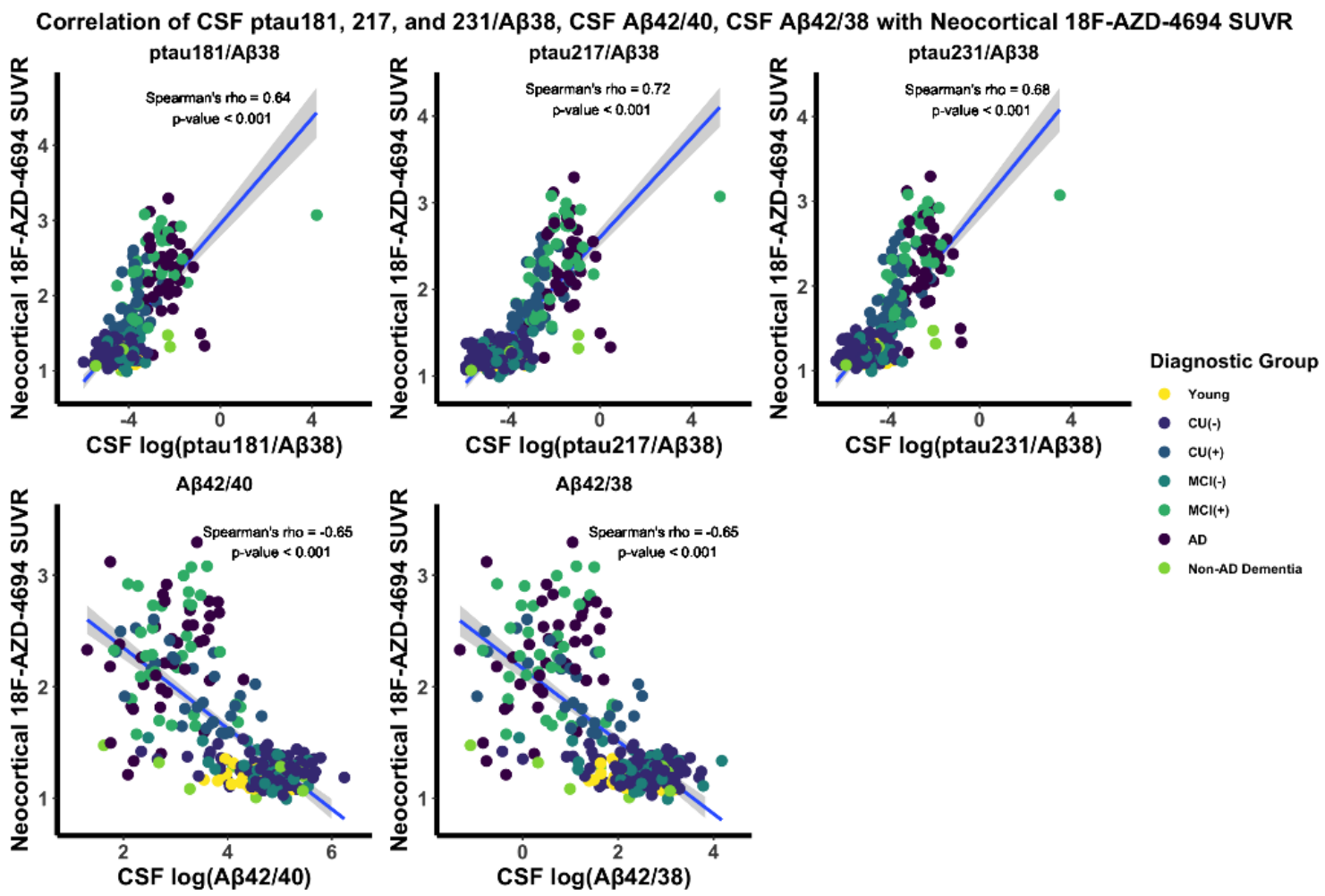
Correlation of CSF ptau181, 217, and 231/Aβ38, CSF Aβ42/40, CSF Aβ42/38 with Neocortical 18F-AZD-4694 SUVR
ptau181/Aβ38
Spearman's rho = 0.64
p-value < 0.001
ptau217/Aβ38
Spearman's rho = 0.72
p-value < 0.001
ptau231/Aβ38
Spearman's rho = 0.68
p-value < 0.001
Aβ42/40
Spearman's rho = -0.65
p-value < 0.001
Aβ42/38
Spearman's rho = -0.65
p-value < 0.001
Neocortical 18F-AZD-4694 SUVR
CSF log(ptau181/Aβ38)
CSF log(ptau217/Aβ38)
CSF log(ptau231/Aβ38)
CSF log(Aβ42/40)
CSF log(Aβ42/38)
Diagnostic Group
Young
CU(-)
CU(+)
MCI(-)
MCI(+)
AD
Non-AD Dementia

Fig3

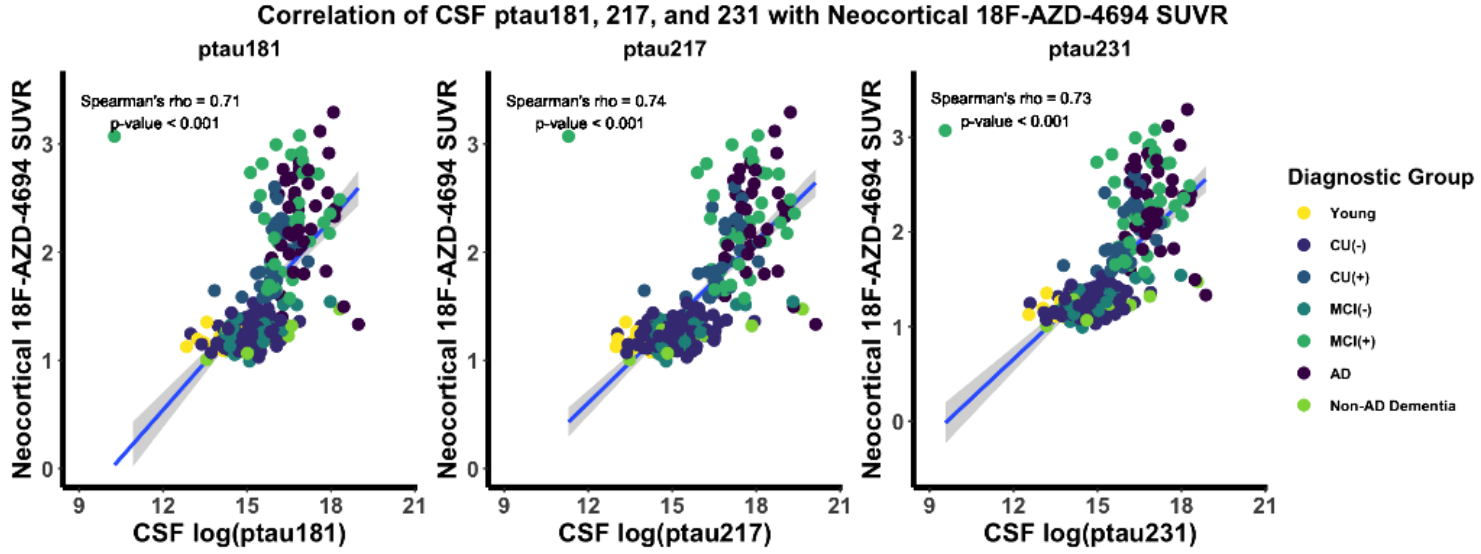
Correlation of CSF ptau181, 217, and 231 with Neocortical 18F-AZD-4694 SUVR
ptau181
Spearman's rho = 0.71
p-value < 0.001
ptau217
Spearman's rho = 0.74
p-value < 0.001
ptau231
Spearman's rho = 0.73
p-value < 0.001
Neocortical 18F-AZD-4694 SUVR
CSF log(ptau181)
CSF log(ptau217)
CSF log(ptau231)
Diagnostic Group
Young
CU(-)
CU(+)
MCI(-)
MCI(+)
AD
Non-AD Dementia

Fig4

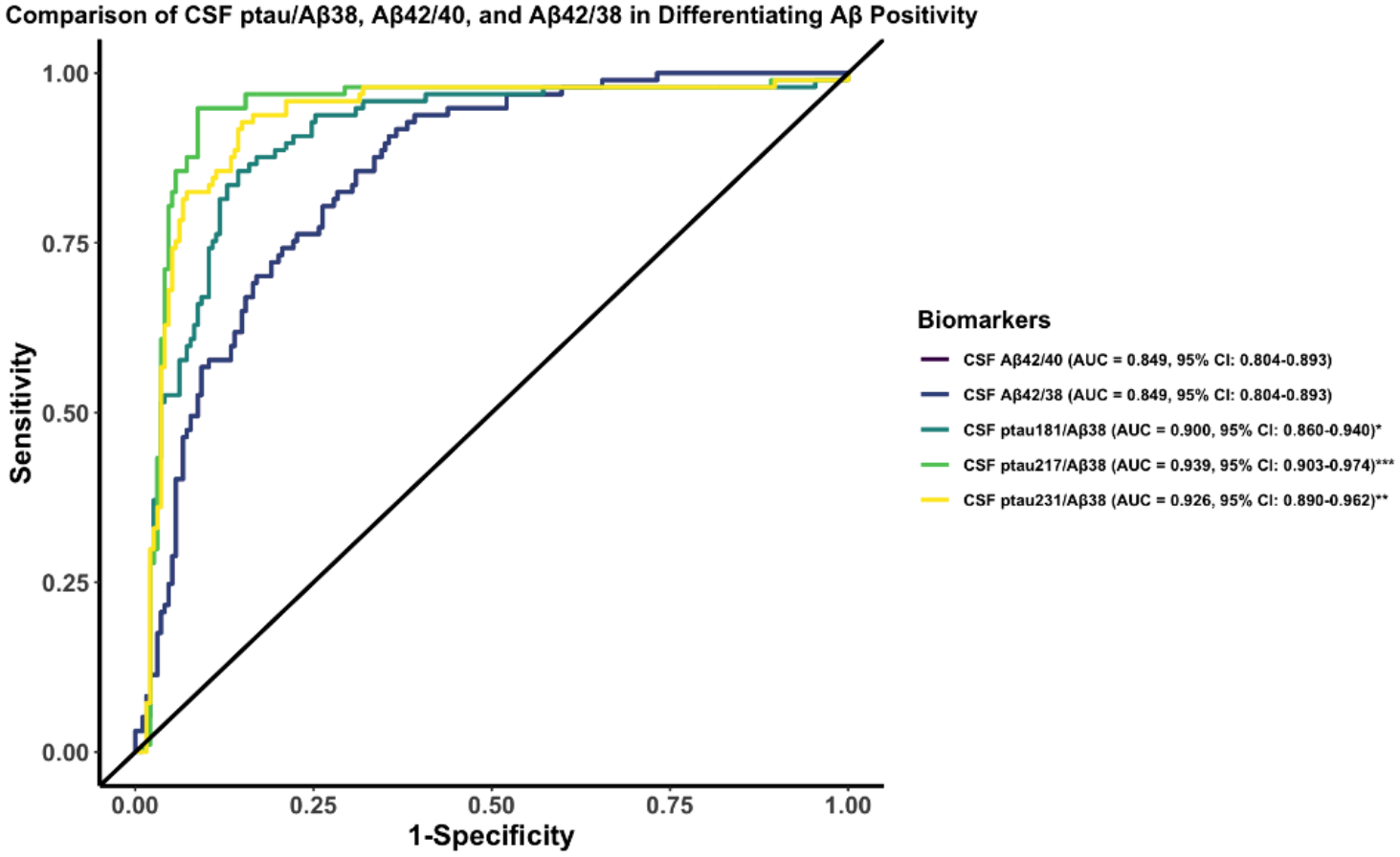
Comparison of CSF ptau/Aβ38, Aβ42/40, and Aβ42/38 in Differentiating Aβ Positivity
Sensitivity
1-Specificity
0.00
0.25
0.50
0.75
1.00
Biomarkers
CSF Aβ42/40 (AUC = 0.849, 95% CI: 0.804-0.893)
CSF Aβ42/38 (AUC = 0.849, 95% CI: 0.804-0.893)
CSF ptau181/Aβ38 (AUC = 0.900, 95% CI: 0.860-0.940)*
CSF ptau217/Aβ38 (AUC = 0.939, 95% CI: 0.903-0.974)***
CSF ptau231/Aβ38 (AUC = 0.926, 95% CI: 0.890-0.962)**

Fig5

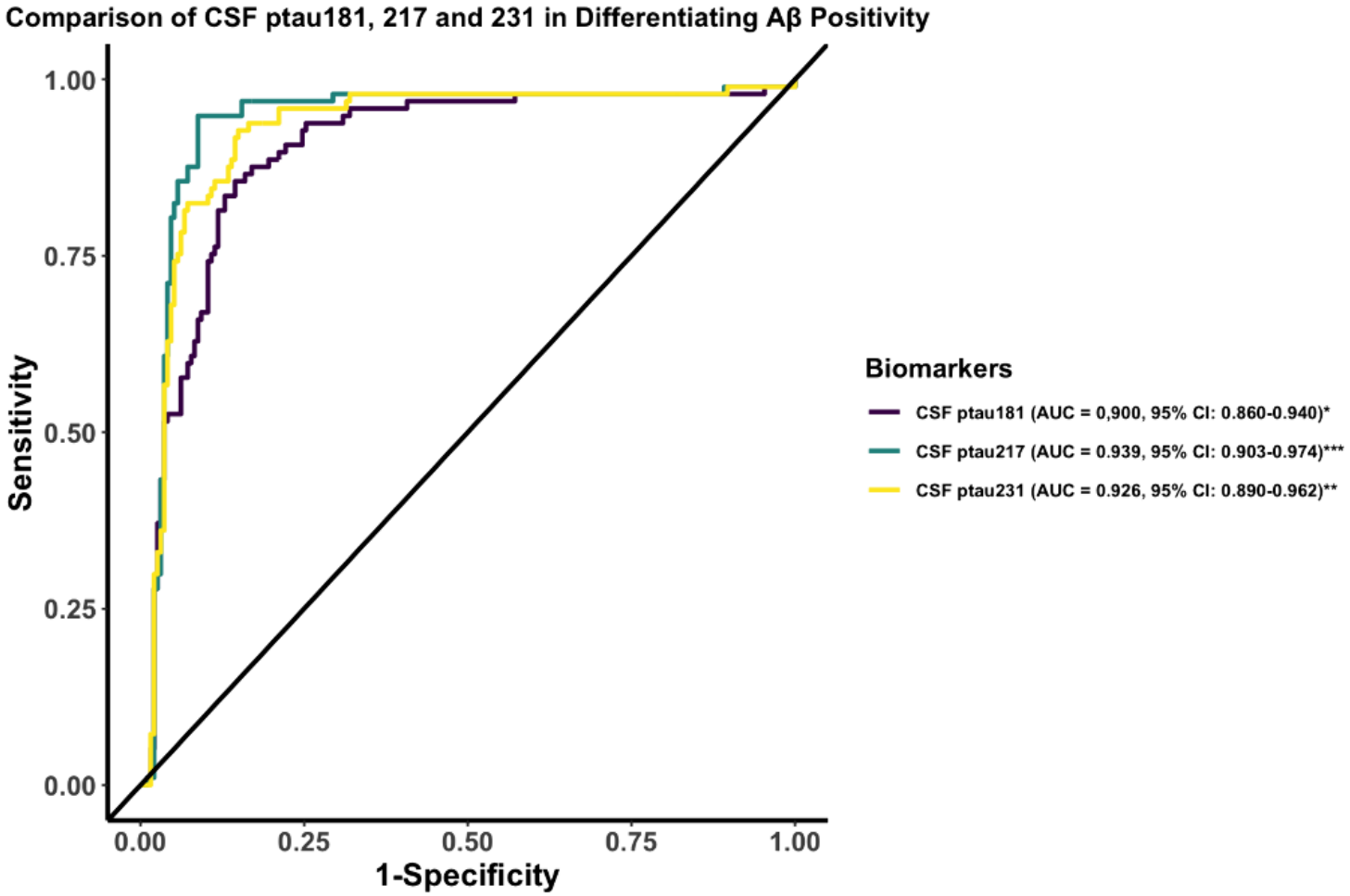

Fig6

Conclusions: CSF ptau181/Aβ38, ptau217/Aβ38, ptau231/Aβ38 are equivalent to CSF ptau181, 217, and 231 regarding discriminating amyloid-PET positivity, but better than conventional CSF Aβ42/40 and Aβ42/38.

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SHIFT 02-375

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

THE AUTOMATED ELECSYS OF THE ALZHEIMER'S DISEASE FLUID BIOMARKERS IN CLINICAL SETTINGS

Qiao-Xin Li[1], Shiji Varghese[1], Christopher Fowler[2], James Doecke[3], Rodrigo Canovas[3], Kevin Taddei,[4], Stephanie Rainey-Smith[5], Vincent Dore[3], Christopher Rowe[6], Ralph Martins[5], Colin Masters[7], Steven Collins[7]
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Aims: Alzheimer's disease (AD) treatment at an early stage with monoclonal antibody treatment is approved by the Food and Drug Administration (FDA) and has brought hope for millions of people afflicted by this malady. Measurement with the Elecsys® platform of Aβ42, P-tau181 and T-tau in fresh cerebrospinal fluid (CSF) is approved by the FDA to confirm underlying AD neuropathology and thereby enable access to the disease-modifying therapies (DMTs). This study reports AD biomarkers in a community setting using the Elecsys® platform and the concordance of the GII CSF biomarkers with PET amyloid imaging.
Methods: CSF samples were collected from Australian Imaging Biomarker and Lifestyle study (AIBL) and referred samples from local hospitals/clinics. All CSF samples were collected into low-binding tubes and measured directly from the collection tube without any pre-analytical handling.
Results: From the 1775 referred CSF samples, 65% had A+, with 41% of the A+ had a profile of A+T+ supporting the diagnosis of AD. Thirty-five percent has A-, with 15% as A-T+. In the AIBL samples (N=79), 47 had CSF A-T- and normal amyloid PET (centiloid (CL) <25). Eight out nine with CSF A+T+ also had PET>25. Five of the PET<25 had CSF A+. Six had A-T+ with a mix of PET status.
Conclusions: The automated Elecsys platform is accessible for further evaluating a diagnosis of AD and offers high throughput and excellent precision. It minimises pre-analytical handling of CSF samples, which increases the reliability of results. The advantage of the CSF test is able to detect the changes of Abeta42 as well P-tau. Our study supports the use of Elecsys® for AD diagnostics in routine clinical practice.

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SHIFT 02-376

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

UTILITY OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS TO PREDICT DISEASE CONVERSION: A HABS-HD STUDY

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Aims: Understanding disease conversion in Alzheimer's Disease (AD) is of tremendous importance given emerging therapies. Limited work has been conducted to examine this among diverse communities utilizing traditional AD biomarkers. This study sought to address this gap by examining the ability for AD biomarkers to predict through machine learning disease conversion across varying race and ethnic groups.
Methods: Data were analyzed on n=1,182 participants (n=212 converters, n=970 non-converters) from the Health and Aging Brain Study – Health Disparities (HABS-HD). AD biomarkers were derived using Single Molecule Array Technology on the HD-X imager and included Amyloid Beta (Aβ) 40, Aβ42, Total Tau, NfL, and ptau181. Support vector machine analyses were conducted to predict disease conversion at follow-up (48 months).
Results: For the total sample, combined AD biomarkers were able to predict disease conversion with an Area Under the Curve (AUC) of 0.64 (Sensitivity [SN] =0.65, Specificity [SP] =0.57). Among non-Hispanic Blacks, accuracy was higher with an AUC of 0.80 (SN=1.00, SP=0.70), which increased to 0.92 with refinement of only amyloid biomarkers (Aβ40 and 42) in the model (SN=1.00, SP= 0.70). Among Hispanics, the combined AD biomarker model predicted disease conversion with an AUC of 0.61 (SN=0.32, SP=0.83) with decreased performance with the refinement of biomarkers. Among non-Hispanic whites, AUC reached 0.86 (SN=0.90, SP=0.49) with no further improvement with refinement of the model.
Conclusions: Taken together, AD biomarkers, combined, produced a higher AUC as compared to individual biomarkers in distinguishing those who converted diagnosis at a follow-up visit. Non-Hispanic whites followed by non-Hispanic Blacks showed higher overall prediction when utilizing AD biomarkers, while models were less specific for Hispanics. This work highlights the further utility of select AD biomarkers in determining disease conversion.

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SHIFT 02-377

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

DISTINGUISHING DEMENTIAS FROM INJURY IN THE ELDERLY: RESULTS FROM THE HEADSMART GERIATRIC FEASIBILITY STUDY.

Timothy Van Meter[1], Nazanin Mirshahi[2], Sally Boyd[1], Danielle Sandsmark[3], Katya Rascovsky[3], Ramon Diaz-Arrastia[3], Justin Weppner[4], Damon Kuehl[5]
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Aims: Distinguishing neurodegenerative disease subtypes using routine blood tests in dementia care in elderly patients requires high accuracy for referral to imaging studies and front-line therapies. Prior analysis of the HeadSMART Geriatric feasibility cohort suggested blood biomarker-based proteins commonly used in AD diagnosis may not distinguish chronic neurological diseases (NDDs) from acute TBI. Subjects enrolled as controls found to be cognitively normal or impaired were compared with dementias to identify biomarkers providing the greatest accuracy for detecting dementia pathologies.
Methods: Elderly subjects(ages 65+) were studied for levels of serum biomarkers. Retrospective neurodegenerative disease specimens were compared with specimens from subjects enrolled in emergency department settings, either presenting with head injury, other non-CNS injuries, or as healthy controls. Sera from dementia subtypes (n= 56; Alzheimer's, Parkinson's, Vascular dementias) were compared with healthy subjects (n=23) or subjects with other injuries (n=153; 101 mTBI,52 non-CNS) characterized by CDR and FAQ informant sections for preinjury neurocognitive status. Custom BRAINBox assays and S-Plex MSD p-Tau assays were performed to measure 15 biomarkers. Alzheimer's Disease and other dementia subtypes were compared to controls to assess biomarker utility in detecting undiagnosed neurodegenerative pathologies (Wilcoxon Tests, ANOVA and ROC curves).
Results: Biomarkers distinguishing AD from other NDDs included pTau (T181 and S217-Tau), consistent with published reports. Synucleins (SNCA,pS129-SNCA) were top performing features classifying PD and AD versus controls, augmented by neuronal/vascular biomarkers (NRGN, vWF) and neuroinflammation markers(IL-6,ST2). Random forest models including IL-6,pTau or IL-6,SNCA or IL-6,pS129-SNCA also had AUCs above 0.85 and accuracies above 75% for detecting dementia-related disease vs non-dementia.
Conclusions: Results suggest additional assays are promising for detection of early dementias to indicate suitability for therapy. Next phase studies follow a longitudinal study design with advanced MRI to assess pathology and neurocognitive trajectories.

SHIFT 02-385

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / FUNCTIONAL MRI
4 - 5 April

INTERHEMISPHERIC DIFFERENCES IN CONNECTIVITY WITHIN AND BETWEEN DIFFERENT BRAIN REGIONS MAY UNDERLIE THE LEVEL OF COGNITIVE DECLINE

Janos Negyesi[1,2,3], Gergo Bolla[1,4], Dalida Berente[1,5], Andras Horvath[1,6]
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Aims: Neuroimaging studies support the idea that there is interhemispheric difference in functional connections at rest between patients with dementia and age-matched healthy controls. In the present observational study, we investigated if the level of cognitive decline would affect the interhemispheric differences of connectivity within and between different brain areas measured by functional magnetic resonance imaging (fMRI).
Methods: Data were collected by 1) the Semmelweis MCI Neuroimaging Cohort (SMNC) and the 2) AlzEpi Cohort Observational Library (ACOL). Two resting-state voxel-based fMRI metrics [local correlation (LCOR) and intrinsic connectivity (ICC)] were analyzed from patients with Alzheimer's disease (AD, n=30) and mild cognitive impairment (MCI, n=17), individuals with subjective cognitive decline (SCD, n=28) and healthy controls (HC, n=54). Laterality index was calculated [LI=(L–R)/(L+R)] for each brain area in each metric and was taken for statistical analyses.
Results: Selected fMRI metrics showed consistent interhemispheric differences between groups. Specifically, LI was lower in AD vs. SCD in LCOR at the thalamus (p=0.028, d=0.369) and in ICC at the occipital pole (p=0.020, d=0.744). In addition, LI in ICC of MCI was higher than in AD (p=0.045, d=0.291) but lower as compared to MCI (p=0.023, d=0.279) at cerebellum 7b area.
Conclusions: Using the two resting-state voxel-based fMRI metrics might be a promising method to identify interhemispheric differences in connectivity within and between different brain regions to detect the level of cognitive decline. Our results indicate that the connectivity within and between specific brain areas increases with MCI as compared to HC, however, it decreases again in AD also as compared to SCD.

SHIFT 02-386

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4 - 5 April

DYNAMIC CONTRAST ENHANCED MRI REVEALS IMPAIRED BLOOD BRAIN BARRIER IN BASAL FOREBRAIN REGION IN PATIENTS WITH ALZHEIMERS DISEASE

Ondrej Lerch[1], David Kala[2], Zuzana Nedelská[1], Haris Hadzic[1], Jakub Otahal[2], Jakub Hort[1]
[1]Second Faculty of Medicine, Charles University and Motol University Hospital, Department Of Neurology, Prague, Czech Republic, [2]Charles University, Second Faculty of Medicine, Department Of Pathophysiology, Prague, Czech Republic

Aims: Blood brain barrier (BBB) is a protective layer of cells that separates the circulatory system from the brain. Its dysfunction is one of the possible mechanisms leading to onset of Alzheimer's disease (AD). Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) allows regional assessment of BBB permeability by estimating local metrics such as K-trans (volume transfer constant). We used DCE-MRI to examine BBB dysfunction in regions affected by early AD pathology - hippocampus, entorhinal cortex (EC) and basal forebrain (BF) nuclei.
Methods: A group of 43 participants – 20 biomarker negative cognitively normal (CN) individuals and 23 biomarker positive patients with mild cognitive impairment or mild dementia (AD) from Czech Brain Aging Study underwent DCE-MRI. K-trans maps were estimated using Patlak algorithm implemented within ROCKETSHIP software toolbox. Segmentations of hippocampal head, body and tail, anterolateral and posteromedial EC and BF nuclei were obtained using in house developed pipeline. Average K-trans values were extracted for each region. Regional differences in BBB permeability between groups were assessed using ANCOVA adjusted for age, sex and ApoE4 positivity.
Results: Participants in the CN group had lower mean K-trans in posteromedial EC ($K\text{-trans}_{CN}= 0.022x10^{-3}min^{-1}$; $K\text{-trans}_{AD}= 0.03x10^{-3}min^{-1}$, p=0.017) and BF area ($K\text{-trans}_{CN}= 0.009x10^{-3}min^{-1}$; $K\text{-trans}_{AD}= 0.005x10^{-3}min^{-1}$, p=0.008), in particular posterior ($K\text{-trans}_{CN}= 0.008x10^{-3}min^{-1}$; $K\text{-trans}_{AD}= 0.004x10^{-3}min^{-1}$, p=0.012) and anterior-intermediate ($K\text{-trans}_{CN}= 0.017x10^{-3}min^{-1}$; $K\text{-trans}_{AD}= 0.008x10^{-3}min^{-1}$, p=0.016) nucleus basalis Meynerti. There were no other differences in regional BBB permeability (p>0.05).
Conclusions: Our data show consistent regional BBB permeability reduction in multiple regions associated with early AD pathology in patients with MCI due to AD and AD dementia. This may imply regional BBB alteration in medial temporal lobe and BF area, suggesting a link between BBB dysfunction and early AD.

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SHIFT 02-387

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4 - 5 April

MEMORY CAPACITY OF BRAIN NETWORKS FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

Mite Mijalkov[1], Massimiliano Passaretti[1], Zhilei Xu[1], Jiawei Sun[1], Daniel Vereb[1], Giovanni Volpe[2], Joana Pereira[1]
[1]Karolinska Institutet, Department Of Clinical Neuroscience, Solna, Sweden, [2]University of Gothenburg, Department Of Physics, Gothenburg, Sweden

Aims: The brain is a complex network of anatomically interconnected regions supporting a range of cognitive functions that have been shown to decline in Alzheimer's disease (AD). Understanding the neurological basis of this decline is crucial for developing early therapeutic interventions. Here, we applied a machine learning technique called reservoir computing to investigate how amyloid-beta (Aβ) pathology, a key early marker of AD, affects brain connectivity patterns and cognitive function in cognitively healthy individuals.
Methods: For each individual, the reservoir was represented by a whole-brain anatomical or functional network derived from diffusion-weighted and functional MR imaging. Reservoir performance was quantified using memory capacity, a measure that reflects the network's ability to retain time varying input signals. We assessed memory capacity in 201 Aβ-negative and 76 Aβ-positive individuals with functional MRI, diffusion-weighted, and tau-PET scans from the Harvard Aging Brain Study. Follow-up scans were available for 132 Aβ-negative and 53 Aβ-positive individuals. Images were preprocessed using standard procedures, and connectivity was extracted from 246 brain regions.
Results: We found that individuals with higher Aβ accumulation had lower memory capacity in their functional brain networks. Furthermore, higher memory capacity in anatomical networks was associated with a reduction in tau burden over time. Finally, high memory capacity in functional networks correlated with improved cognitive performance, including memory retrieval, immediate learning, and delayed recall.
Conclusions: These findings suggest that memory capacity plays a crucial role in predicting AD progression and cognitive function. They also show that well-functioning anatomical and functional networks at baseline may be protective against AD-related neuronal changes. Altogether, this study highlights the potential utility of reservoir computing in understanding the underlying neural mechanisms in AD, and their implications for cognitive decline.

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SHIFT 02-388

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4 - 5 April

MULTI-VIEW/MULTIMODAL ANALYSIS REVEALS THE INTERACTIONS BETWEEN AMYLOID, TAU AND ATROPHY IN THE AGING AND ALZHEIMER'S DISEASE BRAIN

Konstantinos Poulakis[1,2], Yasser Iturria-Medina[1]
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Aims: In this study we investigated the ability and limits of multi-view statistical modeling in identifying the longitudinal associations between multiple neuroimaging-derived biological factors, including brain amyloid, tau and atrophy in cognitively healthy and pathological aging.
Methods: We applied the structural learning and integrative decomposition (SLIDE) multi-view analysis model on various simulated dataset designs and employed post-modeling clustering and variable importance features, to build a pipeline for multimodal neuroimaging data analysis based on latent factors. We trained the model using 2 to 10 datasets simultaneously, with missing data imputation, and clustering with feature importance. Once validated in simulated data, we applied our pipeline to cross-sectional (N=829) and longitudinal (N=310) magnetic resonance imaging (MRI, n=3019), and positron emission tomography (PET) with the (18F)-AV45 (amyloid, n=2065), and AV1451 (Tau, n=1440) tracer datasets from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The sample included cognitively unimpaired (CU), mild cognitive impairment (MCI), and Alzheimer's disease (AD) patients.
Results: The simulated data analysis showed that all the latent factors that were estimated belonged to the ground truth. The type 1 error of the model is very low while the type 2 error may increase after 7 datasets. Next, the whole brain neuroimaging cross-sectional and longitudinal marker analysis revealed 1) cross-sectional and longitudinal interactions between atrophy and tau accumulation markers and 2) within marker cross-sectional and longitudinal interactions. The identified latent factors correlate with various cognitive states; they have predictive diagnostic value, and they assist in the assessment of heterogeneity in AD.
Conclusions: A pipeline for high dimensional-small sample multi-view and multimodal analysis in the neurological context has been developed and validated.

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SHIFT 02-393

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

CASCADED MULTIMODAL DEEP LEARNING IN THE PREDICTION OF CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE

Gianmarco Guarnier[1,2], Janis Reinelt[2], Eóin Molloy[2], Paul Glad Mihai[2], Pegah Einaliyan[2], Sofie Valk[1], Augusta Modestino[2], Matteo Ugolini[2], Aroma Dabas[1,2], Rhys Agombar[2], Karsten Mueller[3], Qiong Wu[1], Anahit Babayan[1], Marco Castellaro[4], Arno Villringer[1], Nico Scherf[1], Konstantin Thierbach[2], Matthias Schroeter[5]
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Aims: Predicting Alzheimer's Disease (AD) progression is vital for optimizing intervention strategies and improving patient care. However, variability in patient decline makes this challenging. TelDem, an AI-powered clinical decision support system (CDSS), aims to address this by predicting cognitive decline using multimodal and real-world clinical data, with a focus on the conversion of Mild Cognitive Impairment (MCI) to AD.
Methods: We applied TelDem to ADNI (n=1,487) and AIBL (n=713) data using a Cascaded MultiModal Mixing Transformer (CMT). We designed our CMT to classify MCI patients into stable or progressive subtypes using demographics, T1-weighted anatomical MRI data, cerebrospinal fluid (CSF) and plasma biomarkers, and behavioral and cognitive scores. We assessed model performance in three approaches: unimodal (T1-weighted MRI), standard clinical (adding cognitive and behavioral scores), and comprehensive (addingCSF and APOE genotype). Finally, we employed a Cross-Modal Fusion Norm (CMFN) metric to explore model decision making.
Results: Unimodal modelling yielded a 63±1.5% balanced accuracy. Performance significantly improved in the standard clinical approach, increasing balanced accuracy to 69±1.8%. The comprehensive model achieved a balanced accuracy of 71% and an AUC of 0.774. CMFN analyses struggled to account for the role of demographics, which were implemented in the earlier blocks of the cascaded chain. Later blocks, however, showed that the model responded differently to CSF tau, p-tau and neurofilament light (NFL) depending on the status as progressive or stable MCI.
Conclusions: These results demonstrate enhanced accuracy for predicting disease progression with a comprehensive multimodal approach. The flexible integration of multimodal data improved diagnostic accuracy beyond that of unimodal and clinical standard modelling. These results position TelDem as a valuable tool for clinical decision-making and advancing research into therapeutic interventions for neurodegenerative diseases.

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SHIFT 02-394

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

LONGITUDINAL EVOLUTION OF POSTERIOR CORTICAL ATROPHY: DIAGNOSTIC DELAYS, OVERLAPPING PHENOTYPES, AND CLINICAL OUTCOMES

Dror Shir[1], Noah Lee[1], Stuart Mccarter[1], Vijay Ramanan[1], Hugo Botha[1], David Knopman[1], Ronald Petersen[1], Bradley Boeve[1], Gregory Day[2], Neill Graff-Radford[2], David Jones[1], Melissa Murray[3], Aivi Nguyen[4], Ross Reichard[3], Dennis Dickson[5], Deena Tajfirouz[6], Jennifer Whitwell[7], Keith Josephs[1], Jonathan Graff-Radford[1]
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Aims: While numerous large studies have assessed posterior cortical atrophy (PCA) cross-sectionally, its longitudinal progression is not well characterized. This study aims to determine PCA's longitudinal trajectory, including the timing of diagnosis, clinical manifestations, and patient outcomes.
Methods: This retrospective study involved 558 participants diagnosed with PCA at the Mayo Clinic between 1995 and 2023. Clinical data, including demographics, neurological evaluations, and cognitive tests from initial presentation and late stages, were extracted from medical records. Participants were categorized as PCA-pure or PCA-plus based on the presence of additional neurodegenerative syndrome criteria. Ophthalmologic assessments and cerebrospinal fluid (CSF) analyses were also documented.
Results: The cohort, with a mean age of symptom onset at 61.4 years (65% female), included 68.1% with early-onset PCA (<65 years old). The average time from symptom onset to diagnosis was 3.6 years. Ophthalmologic evaluations (49%) and procedures (16%) were common before PCA diagnosis, while psychiatric diagnoses were made in 23.4% of cases, particularly among younger females. Initial symptoms included misplacement of items, difficulties with reading and driving, and visual processing issues. Notable signs included constructional apraxia, dyscalculia, simultanagnosia, and space-perception deficits. CSF biomarkers aligned with Alzheimer's disease in 88% of individuals. About 25% presented with additional clinical syndromes, with PCA-plus cases increasing over time. Longitudinal analysis showed a rapid initial cognitive decline, with a slowing rate over 0 to 10 years (coefficient = -4.20 [0.29], $p < 0.001$).
Conclusions: This study highlights the protracted time from symptom onset and frequent misdiagnoses/misattribution of symtoms in PCA. Ophthalmologic evaluations often preceded neurological assessments. Psychiatric diagnoses were more frequent among younger female participants. Improved diagnostic processes and earlier recognition of PCA may enhance the effectiveness of emerging disease-modifying therapies.

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SHIFT 02-395

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

GLYMPHATIC DYSFUNCTION AND ITS ASSOCIATION WITH PLASMA BIOMARKERS AND COGNITIVE IMPAIRMENT IN ALZHEIMER'S DEMENTIA AND MILD COGNITIVE IMPAIRMENT

Nicole Isabella Tan[1], Yi Jayne Tan[1], Thomas Welton[1,2], Sumeet Kumar[2,3], Nicole Keong[2,4], Thomas Teo[1], Kok Pin Ng[2,5,6], Simon Ting[2,5], Hui Jin Chiew[2,5,6], Adeline Ng[2,5,6]
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Aims: The glymphatic system may play a role in neurotoxins clearance, hence glymphatic dysfunction in Alzheimer's Disease (AD) may result in accumulated amyloid-β (Aβ) and phosphorylated tau (pTau) driving cognitive decline. Studying diffusion along the perivascular space via diffusion tensor imaging (DTI) is a relatively novel method of measuring glymphatic clearance efficiency (ALPS index). Lower ALPS index (suggesting lower water diffusivity, impaired clearance) was associated with poorer cognition in AD and MCI and lower CSF Aβ42 levels, but the association between ALPS index and peripheral Aβ42 and pTau remain unknown.
Methods: MCI (n=27) and AD (n=27) patients were included. 3-Tesla DTI-MRI data, color fractional anisotropy map was generated to mark regions of interest (ROI) for ALPS index calculation (averaged between hemispheres). All participants underwent neuropsychological assessment. CSF and plasma total Tau and pTau181 concentrations were determined by ELISAs and ultrasensitive single molecule array, respectively. Linear regression was performed to determine associations between ALPS index, CSF/plasma biomarker levels and cognitive scores, adjusting for age.
Results: In MCI, lower ALPS index was significantly associated with higher plasma pTau181 (β=-0.441, p=0.048) and deficits in the tests of attention, visuospatial, language and working memory domains. In AD, the ALPS index was significantly associated with CSF pTau181 (β=0.520, p<0.001) and CSF total Tau (β=0.593, p=0.005), but not with any cognitive tests.
Conclusions: We report novel associations of CSF pTau & total Tau, plasma pTau181, and cognition, with the ALPS index. Decreased ALPS (suggestive of impaired glymphatic clearance) associated with increased plasma pTau181 and poorer cognition in MCI. In AD, higher ALPS (suggestive of greater clearance) associated instead with higher CSF pTau levels, raising the possibility of potential compensatory mechanisms in dementia. Further studies will include a larger cohort with controls.

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SHIFT 02-396

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4 - 5 April

UTILITY OF LARGE LANGUAGE MODELS TO PREDICT DIAGNOSIS FROM NARRATIVE HISTORY

Tandis Parvizi[1], Sara Silvaieh[1], Evelyn Berger-Sieczkowski[2], Helena Untersteiner[1], Clemens Farr[1], Elena Uhlik[1], Elisabeth Stögmann[1], Raphael Wurm[1]
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Aims: This study aimed to assess the ability of large language models, i.e. ChatGPT, to predict the diagnosis of patients presenting to a tertiary care memory clinic based on the narrative patient history as provided by the treating physician.
Methods: Narrative patient history, demographic data, and final diagnosis were extracted from a prospectively maintained registry at our outpatient memory clinic. The history was combined with a standardized context and diagnosis was restricted to six categories, e.g. AD, FTD, DLB, PPA, Vascular, and Other/Non neurodegenerative. The LLM was tasked to provide a diagnosis based on the patient's history alone. It was prompted individually ('single shot prompting'). The LLM's diagnoses were compared to the true diagnosis as adjudicated by the treating physician. Diagnostic accuracy was calculated for each model and across diagnostic categories. Implementation and statistics were performed in R (Version 4.2.2).
Results: We included 540 patients treated at our clinic between 2019 and 2023. The median age at symptom onset was 67.8 years (interquartile range 57.5 to 74.5). The eventual diagnosis was AD pathology in 54%, DLB in 3.7%, FTD in 3.3%, PPA in 5.7%, Vascular in 1.3%, and Other in 31.6%. The overall accuracy was modest. GPT4 and GPT4o were accurate in 52% each, while GPT4o mini was accurate in 40%. The interrater agreement was modest with a Fleiss's Kappa of 0.45. The models performed significantly better in predicting AD, VaD, and PPA (accuracies ranging from 60% to 86%) than non-degenerative causes (accuracies between 14 and 37%, $p<0.001$).
Conclusions: Large language models can predict the underlying pathology of dementia patients from very crude information at a rate greater than chance but not sufficient for clinical use. Further research into model tuning is warranted.

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SHIFT 02-404

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - GLUCOSE
4 - 5 April

IMPACT OF LEWY BODY (CO-)PATHOLOGY ON HYPOMETABOLISM PATTERNS AND CLINICAL TRAJECTORIES IN AMNESTIC COGNITIVE IMPAIRMENT

Jesús Silva-Rodríguez[1], Miguel Ángel Labrador Espinosa[2], Alexis Moscoso Rial[2], Pascual Sanchez-Juan[3], Michael Schöll[4], Michel Grothe[1]
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Aims: Dementia with Lewy Bodies (LBs) is typically associated with a distinct clinical profile and posterior-occipital hypometabolism pattern on FDG-PET compared to Alzheimer's disease (AD). However, LB pathology is also often found as a comorbid pathology in AD, and the degree to which LB pathology affects the neurodegenerative course and clinical phenotype in those patients is not well understood. Recently developed α-synuclein seed amplification assays (αSyn-SAAs) allow investigating mixed AD-LB in-vivo.
Methods: We analyzed 872 ADNI patients diagnosed with aMCI (N=661) or AD dementia (N=211) who had CSF and FDG-PET data available. Subjects were grouped by AD and LB biomarker results: "AD-/LB-" (N=106), "AD+/LB-" (N=336), "AD+/LB+" (N=158), and "AD-/LB+" (N=68). We compared demographics, APOE4 positivity, hypometabolism patterns, longitudinal cognition (memory vs executive function performance) and the risk for developing hallucinations.
Results: AD+/LB+ patients were more impaired at baseline and progressed faster than AD+/LB-, but retained a comparable amnestic predominant cognitive profile (Fig. 1). By contrast, AD-/LB+ patients were less globally impaired ($p<0.001$) and characterized by a comparably more dysexecutive profile ($p<0.002$). APOE4 positivity was similar between AD+/LB+ and AD+/LB- (72% vs. 75%, $p=0.28$) but significantly lower in AD-/LB+ (28%, $p<0.001$). On FDG-PET, AD+/LB+ showed stronger neurodegeneration than, AD+LB-, but a regionally identical pattern of temporo-parietal hypometabolism (Fig. 2). AD-/LB+ showed a strikingly different posterior-occipital pattern typically associated with DLB. LB+ was not associated with a higher risk for developing hallucinations in AD.
Conclusions: LB co-pathology in AD was associated with faster cognitive decline, but it did not alter the amnestic phenotype or the regional hypometabolic pattern. By contrast, patients with relatively pure LB pathology were characterized by a distinct posterior-occipital hypometabolism pattern and evolved towards a more dysexecutive phenotype over time.

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SHIFT 02-407

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4 - 5 April

AMYLOID-PET POSITIVITY IN THE ABSENCE OF CLINICAL SYMPTOMS: A REVIEW OF NEUROPATHOLOGICAL CORRELATES AND CLINICAL PROGNOSIS

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Aims: The revised criteria by the Alzheimer's Association (AA) Working Group allow diagnosing Alzheimer's disease (AD) in cognitively unimpaired individuals based on abnormal amyloid-β (Aβ)-positron emission tomography (PET) or surrogate "Core 1" biomarkers. As disease-modifying therapies may soon be available for this group, understanding the neuropathological correlates and clinical progression of Aβ-PET-positive, cognitively unimpaired individuals is critical.
Methods: A literature review was conducted to evaluate: (1) associations between Aβ pathology (in vivo or postmortem) and tau pathology, and (2) Aβ-PET positivity and clinical outcomes. Additionally, unpublished analyses of publicly available data (NACC and Tau PET databases) were included.
Results: Public data show that Aβ pathology in cognitively unimpaired individuals is not typically associated with advanced tau pathology (Braak stages ≥ III). Less than 20% of Aβ-positive unimpaired older adults progress to mild cognitive impairment or dementia within five years, with the vast majority of progressors being tau-PET-positive. Aβ-positive individuals with normal tau-PET scans have a slightly increased risk of clinical progression compared to Aβ-negative individuals.
Conclusions: Defining AD solely by Aβ biomarkers in cognitively unimpaired individuals may relegate tau pathology to a staging criterion, differing from traditional neuropathological definitions of AD. Given the low progression risk associated with Aβ positivity alone, tau-PET could be crucial for identifying individuals at higher risk, potentially informing prevention trials and therapeutic decisions.

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SHIFT 02-408

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4 - 5 April

DOPAMINERGIC CORTICAL CHANGES IN ALZHEIMER'S AND LEWY BODIES DISEASES

Andrea Pilotto[1], Alice Galli[1], Arianna Sala[2], Silvia Paola Caminiti[3], Enrico Premi[1], Luca Presotto[4], Claudio Liguori[5], Nicola Mercuri[5], Giovanni Frisoni[6], Valentina Garibotto[6], Barbara Paghera[7], Francesco Bertagna[7], Silvia Lucchini[7], Pietro Tiraboschi[8], Laura Bonanni[9], Daniela Perani[10], Alessandro Padovani[1]
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Aims: To evaluate the differences between cortical dopaminergic vulnerability between Alzheimer's disease and lewy bodies dementia-
Methods: The study consecutively enrolled 56 AD patients (n=22 MCI-AD; n=38 AD-DEM), 45 DLB patients (n=18 pDLB; n=37 DLB-DEM), and 50 age-matched controls (CG). Only AD patients belonging to the AD continuum were included, accordingly to the NIA-AA research criteria. DLB patients who resulted amyloid-positive were excluded from the study. All subjects underwent ^{123}I-FP-CIT DaTSCAN imaging. Between-groups differences in ^{123}I-FP-CIT binding were assessed using ROI-based and voxel-wise analyses on brain regions belonging to ventral and dorsal dopaminergic systems.
Results: In all AD patients, nigrostriatal imaging resulted negative according to a pre-defined ranking scale [2]. As expected, DLB patients were significantly more impaired than AD in striatal regions (i.e., pallidum, putamen, and caudate) both in prodromal and dementia phases. We found significant alterations in bilateral anterior cingulate cortex and parahippocampal gyrus in AD patients even in the MCI phase, when compared to controls and pDLB. In the dementia phase, dopaminergic alterations in AD extended to frontal regions (i.e., olfactory and rectus gyri, and middle frontal cortex). The direct comparison by means of voxel-wise analyses revealed that DLB showed more significant dopaminergic alterations in striatal regions, while AD resulted more impaired in fronto-temporal regions.
Conclusions: This study indicates subtle dopaminergic alterations in AD patients in ventral dopaminergic system mostly involving fronto-temporal cortices, whereas DLB showed lower cortical but higher subcortical alteration. THis study thus confirm the dopaminergic vulnerability within the ALzheimer's and Lewy bodies spectrum, with importan implications for individualized management of cognitive and behavioral shymptoms.

SHIFT 02-409

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4 - 5 April

PROGNOSTIC VALUE OF NEUROINFLAMMATION [11C]PK11195 PET ON LONGITUDINAL COGNITIVE DECLINE AND SURVIVAL UP TO 15 YEARS AFTER PET IN ALZHEIMER'S DISEASE

Roos Rikken[1], Emma Coomans[2], Maqsood Yaqub[1], Anne Van Der Vlies[2], Frederik Barkhof[1], Bert Windhorst[1], Yolande Pijnenburg[2], Wiesje M. Van Der Flier[2], Ronald Boellaard[1], Everard Vijverberg[2], Elsmarieke Van De Giessen[1]
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Aims: Neuroinflammation plays a key role in Alzheimer's disease (AD) pathophysiology. However, whether neuroinflammation has a prognostic effect on disease progression is largely unknown. Therefore, we aim to investigate the role of neuroinflammation as measured using PET on longitudinal cognition and survival.
Methods: We included 28 amyloid-positive participants (N=9 MCI, N=19 AD dementia) and 21 healthy controls from a historical cohort who underwent dynamic [^{11}C]PK11195 (TSPO) PET to quantify neuroinflammation **(table 1)**. Principal component analysis (PCA) was performed to identify relevant [^{11}C]PK11195 signal. Longitudinal MMSE covering a period up to 11 years was used to measure cognitive decline (median: 5.8, range: 0.3-11.6 years). We used linear mixed models with random intercept and slope corrected for age, sex and education to investigate the effect of neuroinflammation on cognition. Survival data were available for all participants, up to 15.7 years (median: 7.3 years, range: 0.4-15.7) after PET. To examine the influence of neuroinflammation on survival time, we used age, sex, and diagnosis adjusted cox proportional-hazards models for both regions.

	HC (N=21)	MCI (N=9)	AD (N=19)
Age			
Mean (SD)	68 (± 7.5)	72 (± 5.5)	69 (± 7.6)
Sex			
f	8 (38.1%)	3 (33.3%)	8 (42.1%)
m	13 (61.9%)	6 (66.7%)	11 (57.9%)
Education (Verhage)			
Mean (SD)	NA (± NA)	4.7 (± 1.3)	5.1 (± 1.3)
Missing	21 (100%)	0 (0%)	0 (0%)
MMSE			
Mean (SD)	29 (± 0.73)	26 (± 1.3)	22 (± 2.6)
Missing	2 (9.5%)	0 (0%)	5 (26.3%)

Results: 2 PCs explaining >10% of variance each were retained. PC1 was most explained by [^{11}C]PK11195 binding in the thalamus, and PC2 related mostly to entorhinal activity **(figure 1)**. [^{11}C]PK11195 in PC1 or PC2 did not predict longitudinal MMSE (PC1: β=-0.03, P=0.963; PC2: β= 0.123, P= 0.335) or survival (PC1: HR=0.90, P=0.13; PC2: HR=0.96, P=0.7) **(figure 2)**.

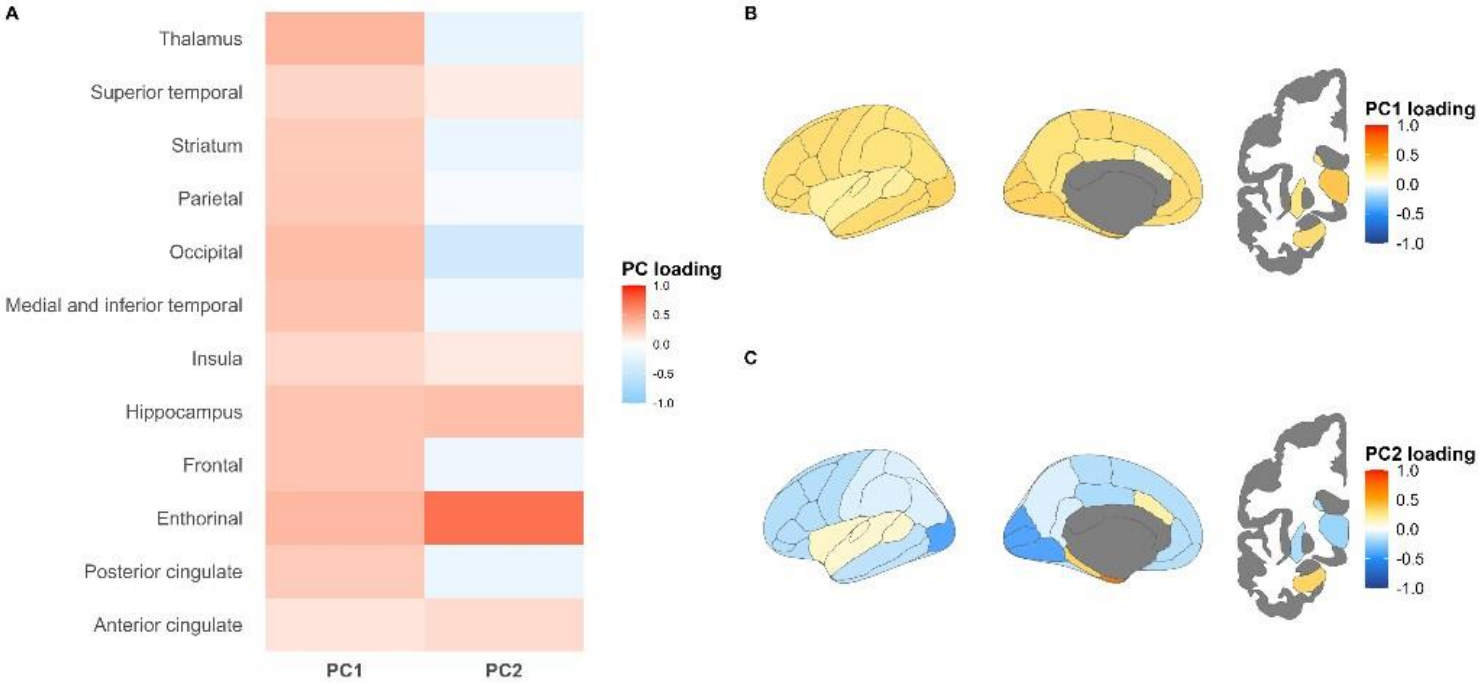

Figure 1 Visualization of PCA results. A) Heatmap showing the contribution of each region to PC1 and PC2. **B)** Regional visualization of contributions to PC1 and PC2. Regional values were extracted from Svarer atlas and superimposed on the corresponding regions from the Desikan-Killiany atlas.

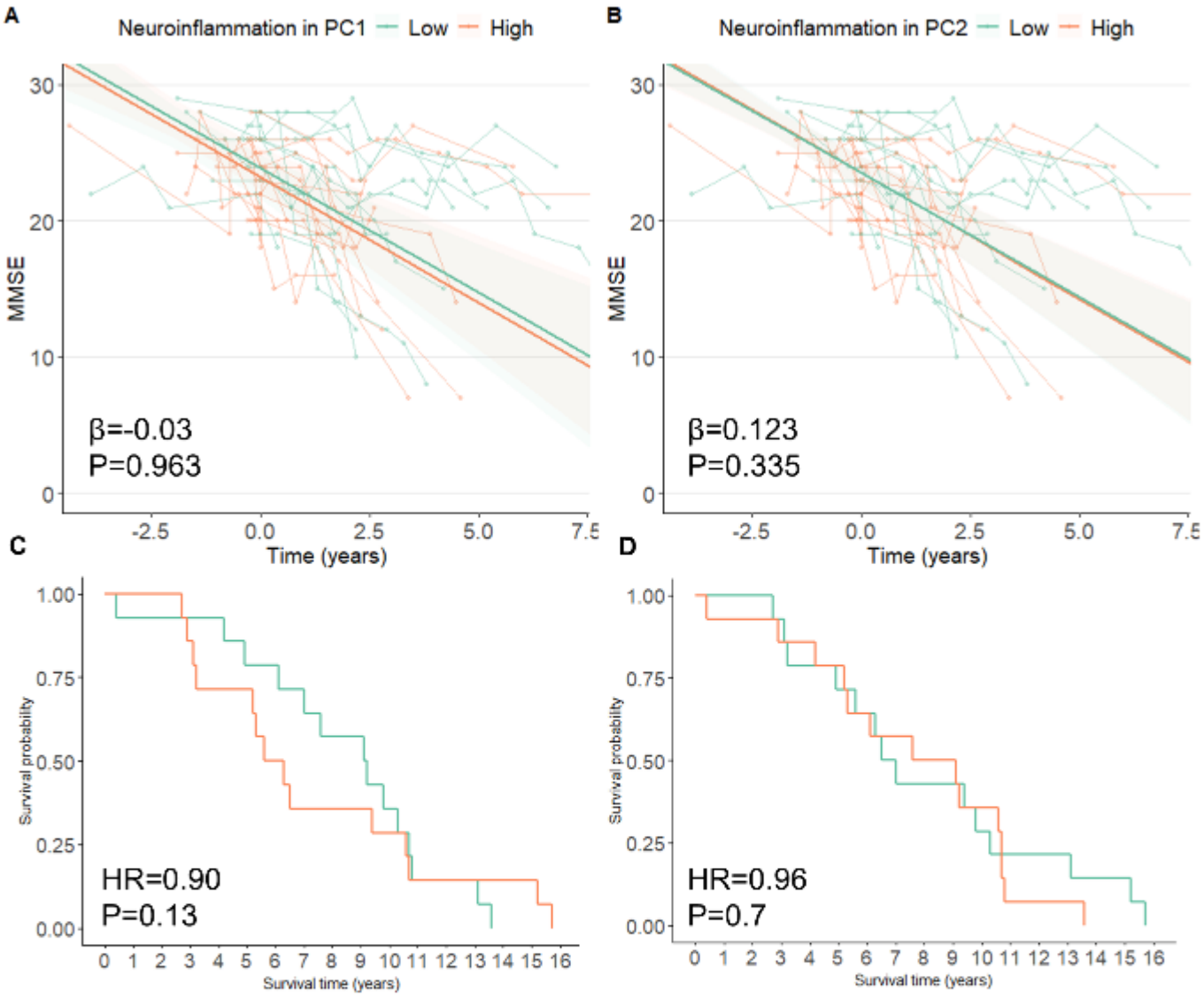

Figure 2 neuroinflammation predicting longitudinal MMSE and survival. AB) Plot showing the prognostic effect of [^{11}C]PK11195 in PC1 and PC2 on longitudinal MMSE. **CD)** Plot showing the prognostic effect of [^{11}C]PK11195 in PC1 and PC2 on survival probability over time. [^{11}C]PK11195 in PC1 and PC2 were dichotomized to the median of the whole group in each PC separately for visualization only, resulting in a low (green) and high (orange) neuroinflammation group.

Conclusions: In this initial set of analyses covering up to 11 year cognitive follow-up and survival information of 15 years after PET, we did not find evidence for neuroinflammation PET predicting cognitive decline or survival.

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SHIFT 02-410

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4 - 5 April

EVALUATION OF A SENSITIVE VISUAL READ ALGORITHM FOR ASSESSING TAU PET IMAGES

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Aims: Developing sensitive visual read algorithms for assessing tau-PET imaging is imperative considering the implementation of the methodology in clinical practice and trials. Here we aimed to compare two visual read algorithms for tau-PET images to semiquantitative measurements and plasma phospho-tau217 (p-tau217).
Methods: 1654 participants were recruited to the BioFINDER-2 study from Memory and Neurology clinics in southern Sweden. All participants underwent [^{18}F]RO948 PET scans and 37 participants additionally underwent a head-to-head [^{18}F]flortaucipir PET scan. PET scans were read visually according to the BioFINDER visual read protocol[1] and the established visual read method for [^{18}F]flortaucipir (FTP-VR)[2]. Comparative analyses were performed against semiquantitative standardized uptake value ratios (SUVRs) in the entorhinal cortex (ERC) and a temporal meta-ROI, and with the ability to estimate plasma p-tau217 status.
Results: Both visual read methods exhibited strong concordance with semiquantitative SUVRs (Figure 1). However, the BioFINDER visual read demonstrated superior sensitivity for tau in the ERC compared to FTP-VR ((mean[95%C.I.]) 0.912[0.881-0.936] vs. 0.761[0.719-0.8]; p<0.0001), while maintaining a comparable specificity (0.951[0.937-0.962] vs. 0.949[0.935-0.961]; p=0.77). The BioFINDER visual reads displayed heightened sensitivity (0.952[0.925-0.971] vs. 0.925[0.893-0.95]; p=0.008) albeit with a lower specificity (0.909 [0.891-0.924] vs. 0.955[0.942-0.965]; p<0.0001) for detecting tau in the temporal meta-ROI. Further, the BioFINDER visual reads exhibited higher sensitivity (0.709[0.667-0.749]) compared to FTP-VRs (0.641 [0.597-0.683]; p<0.0001) for detection of p-tau217 abnormality. The inter-rater reliability of the BioFINDER algorithm was excellent (weighted Cohen's kappa [κ]=0.87[0.82-0.93]) and intra-rater reliability almost perfect (κ=0.94[0.89-0.98]).

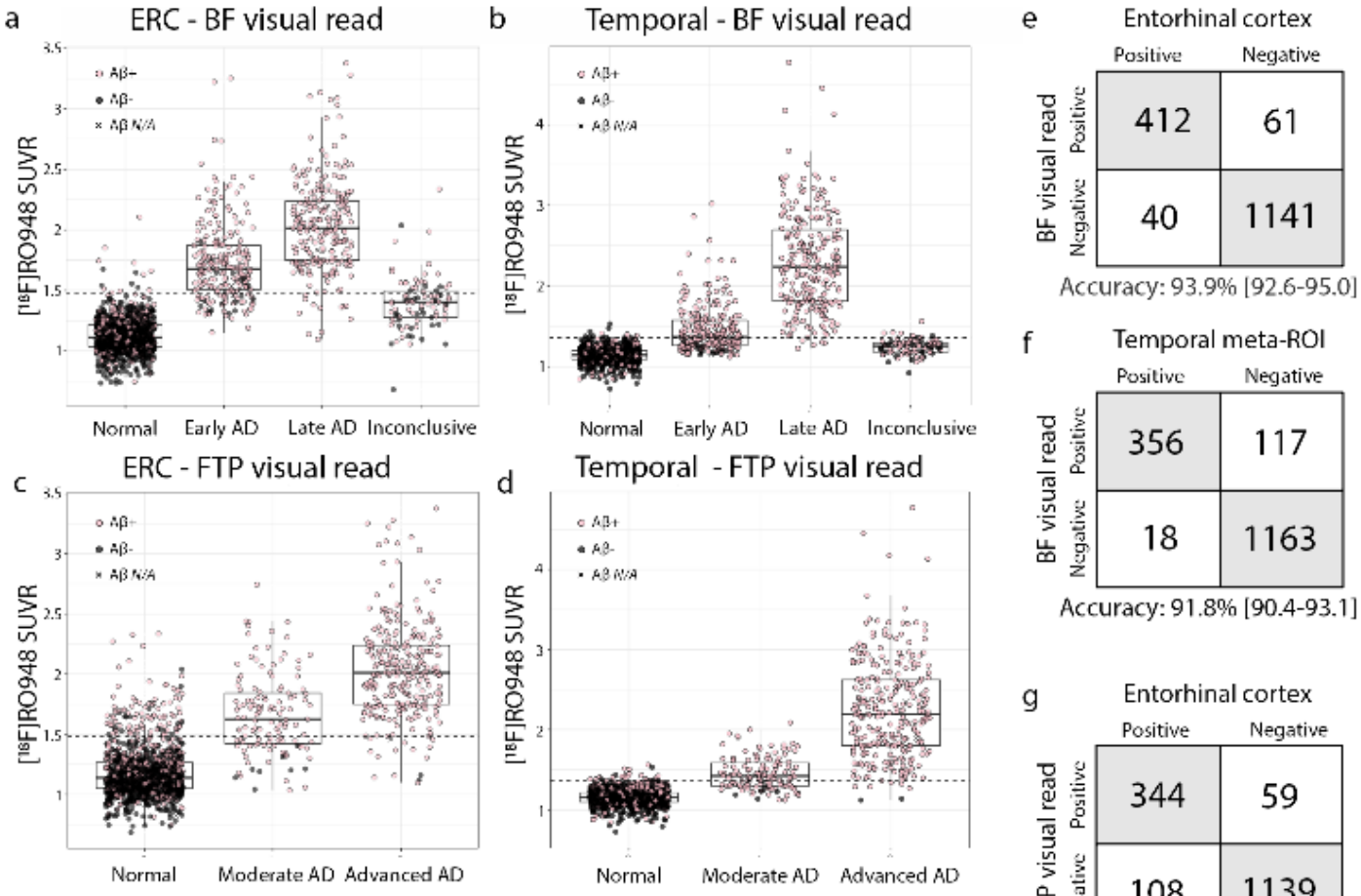

Figure 1. Comparison of visual read algorithms to semiquantitative measurements. a-b) SUVR values in the a) entorhinal cortex and b) in a temporal meta-ROI in the different BioFINDER visual read categories. Pink dots indicate Aß-positive and black dots Aß-negative participants. c-d) SUVR values in the c) entorhinal cortex and d) in a temporal meta-ROI in the different FTP visual read categories. Pink dots indicate Aß-positive and black dots Aß-negative participants. Tables in e-f) show the concordance between BioFINDER visual reads and the SUVR measurements in e) the entorhinal cortex, and f) the temporal meta-ROI, as well as the accuracies for the visual read in predicting abnormal semiquantitative values [95% confidence intervals in square brackets]. Tables in g-h) show the concordance between FTP visual reads and the SUVR measurements in g) the entorhinal cortex, and h) the temporal meta-ROI. Dashed lines in graphs represent semiquantitative cutoffs (1.48 in ERC and 1.36 in temporal meta-ROI). Aß- – Aß negative; Aß+ – Aß positive; MCI – mild cognitive impairment; ROI – region of interest; SCD – subjective cognitive decline; SUVR – standardized uptake value ratio.

Conclusions: The BioFINDER algorithm provides a more sensitive algorithm for detecting early tau uptake compared to the established FTP-VR algorithm and shows a similar performance when using [^{18}F]RO948 and [^{18}F]flortaucipir images, indicating that the visual read method can easily be applied to [^{18}F]flortaucipir PET scans.

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1. Smith R, Hagerstrom D, Pawlik D, et al. Clinical Utility of Tau Positron Emission Tomography in the Diagnostic Workup of Patients With Cognitive Symptoms. *JAMA Neurol.* Jul 1 2023;80(7):749-756. doi:10.1001/jamaneurol.2023.1323
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SHIFT 02-411

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4 - 5 April

RADIOSYNTHESIS AND IN VIVO EVALUATION OF SIX CARBON-11 RADIOTRACERS FOR IMAGING THE SIGMA-1 RECEPTOR IN ALZHEIMER'S DISEASE

Anil Soda[1], Tianyu Huang[1], Wenjuan Zhou[1], Hong Chen[1], Hao Jiang[1], Sandip Jadhav[1], Zhimin Xing[1], Linlin Tian[2], Stephen Moerlein[1], Joel Perlmutter[2], Ruiqing Ni[3], Tammie Benzinger[1], Zhude Tu[1]
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Aims: Alzheimer's disease (AD) is the primary cause of senile dementia and a progressive neurological condition. Despite substantial research efforts, the exact cause of AD remains unclear. Sigma-1 receptor (σ_1R) plays a key role in various physiological and pathological conditions in the central nervous system. Herein, we report our efforts on development and validation of six C-11 labeled radioligands for imaging σ_1R in brain. Our goal is to identify a promising σ_1R radiotracer for clinical investigation of patients with AD.
Methods: We synthesized and radiosynthesized six radiotracers (-)[^{11}C]**TZ3114**, (+)[^{11}C]**TZ3114**, (-)[^{11}C]**TZ9667**, (+)[^{11}C]**TZ9667**, (-)[^{11}C]**TZ96105** and (+)[^{11}C]**TZ96105** and measured *in vitro* binding potency and selectivity for σ_1R. The tissue distribution study was performed for (-)[^{11}C]**TZ3114** in adult male Sprague-Dawley rats. Brain PET imaging studies of these six radiotracers were performed in male cynomolgus macaques with 120 min dynamic scans. Radiometabolite analysis of (-)[^{11}C]**TZ3114** was performed for macaque plasma samples collected during the PET scans.
Results: The six C-11 radiotracers were synthesized with a yield of 16-20%, high specific activities and purities. The rat brain uptake of (-)[^{11}C]**TZ3114** was high with %ID/gram value of ~1.8 at 5 min and washed out quickly from the brain. PET imaging in monkeys revealed that all six radiotracers entered the brain well with good uptake. Plasma radiometabolite analysis showed no lipophilic radiometabolite for (-)[^{11}C]**TZ3114** at 60 min post-injection.
Conclusions: Our *ex vivo* biodistribution and PET brain studies suggested that (-)[^{11}C]**TZ3114** has good brain uptake with highly favorable brain washout kinetics, and good *in vivo* stability with no radiometabolites that enter the brain that could confound PET measurements. Together, our data suggested that (-)[^{11}C]**TZ3114** is a promising PET tracer for quantifying σ_1R levels in the brain of living animals.

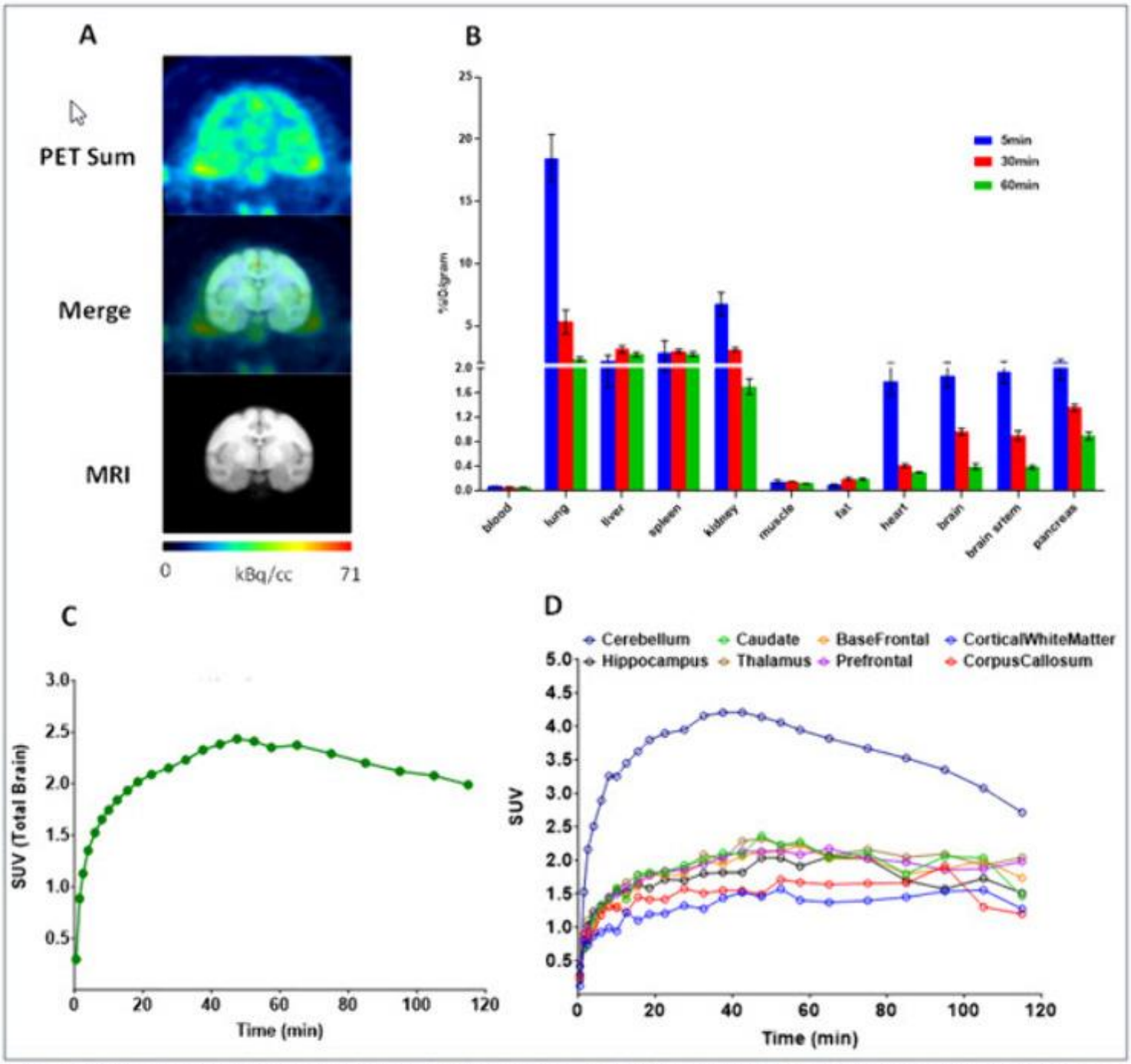

Figure: A) Summed PET image (top): Summed PET image overlaid on MRI (middle): MR image (down); B) Tissue distribution of (-)[^{11}C]**TZ3114** in male SD rats (mean ± SD, %ID per g, n=4); C) Time tissue activity curve for microPET study in the brain, SUV: standardized uptake value; D) Brain tissue time activity curve (TAC) from the baseline scan.

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SHIFT 02-417

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4 - 5 April

MULTILINGUALISM AND NEURODEGENERATION: INVESTIGATING THE DOSE-EFFECT RELATIONSHIP IN A SINGAPOREAN COHORT

Elenor Morgenroth[1], Nicole Isabella Tan[1], Yi Jayne Tan[1], Kok Pin Ng[2,3,4], Hui Jin Chiew[2,3,4], Simon Ting[2,4], Shahul Hameed[2], Adeline Ng[2,3,4]
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Aims: Identifying modifiable risk factors for neurodegenerative disorders is crucial for early prevention strategies. Bilingualism has been shown to act as a protective factor against dementia; however, the impact of speaking more than two languages on neurodegeneration remains unclear. Furthermore, the effect of multilingualism on regional atrophy in the brain is underexplored. Singapore's multilingual population presents a unique opportunity to investigate this phenomenon, given its high prevalence of individuals fluent in three or more languages. This study aimed to explore the relationship between multilingualism and neurodegeneration, specifically assessing whether there is a dose-effect relationship between speaking more languages and brain atrophy.
Methods: We recruited 57 patients from the National Neuroscience Institute's memory clinic, with a mean age of 67.23 years (SD=9.29). Of these patients, 7% were neurologically healthy, 72% were diagnosed with subjective or mild cognitive impairment, 14% with Alzheimer's disease, and the rest were diagnosed with other or mixed neurodegenerative diseases. We categorized participants by the number of languages spoken: 18 spoke one, 14 spoke two, and 25 spoke three or more languages. The most commonly spoken languages were English (92%), Mandarin Chinese (63%) and other Chinese dialects. Data on the age of language acquisition and literacy in each language were not available. Structural brain imaging using a 3T Philips MRI scanner and segmentation was performed.
Results: Increased multilingualism was associated with larger volumes in the right lingual gyrus and left inferior frontal gyrus pars opercularis. Bilingual individuals had a larger right parahippocampal gyrus compared to the two other groups. Neither effects survived correction for multiple comparisons.
Conclusions: Multilingualism, particularly speaking three or more languages, may be linked to specific neuroanatomical differences, offering insights into its potential protective effects against neurodegeneration.

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SHIFT 02-418

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4 - 5 April

ASSOCIATION BETWEEN CSF LRRK2 LEVELS AND CORTICAL MICROSTRUCTURAL DISARRAY IN PARKINSON'S DISEASE: INSIGHTS INTO A POTENTIAL BIOMARKER FOR CORTICAL INTEGRITY

Mario Torso, Ged Ridgway, Ian Hardingham, Steven Chance
Oxford Brain Diagnostics Ltd, Oxford, United Kingdom

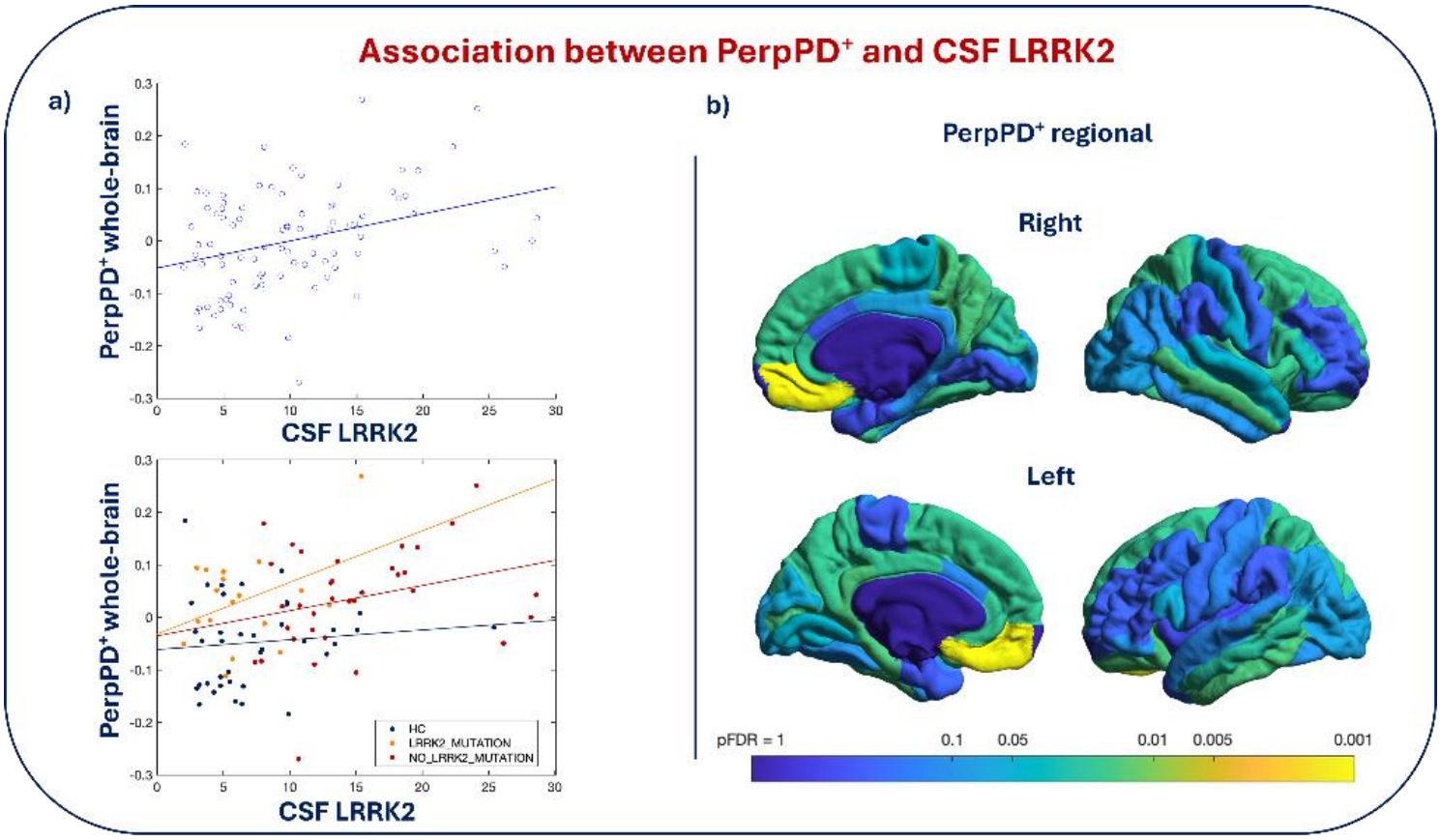
Aims: Leucine-rich repeat kinase 2 (LRRK2) protein is implicated in the pathogenesis of Parkinson's disease (PD) and a potential therapeutic target for the treatment of PD. Levels of LRRK2 in CSF are a potential biomarker for disease progression but the relationship with cortical integrity remains unclear. This study investigated the association between LRRK2 levels and cortical changes, in prodromal PD and early-moderate PD.
Methods:

Table 1 Demographic and clinical characteristics

	HEALTHY CONTROLS (n=38)	LRRK2-MUTATION (n=18)	NO-LRRK2-MUTATION (n=34)
AGE mean (sd)	61.6 (10.9)	62.9 (7.7)	62.3 (8.3)
SEX female % (n)	34.2 (13)	50 (9)	32.3 (11)*#
Disease duration mean (SD)	-	3.3 (2.3)	2.3 (0.9)
MoCA mean (sd)	28.1 (1.1)	27.2 (2)	27.2 (2.7)
MDS - UPDRS – pt III mean (sd)	0.58 (1.6)	9.1 (11.2) *	21.4 (13.3) *#
MDS - UPDRS total mean (sd)	2.66 (2.6)	19 (24.9) *	34.9 (19.4) *#
MDS - UPDRS HY mean (sd)	0	0.7 (1.1) *	1.53 (0.7) *#
CSF LRRK2 (pg/mL), mean (sd)	7.4 (4.7)	6.5 (3.6)	14.9 (5.8) *#

*Significantly different compared to HEALTHY CONTROLS;
#Significantly different compared to LRRK2-MUTATION

Ninety participants [Table1] with LRRK2 levels from the Parkinson's Progression Markers Initiative (PPMI) included: 38 healthy controls, 18 LRRK2-MUTATION carriers (11 prodromal-PD, 7 manifest-PD) and 34 NO-LRRK2-MUTATION carriers (5 prodromal, 29 manifest). T1-structural and diffusion-weighted MRI scans were used to extract cortical volume, cortical thickness and three cortical microstructural measures: the angle between the radial minicolumnar direction and the principal diffusion direction (AngleR); the diffusion parallel with the minicolumns (ParlPD), and the diffusion perpendicular to the minicolumns (PerpPD^{+}) [PMID:31355989; PMID:33174658; PMID:36281682]. Association between LRRK2 levels and cortical whole-brain and regional metrics were tested with linear models, adjusting for sex and variations in scanner software or protocol, with false discovery rate correction (pFDR<0.05).
Results:



Results revealed significant association between CSF LRRK2 and cortical microstructural values. Specifically, LRRK2 concentrations were positively correlated with whole-brain PerpPD$^+$ values (η_p^2 = 0.114; pFDR = 0.005) [Figure1a]. Figure1b shows a wide pattern of regional association between LRRK2 and PerpPD$^+$ values in cortical regions known to be affected in PD, including the frontal, parietal and temporal regions. No significant associations between LRRK2 levels and macrostructural metrics (cortical volume and thickness) were detected.

Conclusions: These findings highlight the utility of cortical disarray measures from diffusion MRI for understanding the pathophysiological changes in PD, and their potential for tracking cortical changes and responses to treatments targeting LRRK2.

SHIFT 02-419

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4 - 5 April

CORTICAL MICROSTRUCTURAL MEASUREMENTS FROM DIFFUSION MRI CORRELATE WITH PLASMA GFAP IN ALZHEIMER'S DISEASE USING FNIH ROCHE AND QUANTERIX ASSAYS

Mario Torso[1], Ged Ridgway[1], Ian Hardingham[1], Steven Chance[1], Alzheimer's Disease Neuroimaging Initiative (Adni)[2]
[1]Oxford Brain Diagnostics Ltd, Oxford, United Kingdom, [2]ADNI, San Francisco, United States of America

Aims: Plasma glial fibrillary acidic protein (GFAP), a marker of astroglial activation, has emerged as a promising biomarker for neuroinflammation in Alzheimer's disease (AD). We have previously demonstrated correlations between CSF neuroinflammation-associated biomarkers and cortical disarray measurements from diffusion MRI [PMID:36281682]. This study investigates the association between plasma GFAP measured using two different immunoassays and cortical microstructural measures.
Methods:

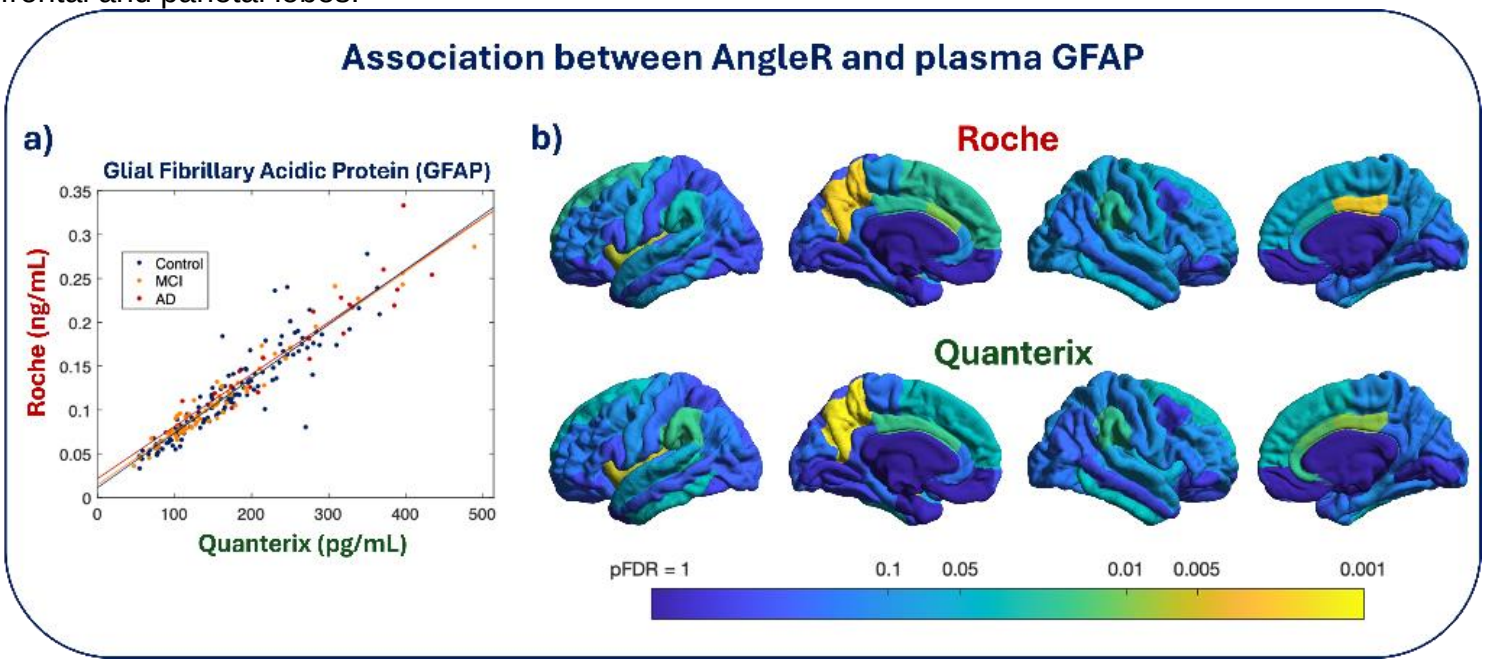
Table 1 Demographic and clinical characteristics

	Controls (n=129)	MCI (n=66)	AD (n=20)
Age mean (sd)	77.4 (6.9)	76.8 (6.3)	78.7 (9.1)
Sex female % (n)	53.5 (69)	36.4 (24)	55 (11)
MMSE mean (SD)	28.9 (1.4)	28.2 (2.3)	20.1 (5.7))*#
CDR global mean (sd)	0	0.51 (0.2)*	1.2 (1.1)*#
Cortical Volume Fraction mean (sd)	0.29 (0.02)	0.28 (0.02)	0.25 (0.03)*#
Cortical Thickness mean (sd)	2.45 (0.1)	2.44 (0.1)	2.31 (0.2)*#
Hippocampal Volume Fraction mean (sd)	0.0049 (0.0006)	0.0046 (0.0007)*	0.0038 (0.0009)*#
Amyloid PET SUVR mean (sd)	1.1 (0.2)	1.1 (0.2)	1.4 (0.2)*#

*Significantly different compared to Controls;
#Significantly different compared to MCI

Two hundred fifteen participants [Table1] from ADNI with Roche and Quanterix GFAP levels from the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium were included in the study. T1-structural and diffusion-weighted MRI scans were used to extract a cortical microstructural measure previously shown to be associated with neuroinflammation [PMID:36281682]: the angle between the radial minicolumnar direction and the principal diffusion direction (AngleR) [PMID:31355989; PMID:33174658]. Associations between GFAP levels and cortical whole-brain and regional metrics were tested with linear models, adjusting for sex, amyloid PET SUVR (cerebellum reference) and variations in scanner model or protocol, with false discovery rate correction (pFDR<0.05).
Results: At whole brain level, our analyses revealed significant positive correlations between plasma GFAP (for either assay), and increased cortical AngleR (Roche η_p^2= 0.047, pFDR= 0.002; Quanterix

η_p^2= 0.041, pFDR= 0.006) The two different assays were broadly consistent [Figure1a]. Regional analysis [Figure1b] showed a wide pattern of association between plasma GFAP levels and microstructural changes in regions commonly involved in AD pathology progression, spanning temporal, frontal and parietal lobes.



Conclusions: These results suggest that measures of cortical disarray can provide additional information on neuroinflammation in different cortical regions and, in combination with plasma GFAP biomarkers, may be useful for measuring neuroinflammation throughout the course of Alzheimer's disease and for assessing potential responses to targeted treatments.

SHIFT 02-422

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4 - 5 April

ENGINEERED LIPOSOMES FOR THE TARGETED DELIVERY OF EPIGALLOCATECHIN INHIBIT AB FIBRILLATION

Ângela Ferreira[1,2], Andrade Stéphanie[1,2], Maria Ramalho[1,2], Joana Loureiro[1,2,3], Maria Pereira[1,2]
[1]LEPABE, Porto, Portugal, [2]Alice, Porto, Portugal, [3]FEUP, Department Of Metallurgical And Materials Engineering, Porto, Portugal

Aims: Alzheimer's disease (AD) is a severe neurodegenerative disorder with no cure, highlighting the need for new treatment strategies. One approach is targeting the brain with compounds that reduce amyloid β (Aβ) plaques and slow disease progression. Epigallocatechin (EGC) shows promise but struggles with low bioavailability and difficulty crossing the blood-brain barrier. Nanoparticles have emerged as a solution to encapsulate bioactive compounds and address their limitations. Thus, this study aims to develop engineered liposomes to direct EGC to the AD brain.
Methods: Four formulations of liposomes, combining different phosphatidylcholines with cholesterol and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:0 PEG2000 PE) (82:15:3 molar ratio), were tested to encapsulate EGC using the thin-film hydration method. Their properties were analyzed by dynamic light scattering, electrophoretic light scattering, transmission electron microscopy, and Fourier-transform infrared spectroscopy (FTIR). Liposomes' antioxidant activity was assessed with the DPPH assay, and the Thioflavin T (ThT) fluorescence assay was used to test their ability to prevent Aβ aggregation.
Results: All formulations had sizes under 180 nm and neutral zeta potentials, making them suitable for drug delivery. EGC was successfully encapsulated with a maximum encapsulation efficiency of 38±3%. Liposomes' functionalization with Tf was successfully confirmed by FTIR, with 418±20 Tf molecules per liposome, enhancing the targeted delivery of EGC to the brain. Moreover, the results showed that EGC-loaded Tf-functionalized liposomes exhibited antioxidant activity in a dose-dependent relationship (47±10% at 12.5 µg/mL) and that the EGC's antioxidant activity was preserved after its encapsulation. Furthermore, ThT data showed that EGC-loaded Tf-functionalized liposomes completely inhibited the formation of Aβ fibrils.
Conclusions: The developed liposomes presented suitable physicochemical properties, adequate antioxidant properties, and robust anti-amyloidogenic activity, thus being a promising strategy for AD therapy.

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SHIFT 02-433

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / APOE & LIPOPROTEIN-BASED
4 - 5 April

PROFILING PROTEOMIC SIGNATURES OF APOE4 IN THE HUMAN LIVER

Maja Sjödahl[1], Henrietta Nielsen[1], Kalicharan Patra[1], Andreas Giannisis[1], Anezka Niesnerova[1], Ewa Ellis[2]
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Aims: The *APOE*4 allele is the strongest genetic risk factor for Alzheimer's disease (AD). Results from previous studies, including our own, suggest a yet understudied role of the liver in the *APOE*4-promoted risk of AD. Preliminary data from our lab suggest that 624 genes are differentially expressed in *APOE*4-livers and we recently showed that *APOE* genotype also dictates the hepatic lipidome. Here we aimed to profile the hepatic proteome from *APOE*4 vs non-*APOE*4 donors using state-of-the-art proteomics.
Methods: Pellets of isolated, frozen and never-cultured, primary human hepatocytes from a total of 75 donors were lysed, digested by RapiZyme Trypsin and prepared for LC-MS/MS analysis. TMT- isobaric labeling was used for relative quantification. The mass spectrometry analysis was performed by the Clinical Proteomics Mass Spectrometry facility Karolinska Institutet/ Karolinska University Hospital/ Science for Life Laboratory in Stockholm Sweden. MSGF+ and Percolator in the Nextflow platform (https://github.com/lehtiolab/ddamsproteomics, v2.17) was used to match MS spectra to the *Ensembl* Homo sapiens (111) protein database. Results are reported as log2 transformed normalized TMT ratios and express the relative abundance of each protein in each sample.
Results: Forty eight percent of the donors were female, thirty two percent carried the *APOE*4 allele and the donor age ranged between 1-86 years. A total of 10941 peptides corresponding to on average 9662 proteins were identified. Results from unbiased comparisons between *APOE*4 versus non-*APOE*4 donors propose differentially altered concentrations of various proteins including, but not limited to, APBA3, TERB1, ASPM, RRM2 and ZNF219.
Conclusions: Our results propose that the *APOE*4 genotype translates to a specific hepatic proteomic phenotype. Further studies are needed to elucidate the physiological relevance of the *APOE*4 hepatic proteome to the risk and development of AD.

SHIFT 02-438

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4 - 5 April

STRUCTURE-BASED VACCINES TARGETING DISCONTINUOUS AB EPITOPES PREVENT AMYLOID PLAQUE DEPOSITION IN MALE 5XFAD MICE

Aishwarya Sriraman[1], Karthivashan Govindarajan[2], Serene Wohlgemuth[1], Kenneth Oliveros[1], José Flores-Fernández[1], Jialing Liu[3], Satyabrata Kar[4], Holger Wille[1]
[1]Centre for Prions and Protein Folding Diseases, University of Alberta, Biochemistry, Edmonton, Canada, [2]Centre for Prions and Protein folding diseases, Medicine (neurology), Edmonton, Canada, [3]University of California, San Francisco & San Francisco Veterans Affairs Medical Center, Neurosurgery, San Francisco, United States of America, [4]University of Alberta, Medicine, 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 beta-sheet rich conformations and form oligomers and amyloid fibrils. Many attempts have been made to develop vaccines as prophylactics for AD employing these proteins in their linear form, but lacked structural specificity. Here, we present a novel approach to design vaccines based on the structures of Aβ fibrils that present their epitopes in a structurally-controlled manner.
Methods: The innocuous HET-s protein adopts a beta-sheet rich conformation in its native state and was engineered to carry select Aβ surface epitopes in a discontinuous and structurally-controlled manner. Vaccines were expressed in *E. coli*, purified, refolded, controlled for their structural fidelity, and used to immunize 5xFAD transgenic mice. The brains of unimmunized and immunized 5xFAD mice were collected at ~200 days of age and analyzed for their Aβ plaque load.
Results: As expected, unimmunized 5xFAD mice showed widespread Aβ plaque deposition throughout their cortex and hippocampus. 5xFAD mice immunized with unmodified HET-s displayed no benefit and had essentially indistinguishable Aβ plaque loads from unimmunized animals. Mice that were immunized with the structure-based vaccines had significantly reduced Aβ plaque deposits, but showed pronounced sex differences: female 5xFAD mice had a ~50% overall reduction in their plaque load, while many male 5xFAD mice were essentially devoid of Aβ plaques.
Conclusions: Structure-based vaccines targeting surface-exposed, discontinuous Aβ epitopes can prevent Aβ plaque deposition in male 5xFAD mice. However, immunized female 5xFAD mice display less benefit from the vaccines. Further investigations are needed to elucidate the underlying mechanisms for the observed sex differences and to increase the prophylactic efficacy of the novel vaccines.

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SHIFT 02-439

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4 - 5 April

PEPTOIDS AS POTENTIAL DUAL-TARGET THERAPEUTICS TO REDUCE S100B-INDUCED RAGE-ASSOCIATED NEUROINFLAMMATION AND AMYLOID-BETA AGGREGATION IN ALZHEIMER'S DISEASE

Mihyun Waugh[1], Amy Veihdeffer[1], Michael Kaven[1], Nicholas Truex[2], Shannon Servoss[3], Melissa Moss[4]
[1]University of South Carolina, Biomedical Engineering, Columbia, United States of America, [2]University of South Carolina, Chemistry And Biochemistry, Columbia, United States of America, [3]University of Arkansas, Chemical Engineering, Fayetteville, United States of America, [4]University of South Carolina, Chemical Engineering; Biomedical Engineering, Columbia, United States of America

Aims: We demonstrate peptoids JPT1 and JPT1a as dual-modulators of RAGE-mediated neuroinflammation and amyloid-β (Aβ) aggregation. Specifically, we assess the effect of peptoids on S100B-induced inflammation through cytokine release and viability of neuronal cells treated with cytokines and/or Aβ aggregates as well peptoid modulation of Aβ aggregation. Additionally, we demonstrate nanomolar binding affinity between sRAGE and the peptoids and evaluate their ability to competitively bind to RAGE in the presence of S100B.
Methods: SPR is used to measure peptoid-sRAGE binding affinity as well as the ability of peptoids to compete against S100B for RAGE binding. Multiplex assay is performed to evaluate peptoid attenuation of S100B-induced pro-inflammatory cytokine release from THP-1 macrophages. These supernatants are used to treat SH-SY5Y neuronal cells in combination with Aβ to assess peptoid neuroprotective effects via neurite growth and cell viability. The influence of peptoids on the Aβ aggregation is determined via thioflavin T fluorescence. Lastly, molecular modeling simulations are conducted to predict peptoid binding site on RAGE in the presence of S100B.
Results: THP-1 macrophages exposed to S100B exhibited significantly reduced levels of proinflammatory cytokines when simultaneously treated with peptoid (Figure 1). Furthermore, the presence of peptoids during Aβ aggregation reduced the amount of aggregates (Figure 2) while also reducing lag time to aggregate formation.

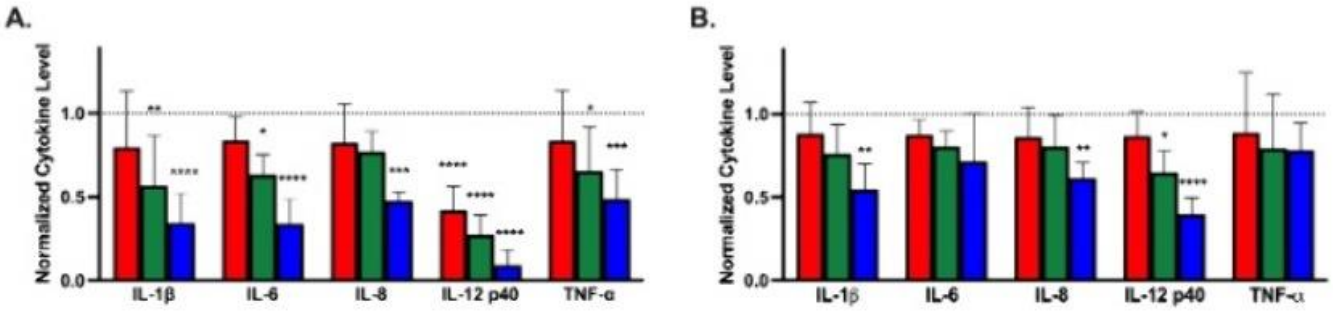

Figure 1. THP-1 macrophages exposed to 0.05 µg/mL S100B were co-treated without or with 10 (red), 20 (green), or 50 µM (blue) JPT1 (panel A) or JPT1a (panel B). Quantified cytokine levels were normalized to the positive control, indicated by dotted line at y = 1.

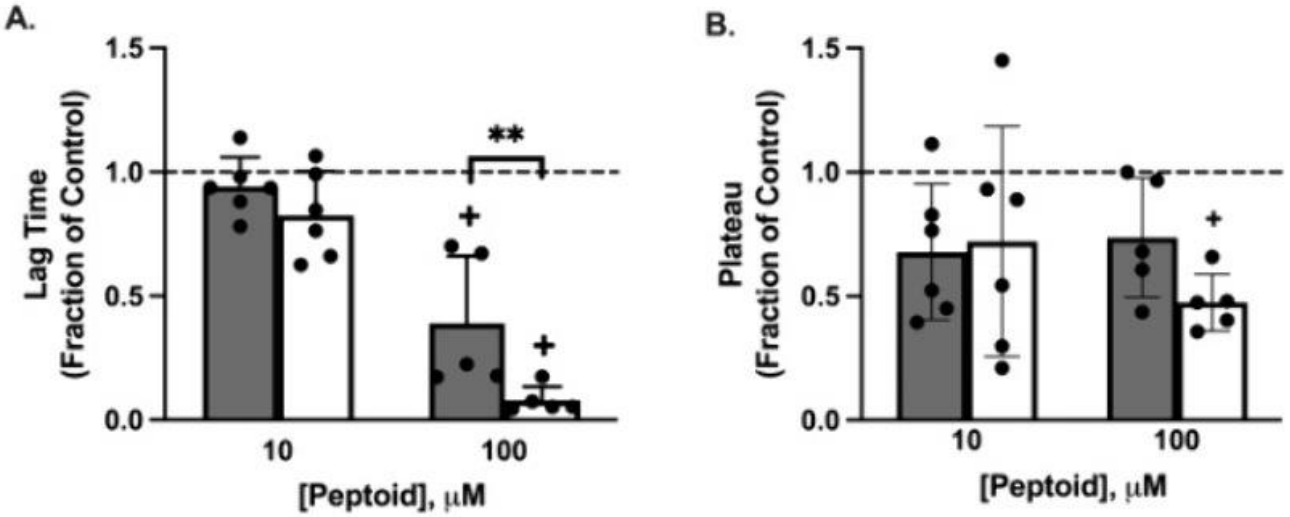

Figure 2. $A\beta_{1-40}$ monomer aggregation was observed without or with JPT1 (grey) or JPT1a (white). Lag time (panel A) and plateau (panel B) of aggregation were quantified as a fraction of control, indicated by dotted line at y = 1.

Conclusions: Peptoids JPT1 and JPT1a significantly attenuate pro-inflammatory cytokine responses induced by RAGE ligand S100B and associated neuronal toxicity. Such result implicates peptoids as potential therapeutic agents for not only AD but also for other inflammation-associated illnesses. Because these peptoids also exhibit the ability to modulate Aβ aggregation, they may function as dual-target therapeutics for AD.

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SHIFT 02-444

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
4 - 5 April

A FUNCTIONAL GENOMICS APPROACH TO IDENTIFY DRUG TARGETS WITHIN THE INFLAMMASOME: RATIONAL DESIGN OF NOVEL, LOW-TOXICITY INHIBITORS

Falak Sher[1], Jason C Ngo[2], Marta Olah[2]
[1]Columbia University Medical Center, Neurology, New York, United States of America, [2]CUMC, New York, United States of America

Aims: The inflammasome drives neuroinflammation in neurodegenerative diseases e.g AD and PD. Targeting inflammasome offers a promising therapeutic strategy. However, current inhibitors have limited efficacy. Developing precise inhibitors that suppress activation with minimal toxicity is essential for advancing neuroinflammatory treatments. Aims: Our goal was to create a functional genomics toolkit to study microglial inflammasome activation and identify drug targets. This involved developing a CRISPR-Cas9 screening platform to pinpoint key regions and applying machine learning to design low-toxicity inhibitors.
Methods: We developed an improved protocol for differentiating microglia from induced pluripotent stem cells (iPSCs), optimized for functional genomic screens. Using this platform, we generated a CRISPR-Cas9 library consisting of over 6,000 sgRNAs targeting all known subunits and variants of the inflammasome complex, perturbing virtually every amino acid within these proteins. We employed an ASC speck formation assay to quantify the effects of each perturbation on cell toxicity and inflammasome activation. Data from this screen were integrated with machine learning and AI-based approaches to identify critical amino acid residues within NLRP3 and ASC that can be targeted for the development of novel, rational inflammasome inhibitors.
Results: Our comprehensive CRISPR-Cas9 screen identified specific regions within NLRP3 and ASC that are essential for inflammasome activation but can be selectively inhibited to minimize cellular toxicity. By integrating these findings with compound databases such as PubChem, we have identified several promising compounds that can effectively inhibit inflammasome activation while exhibiting minimal toxicity in vitro.
Conclusions: Conclusion: This study advances the rational design of inflammasome inhibitors. Our machine learning-guided CRISPR screening identified novel compounds that could overcome the limitations of existing inhibitors. These findings lay a strong foundation for developing safer, more effective therapies for neuroinflammatory and other inflammasome-related diseases.

SHIFT 02-445

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE
4 - 5 April

ANNEXIN A6 MEMBRANE REPAIR PROTEIN PROTECTS AGAINST AMYLOID-INDUCED DYSTROPHIC NEURITES AND TAU PHOSPHORYLATION IN ALZHEIMER'S DISEASE MODEL MICE

Katherine Sadleir, Jelena Popovic, Karen Gomez, Abigail Edwards, Armana Patel, Makenna Ley, Joanna Guo, Robert Vassar
Northwestern University, Neurology, Chicago, United States of America

Aims: In Alzheimer's disease brain, amyloid plaques form first and likely cause tangles, but the mechanistic link between them is unclear. One hypothesis is that accumulation of pathological phospho-tau in peri-plaque dystrophic neurites is the link between amyloid deposition and development of tau pathology. We hypothesize that axonal contact with plaque β-amyloid causes membrane damage and calcium influx resulting in aberrant kinase and calpain activation, then tau hyperphosphorylation and aggregation. We aim to 1) assess calcium and calpain activity in dystrophic neurites 2) overexpress membrane repair protein Annexin A6 to decrease dystrophic neurites and their accumulation of phospho-tau 3) assess the potential of recombinant Annexin A6 as a therapeutic approach.
Methods: AAV was used to express a calcium or calpain sensor or Annexin A6-GFP in neurons of 5XFAD amyloid mouse. Calcium was measured by live slice microscopy, while calpain activity was quantified by immunoblot and FRET imaging. Dystrophic neurons were quantified by immunofluorescence, as were phosphorylated forms of tau, JNK and CaMKII. Recombinant A6 was stereotaxically injected into 5XFAD and NLGF brains, and localization assessed by immunofluorescence.
Results: In 5XFAD dystrophic neurites, calcium and calpain activity were increased. Overexpression of Annexin A6 reduced the amount and size of dystrophic neurites, and accumulation of tau p181. Human and mouse dystrophic neurites contained p-JNK, and p-CaMKII, known tau kinases and p-tau. Recombinant A6 localized to dystrophic neurites, indicating ability to bind damaged neuronal membranes in vivo.
Conclusions: Plaque-associated dystrophic neurons are sites of calcium elevation and calpain activation, likely due to membrane damage by amyloid, as overexpression of membrane repair protein Annexin A6 decreased dystrophic neurites. Recombinant A6 shows promise as a novel AD therapeutic targeting membrane damage, and current work is further testing this hypothesis.

SHIFT 02-446

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE
4 - 5 April

TARGETING EEF2 DYSFUNCTION TO AMELIORATE IMPARIMENTS OF SYNAPTIC TRANSMISSION AND COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE MOUSE MODELS

Lei Shi
Jinan University, Guangzhou, China

Aims: Protein homeostasis disruption is one of the main causes for synaptic dysfunction in Alzheimer's disease (AD). Accumulating evidence suggests that hyperphosphorylation of eukaryotic elongation factor 2 (eEF2), leading to inhibition of eEF2 activity and hence the repression of mRNA translation elongation, is identified in the hippocampus and cortex of both AD patients and animal models. Targeting eEF2 and its unique kinase eEF2K have shown great potential for the treatment of AD. This study aims to identify new eEF2K/eEF2 modifying compounds and explore their effects for ameliorate synaptic and cognitive dysfunction in AD mouse models.
Methods: Aβ-damaged primary hippocampal neurons and acute hippocampal slices were examined as in vitro models. APP/PS1 and 5XFAD mice were used as animal models. Protein synthesis levels were measured using puromycylation, FUNCAT, and polysome profiling. Spine morphology was measured by immunofluorescence in vitro, and Golgi staining in vivo. Synaptic transmission is measured by whole-cell patch clamp recordings. Neuronal and glial cells were labled by specific cell type markers by immunofluorescence. Cognitive function was meaused by behavior tests including novel object recognition, Morris water maze, and Barnes maze. Small molecule-protein interaction was determined by BiAcore.
Results: We identified a new blood barrier-penetrable small molecular compound, which could bind and activate eEF2, thus promoting protein synthesis and synaptic transmission. This compound shows promissing effects on alleviating cognitive impariments in both APP/PS1 and 5XFAD mice.
Conclusions: This study identifies a new eEF2-targeting compound which shows promising effects on ameliorating synaptic and cognitive impairment in AD mouse models.

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SHIFT 02-449

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4 - 5 April

INTRODUCTION OF A NOVEL SET OF SURFACE-MODIFIED LIPOSOMES AS A NANOCARRIER TO ENHANCE DRUG DELIVERY FOR ALZHEIMER'S THERAPY

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Aims: A limitation in the treatment of Alzheimer's disease is the inability of therapeutics to cross the blood-brain barrier (BBB). The explanations may be ascribed to two main contributors: i) most of the drugs cannot cross the blood-brain barrier (BBB), hindering effective treatment in the brain; ii) pharmaceuticals frequently lack selectivity and specificity, therefore diminishing the efficacy. Hence, the objective of this work was to engineer innovative liposomes as promising nanocarriers for drug administration across the BBB. This is achieved by altering the liposomes with a fluorine source to improve their permeability across the brain and a protein that enhances their affinity for the BBB.
Methods: The present work employed synthetic phospholipids to synthesize liposomes via the lipid hydration technique. The liposomes underwent surface modification using a fluorine source and targeting molecules. Their selectivity to the brain cells was evaluated *in vitro* using brain endothelial cells and *in vivo* using wild-type mice.
Results: The nanocarriers demonstrate to be stable for 6 months at 4 °C. The data from the *in vitro* uptake investigation indicated that protein-modified liposomes were absorbed more effectively than both fluorinated and dual-functionalized. An expected outcome was that the abundance of fluorine sources might obscure the impact of the targeting molecules when combined. The *in vitro* confirmation of the non-toxicity of the fluorinated liposomes enabled the determination that all the controls of fluorinated liposomes were non-toxic and suitable for *in vivo* use. In addition, the dual-functionalized liposomes have shown the ability to penetrate the brain even after 2 hours in wild-type mice.
Conclusions: These novel liposomes class show great potential as carriers to enhance existing Alzheimer's therapy and, additionally, provide a foundation for drugs that were unsuccessful in earlier clinical trials.

SHIFT 02-450

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4 - 5 April

TARGETING CHOLESTEROL METABOLISM FOR ALZHEIMER'S PREVENTION AND THERAPY IN WOMEN: EXPLORING CYP46A1 ACTIVATION AND SEX-SPECIFIC BIOMARKERS

Silvia Maioli[1], Ljerka Delac[2], Ines Da Costa Moreira[2], Maria Latorre Leal[2], Michelle Dunk[2], Ivan Nalvarte[2]
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Aims: Women represent approximately 70% of Alzheimer's disease (AD) cases, a disparity not fully explained by longevity alone. Estrogen loss during menopause is thought to exacerbate AD risk factors, including disrupted brain cholesterol metabolism, contributing to neurodegeneration. Our findings show that activating CYP46A1, an enzyme that clears brain cholesterol by converting it into 24S-hydroxycholesterol (24SOH), counteracts cognitive decline in aging and estrogen-deprived female mice *(Latorre Leal M et al, Science Advances 2024)*. With this project, we aim to: - Activate CYP46A1 to counteract neurodegeneration in women at elevated risk of AD. - To identify early biomarkers for predicting susceptibility to AD in women
Methods: We evaluate the effects of CYP46A1 activation in aged wild-type subjected to estrogen deprivation and in App $^{N\text{-}L\text{-}F}$ knock-in mice. We use behavioral assessments, molecular analyses, and cultured primary brain cells to investigate the underlying mechanisms. We also analyze data from human cohorts to explore associations between oxysterol levels, estrogen, and AD biomarkers in women.
Results: In aged App $^{N\text{-}L\text{-}F}$ knock-in mice, CYP46A1 activation shows positive effects in reducing neuroinflammation and improving metabolic functions, exclusively in female animals. Human studies reveal that elevated 24SOH levels correlate with reduced AD in women, positioning 24SOH as a potential sex-specific diagnostic tool.
Conclusions: Our data suggest that targeting cholesterol metabolism through CYP46A1 activation can protect women at higher risk for AD. This strategy presents a possible alternative to estrogen-based hormone therapies, which have shown protective effects when administered at the onset of menopausal symptoms but fail to reverse disease progression at later stages. Finally, identifying sex-specific biomarkers, such as 24SOH, may enable earlier diagnosis and personalized interventions, addressing a significant gap in AD treatment strategies for women.

SHIFT 02-451

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4 - 5 April

POTENTIAL OF AMYLOID PRECURSOR PROTEIN (APP) AND TAU PEPTIDES TOWARD THE TREATMENT OF ALZHEIMER'S DISEASE (AD).

Ruth Maron
Weizmann Institute of Science, I Dept. Of Immunology & Regenerative Biology, Rehovot, Israel

Aims: POTENTIAL OF AMYLOID PRECURSOR PROTEIN (APP) AND TAU PEPTIDES TOWARD DRUG DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE (AD). Ruth Maron, Sapir Havusha-Laufer, Yaron Vinik,Michael Tsoory, Dan Frenkel, Meir Wilchek, Irit Sagi, Ruth Arnon. Ruth Maron, Dept. of Immunology & Regenerative Biology, Weizmann Institute of Science, Israel The hypothesis behind our reaserch is based on the findings that an interaction between APP and TAU plays a role in the induction and/or progression of AD. Disruption of this association may therapeutically prevent the cognitive ability deterioration seen in AD as well as fight neuronal loss.
Methods: In-vitro assement (by Elisa) of APP1 peptide (390-412) and Tau1 peptide (19-340) ability, to inhibit the interaction between APP and TAU proteins. In vivo nasal or feeding of young or older 5xFAD trangenic (Tg) mice, for 4-7 months with mix, Flex or Rigid peptides. Mice were tested by Y-maze and nesting for behavior and brains excised and imaged for Perineuronal nets (PNN) in the cortex.
Results: APP1 and Tau1 in a mixture or linked together are able to inhibit the interaction between APP and Tau protein. In-vivo nasal or feeding to young or older 5xFAD transgenic (Tg) with linked peptides demonstrate a cognitive ability not significantly different from littermate control. PNNs in the cortex are degrated in AD pathology. Nasal Flex treatment demonstrated increased cortical PNN density in addition to improved cognition.
Conclusions: We sought to evaluate the therapeutical potential of APP and Tau peptides linked together in treatment of AD. Nasal treatment of AD Tg mice with Flex biotin labelled peptide was identified around plaques in the hyppocampus. Flex treatment is able to restore the cognitive ability of AD mice as well as PNN density.

SHIFT 02-452

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4 - 5 April

EXTRA VIRGIN OLIVE OIL AND AD: FROM BENCH TO BEDSIDE

Domenico Pratico
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Aims: Alzheimer's disease (AD) is a chronic neurodegenerative condition characterized by the presence of misfolded protein deposits (amyloid beta, Ab, and tau), neuroinflammation, oxidative stress and blood-brain-barrier dysfunction. While current treatment options do not provide a cure, emerging evidence strongly suggests that some preventative measures could be adopted to prevent or delay the onset of the disease. Adherence to the Mediterranean diet has been shown to reduce the risk to developing mild cognitive impairment (MCI) and AD, and to even slow down the progression of MCI to AD. A key component of the Mediterranean diet is the daily consumption of extra-virgin olive oil (EVOO), which represents the biggest portion of the daily fat intake and a source of phenolic compounds such as oleocanthal, oleuropein.
Methods: Consistent pre-clinical data in the literature indicate that EVOO directly influences some of the key neuropathologic aspects of AD, such as Ab metabolism and aggregation, tau phosphorylation and tangles formation, neuroinflammation, oxidative stress and blood-brain barrier dysfunction.
Results: Epidemiologic studies have confirmed the beneficial effects of EVOO in reducing brain aging and cognitive decline as well as the risk to develop AD and related dementias. Randomized clinical trials investigated the potential therapeutic effect of EVOO in MCI patients showed improvement of cognitive performance, brain connectivity and functionality, amelioration of cognitive tests and memory tasks, reduced blood brain barrier permeability and blood biomarkers for AD pathology.
Conclusions: In conclusion, although strong support exists for the idea that chronic consumption of EVOO may represent an effective therapeutic strategy against AD since it holds promising potential for prevention and treatment of this complex disease, further research is urgently needed to solidify these findings.

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SHIFT 02-462

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
4 - 5 April

RETINOID SIGNALLING MODULATES AMYLOID BETA PROCESSING AND MITOCHONDRIAL FUNCTION IN ALZHEIMER'S DISEASE MODELS

José João Mendonça Vitória[1], Diogo Trigo[2], Odete Da Cruz E Silva[1]
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Aims: Alzheimer's Disease(AD) notably features amyloid beta(Aβ) plaque buildup, accompanied by metabolic dysfunction; impaired retinoid signalling has also been corelated with AD onset and progression. Retinoid acid receptors(RAR) are nuclear factors modulating a series of crucial cell signalling pathways, such as proteostatic modulation or mitochondrial homeostasis regulation, but their impact in AD pathophysiology is yet to be fully characterized and its therapeutic potential remains undelivered. This study aims to explore retinoid signalling as a potential therapeutic approach for AD, with a molecular focus on amyloid precursor protein(APP) processing and metabolic function.
Methods: Using a differentiated neuronal cell line, we dissected the effects of isoform-specific RAR activation on APP processing, while also monitoring mitochondrial health and function. Employing a combination of biochemical assays and live imaging protocols, we monitored APP β-cleavage, secretase and phosphorylation activities, and mitochondrial homeostasis, with a particular focus on the link between reactive oxygen species (ROS) production and Aβ-induced stress.
Results: While RARα activation significantly reduced APP β-cleavage, activation of RARβ resulted in an even more dramatic decrease in Aβ production. These effects were accompanied by alterations in secretase protein levels, suggesting a phosphorylation-dependent regulatory mechanism. These were also reflected in metabolic fitness, as retinoid activation rescued mitochondrial function in response Aβ-induced stress and mitigated energy disruption, preserving mitochondrial membrane polarisation and reducing ROS production.
Conclusions: Modulating APP processing and restoring metabolic function are unmet therapeutic in AD. Our findings reiterate the dual beneficial effect of RAR signalling in AD models, by specifically acting on amyloid deposition, favouring non-amyloidogenic APP processing, and by acting on metabolic homeostasis, with a protective effect against associated oxidative stress. This modulation is isoform-specific, and occurs by modulating both secretase levels and activity, independently.

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SHIFT 02-463

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
4 - 5 April

DELETION OF THE PRESENILIN-LIKE PEPTIDASE SPPL2B SIGNIFICANTLY REDUCES NEUROINFLAMMATION AND ABETA PRODUCTION IN A PRE-CLINICAL MODEL OF ALZHEIMER'S DISEASE

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Aims: The brain-specific signal peptide peptidase 2b (SPPL2b) has emerged as a promising therapeutic target in Alzheimer's disease (AD). SPPL2b is involved in the cleavage of AD-related proteins such as BRI2, inflammation-associated proteins like CD74, TNFα, Clec7a, and Lox-1, as well as synaptic function proteins including Neuregulin-1 and VAMP1-4. SPPL2b is predominantly expressed in the hippocampus and cortex—regions critically affected by AD pathology. This work explores the pathophysiological role of SPPL2b in AD progression and investigates the potential of inhibiting SPPL2b activity as a novel therapeutic strategy.
Methods: To characterize the role of SPPL2b in the APP cleavage process and neuroinflammation, we used primary cell cultures of neurons and glia. Additionally, we assessed the therapeutic potential of inhibiting SPPL2b by employing a novel AD mouse model generated through the crossbreeding of *App*$^{NL\text{-}G\text{-}F}$ knock-in mice with SPPL2b-deficient mice. Both primary cells and brain samples were analyzed using Western blotting, immunoprecipitation, immunofluorescence, Golgi staining, and quantitative PCR (qPCR)
Results: The results demonstrated a substantial reduction in soluble APP, Aβ40, and Aβ42 levels in the conditioned media of SPPL2b KO neurons. Most importantly, we observed a notable decrease in brain Aβ plaque deposition and a significant reduction in both cortical and hippocampal gliosis in SPPL2b KO/*App*$^{NL\text{-}G\text{-}F}$ mice, as well as an enhanced interaction between BRI2 and APP. Preliminary data also indicate that the deletion of SPPL2b partially reverses the loss of dendritic spines observed in the *App*$^{NL\text{-}G\text{-}F}$ model.
Conclusions: The results of this study establish a critical link between SPPL2b and the development of Aβ pathology in AD. In light of the urgent need for novel strategies to prevent and mitigate AD progression, this research underscores the importance of targeting SPPL2b as a promising therapeutic approach.

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SHIFT 02-470

On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES: THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES
4 - 5 April

THE THERAPEUTIC POTENTIAL OF DYR533, A NOVEL DYRK1A INHIBITOR, IN SLOWING TAU PATHOGENESIS AND NEUROINFLAMMATION IN FRONTOTEMPORAL DEMENTIA, ALZHEIMER'S DISEASE, AND DOWN SYNDROME.

Ramon Velazquez[1], Samantha Bartholomew[1], Julie Turk[1], Wendy Winslow[2], Savannah Tallino[1], Jessica Judd[1], Samantha Rockey[3], Christopher Foley[3], Christopher Hulme[3], Travis Dunckley[1]
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Aims: Therapeutic interventions are needed to slow tau pathogenesis and neuroinflammation in disorders such as frontotemporal dementia (FTD), Alzheimer's disease (AD) and Down syndrome (DS). The dual-specificity tyrosine phosphorylation-regulated kinase 1a (Dyrk1a) directly phosphorylates tau and is upregulated in FTD, AD, and is triplicated on chromosome 21 in DS. The goal of this work was to test the efficacy of our novel Dyrk1a inhibitor termed DYR533, in reducing tau pathogenesis and neuroinflammation in models of FTD (PS19), AD (3xTg-AD), and DS (Ts65Dn).
Methods: All animal models were dosed with DYR533 prior to elevations in pathogenic tau. Four-month-old PS19 mice and non-transgenic (NonTg) controls were given daily intraperitoneal injections of either 1.0, 2.5, or 5.0 mg/kg of DYR533 or a vehicle control for 4 months. Prior to the presence of amyloid-β (Aβ) and tau pathogenesis, 7.5-month-old female 3xTg-AD and NonTg mice were dosed with DYR533 (using similar doses) up to 10 months. Prior to the presence of endogenous soluble Aβ and tau accumulation, 4.5-month-old Ts65Dn and 2N (control) mice were dosed with either 0.625, 2.5 or 10 mg/kg DYR533 or a vehicle for approximately 3.5 months.
Results: DYR533 significantly reduced Dyrk1a protein levels in the brains of all animal models, in addition to reducing phosphorylated tau (ptau) at pathologically relevant epitopes, threonine (t) 217 and 181, Serine (s) 396, and the pro-inflammatory cytokine TNF-α in brains of PS19 mice. 3xTg-AD mice consistently showed reductions in ptau t217, t181, s396, TNF-α, and soluble cortical $A\beta_{42}$. Similarly, Ts65Dn mice showed reduced soluble ptau t181 and TNF-α.
Conclusions: Collectively, this work supports the efficacy of DYR533 in mitigating hallmark pathologies and improving neuroinflammation observed in the FTD, AD and DS brain, which may springboard DYR533 for advancement into clinical trials.

SHIFT 02-478

On-Demand Oral Poster on Board - Shift 02
DP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4 - 5 April

LOSS OF TDP-43 ELICITS DEGENERATIVE INHIBITORY NEURONS AND INFLAMMATORY GLIAL CELLS

Yun Li
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Aims: TDP-43, an RNA-binding protein important for RNA processing, is a key protein whose loss-of-function is implicated in multiple neurodegenerative disorders including frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD). We previously reported that TDP-43 nuclear depletion in the medial prefrontal cortex (mPFC) triggered early hyperactivity followed by hypoactivity before neuron loss. The molecular mechanisms underlying such aberrant neural activity prior to neurodegeneration remain elusive.
Methods: We performed single nucleus-RNA sequencing (snRNA-seq) to study the convergent and divergent neurodegenerative pathways following short-term or long-term depletion of TDP-43 in the mPFC, compared to 5xFAD mice, an AD mouse model displaying amyloid β plaque pathology.
Results: We revealed that TDP-43 nuclear depletion triggered dysfunctions in both excitatory and inhibitory neurons in the mPFC. Importantly, inhibitory neurons were degenerated before excitatory neurons upon TDP-43 depletion. GABAergic neurodegeneration were likely driven by compromised mitochondrial function and dysregulated homeostasis triggered by TDP-43 depletion. We also demonstrated a remarkable neuroinflammation, evidenced in both short-term and long-term TDP-43 depleted samples.
Conclusions: Our results revealed a strong GABAergic involvement in early stages driven by TDP-43 loss-of-function, suggesting that GABAergic system is vulnerable to TDP-43 pathology and could be considered as a potential target for developing therapeutic strategies and biomarkers for early detection in TDP-43 linked AD related dementia.

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SHIFT 02-480

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4 - 5 April

MODELLING NEUROINFLAMMATION IN HUMAN ASTROCYTES

Tamara Modebadze, Sarah Mccafferty, Megan Paterson, Hollie Scott, Benjamin Hall, Mark Barbour, Mark Gurney, Elise Malavasi
Concept Life Sciences, Edinburgh, United Kingdom

Aims: Astrocytes, major glial cells of the central nervous system, assume a pro-inflammatory neurotoxic phenotype in response to neuroinflammatory cues. They promote chronic neuroinflammation, a common feature of many neurodegenerative diseases that exacerbates neuronal damage and disease severity. The aim of this study was to develop an in vitro astrocyte polarisation assay of high reproducibility and translational value. Using human induced pluripotent stem cell (iPSC)-derived astrocytes, we established a reliable pro-inflammatory activation protocol validated by observed transcriptional changes and upregulation of secreted proteins.
Methods: Human iPSC-derived astrocytes were seeded into 96-well plates and, after a period of culture, treated with 100 ng/mL Dexamethasone or Vehicle (0.1 % DMSO) for 1 hour. Astrocytes were then stimulated with the TIC cytokine cocktail (TNFα, IL-1α, and C1q) for a further 24 hours. Supernatants were then collected and used for cytokine secretion profiling (via Luminex Multiplex) and generation of concentrated astrocyte-conditioned medium (ACM). Expression of polarisation markers in astrocytes was assessed at the mRNA level via qPCR or bulk RNAseq. Gene expression (qPCR) and cytokine secretion experiments were performed over three independent experiments and batches of cells.
Results: demonstrate a distinct shift in the transcriptomic signature of astrocytes upon stimulation. Astrocytic polarisation induced robust secretion of IL-6, IL-8, and CXCL10. Dexamethasone treatment reliably inhibited cytokine / chemokine production and upregulation of several polarisation markers (*IL6*, *GBP2*) induced by the TIC stimulation.
Conclusions: The human astrocyte polarisation assay offers a valuable translational platform for interrogation of the molecular mechanisms underlying astrocytic activation. It is suitable for developing targeted therapies modulating astrocyte activity in neuroinflammation. A functional neurotoxicity assay using ACM is in development, and, once validated, will complete a suite of assays modelling astrocytic role in neurodegeneration.

SHIFT 02-484

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
4 - 5 April

BREAKING BOUNDARIES: HOW DIGITAL MOVEMENT ENDPOINTS OUTPERFORM CLINICAL SCALES IN TRACKING DISEASE PROGRESSION IN PEOPLE WITH PARKINSON'S DISEASE

Vrutangkumar Shah, Kristen Sowalsky, Fay Horak
Clario, Portland, United States of America

Aims: The integration of digital technology in healthcare is opening new avenues for tracking disease progression, particularly in neurological disorders like Parkinson's disease. This literature review examines the comparative advantages of digital movement endpoints over traditional clinical scales in monitoring disease progression in these disorders. The focus is on their potential to enhance the design of clinical trials and improve patient outcomes.
Methods: A thorough review of current studies was conducted to compare digital movement endpoints with traditional clinical scales in Parkinson's disease. Key parameters evaluated include the sensitivity and precision of these endpoints in detecting subtle motor function changes. The impact of digital measures on reducing sample size requirements and improving the efficiency of drug efficacy assessments in clinical trials was also analyzed.
Results: The review reveals that digital movement endpoints show superior precision and sensitivity compared to traditional clinical scales, particularly in detecting subtle changes in motor function in Parkinson's disease. These digital measures have been found to reduce the necessary sample sizes in clinical trials, thereby enhancing the efficiency of testing new drug interventions.
Conclusions: Digital movement endpoints outperform traditional clinical scales in tracking disease progression in Parkinson's disease. They hold great potential to significantly improve clinical trial design and accelerate the drug approval process by reducing sample sizes and improving the sensitivity of drug efficacy assessments. These findings support the adoption of digital endpoints as essential tools in future clinical trials, promising to advance both therapeutic development and patient care for individuals with Parkinson's disease.

SHIFT 02-485

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
4 - 5 April

DNA CO-METHYLATION NETWORKS SHOW ONTOLOGICAL ENRICHMENT FOR DISEASE RELEVANT PROCESSES WITHIN HUNTINGTON'S DISEASE AFFECTED CELL TYPES

Greg Wheildon[1], Luke Weymouth[1], Joshua Harvey[2], Adam Smith[2], Rebecca Smith[1], Claire Troakes[3], Katie Lunnon[2]
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Aims: Huntington's disease (HD) is an autosomal dominant condition causing severe neurodegeneration in the striatum. In an epigenome wide association study of DNA methylation (DNAm) in HD, we identified changes within the striatum. We applied weighted gene co-expression network analysis (WGCNA) to investigate disease associated differential DNAm within a biological context, through post-hoc analysis.
Methods: 42 striatum, entorhinal cortex and cerebellum DNA samples, from 22 control and 20 HD donors, were selected and matched for sex and age. Bisulfite converted DNA was profiled using the Illumina EPIC array. Following quality control, variance attributable to co-variates was regressed from the normalised data, before WGCNA was applied. Identified co-methylation networks, termed modules, were correlated with traits of interest, before subsequent gene ontological, pathway, and expression weighted cell type enrichment analyses were performed.
Results: Three modules in the striatum were significantly correlated with HD status, did not correlate with confounding variables, and displayed a significant difference between the module eigengene values of the control and HD groups. The modules contained probes annotated to genes with enrichment for disease relevant pathways, including terms relating to neuronal function. Two of the modules also showed significant enrichment in disease affected neuronal subtypes.
Conclusions: This study highlights how DNA co-methylation networks are altered in HD affected cell-types in the striatum. Environmental factors contribute to variation in HD age of onset (AOO), therefore differential DNAm may impact this, and thus, HD associated modules offer potential cellular pathways to target for pharmacological intervention to delay onset. It is critical to identify the cell type specificity of these changes and future studies should use fluorescent activated nuclei sorting to investigate any potential relationship between DNAm and AOO in a cell type specific context.

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On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
4 - 5 April

ASSOCIATIONS OF COMBINED ACCELERATED BIOLOGICAL AGING AND GENETIC SUSCEPTIBILITY WITH INCIDENT DEMENTIA: A PROSPECTIVE STUDY IN THE UK BIOBANK

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Aims: Accelerated biological ageing has been verified to be a critical risk factor for a number of age-related diseases, but its role in dementia remained unclear. This study evaluated the associations between accelerated biological aging and dementia, and the moderating role of accelerated biological aging in the genetic susceptibility to the disease.
Methods: We included 200,731 participants in the UK biobank. Nine clinical blood biomarkers and chronological age were used to calculate Phenotypic age acceleration (PhenoAgeAccel), which is a novel indicator for accelerated biological aging. The associations of PhenoAgeAccel with dementia were assessed by Cox proportional hazard models. The interactions between genetic susceptibility and biological aging were tested on both multiplicative and additive scales.
Results: These findings showed individuals who were in the highest quartile of PhenoAgeAccel had a higher risk with incidence of dementia compared to individuals in the lowest quartile of PhenoAgeAccel (HR: 1.145 (95%CI: 1.050, 1.249)). Furthermore, compared to individuals with biologically younger and low APOE ε4 related genetic risk, individuals with biologically younger and high APOE ε4 related genetic risk (HR:3.048 (95%CI: 2.811, 3.305)) had a higher risk of dementia than individuals with biologically older and high APOE ε4 related genetic risk (HR: 2.765 (95%CI: 2.523, 3.029)). Meanwhile, referring to low dementia PRS and biologically younger, the risk of dementia increased by 72.7% (HR: 1.727 (95%CI: 1.538, 1.939) in the biologically younger and high PRS group, and 58.7% (HR: 1.587 (95%CI: 1.404, 1.793) in the biologically older and high PRS group, respectively.
Conclusions: Accelerated biological aging could bring the extra risk of dementia, but attenuate the effects of genetic risk on dementia. These findings provide insights for precise prevention and intervention of dementia.

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SHIFT 02-487

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

STANDARDIZED DIFFUSION TENSOR IMAGING BIOMARKERS TO CHARACTERIZE ALZHEIMER'S DISEASE PROGRESSION IN MCI PATIENTS

Martin Grange, Jean-Baptiste Martini, Arthur Bézie, Florence Kocher, Vincent Perlbarg
Braintale, Paris, France

Aims: White matter abnormalities have been documented in Alzheimer's disease, particularly through the use of diffusion tensor imaging (DTI). However, translating these findings into clinical practice has posed a significant challenge. BrainTale-care, a CE-marked solution, addresses this issue by offering standardized DTI biomarkers. This study aims to evaluate these biomarkers to detect white-matter changes and to identify patients with rapid cognitive decline among those with dementia and mild cognitive impairment (MCI).
Methods: DTI data were acquired from 476 subjects from the ADNI database, including 201 healthy volunteers, 175 individuals with Mild Cognitive Impairment (MCI), and 100 patients with dementia. Among the MCI patients with at least 2 exams, 93 stayed MCI whereas 23 converted to dementia. MRI scans were conducted at baseline and during follow-up periods ranging from 3 months to 11 years. BrainTale-care v6.0 was used to extract the FA-(MD-/AD-/RD-) index19 and index19-change, which capture respectively the spatial extension of white-matter abnormalities and their changes between baseline and follow-up. These data were acquired using 30 different MRI protocols and calibrated with brainTale-care to minimize intercenter disparities in DTI metrics. Comparisons between dementia, MCI, and CN patients and between converting and non-converting MCI patients, were performed using Mann-Whitney U-tests for group comparisons.
Results: Post-hoc tests revealed that all index19 markers were significantly worse in dementia patients compared to MCI patients, CN patients, and MCI and CN patients ($p < 0.01$ for all tests). Additionally, a significant increase in MD-index19 change was observed in converting patients compared to non-converting MCI patients ($p < 0.020$).
Conclusions: These findings suggest that standardized biomarkers from the brainTale-care platform, may serve as potential biomarkers for tracking disease progression and predicting conversion from MCI to dementia.

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SHIFT 02-488

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

EVALUATING THE UTILITY OF NEUROFILAMENTS IN ASSESSING SYMPTOMS OF PATIENTS WITH CSF1R-RELATED DISORDER

Tomasz Chmiela[1,2], Mercedes Prudencio[3], Leonard Petrucelli[3], Zbigniew Wszolek[1]
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Aims: Colony-stimulating factor-1 receptor (CSF1R)-related disorders are rapidly progressive neurodegenerative disorder. Recent advancements have introduced potential symptomatic and prophylactic treatment options, leading to increased interest in biomarkers. These biomarkers could play a crucial role in monitoring disease progression and assessing the effectiveness of therapies.Aim of this study is to assess correlation between biomarker and clinical status of individuals with pathogenic CSF1R variants
Methods: Biomarkers were evaluated in 31 individuals with pathogenic CSF1R variants (including 17 symptomatic and 14 asymptomatic) and 30 controls. The neurofilament level was assessed in in both plasma and cerebrospinal fluid (CSF). All patients with CSF1R mutations underwent a structured neurological examination and clinical data were correlated with neurofilament levels.
Results: Plasma and CSF NFL levels were elevated in symptomatic patients compared to asymptomatic and control subjects (62.1±25.3 vs. 8.5±2.9 and 7.3±3.8 pg/ml; $p>0.001$ for plasma NFL and 3702.0±3107.9 pg/ml vs. 465.8±196. 7 and 537.8±321.0; $p=0.0193$), NFL level correlated with clinical data based on neurological examination with correlation coefficients of $r=0.9759$ ($p<0.001$) for plasma and $r=0.9135$ ($p<0.001$) for CSF level. NFL level showed strong correlation with MoCA score $r=0.9005$ ($p<0.001$) for plasma and $r=0.9089$ ($p<0.001$) for CSF level.
Conclusions: Plasma and CSF NFL levels appear to be reliable biomarkers for assessing clinical status and could potentially be used to monitor disease progression and treatment efficacy.

SHIFT 02-489

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

USE OF INNOVATIVE MULTI-OMICS PLATFORMS TO STUDY NEURODEGENERATIVE DISEASE

Kerry Shea, Lucy Frost, Irma Berrueta Razo, Ana-Maria Nastase, Eleanor Platt, Tara Bowen, Maike Langini, Tj Allen, Fiona Yau, Regine Anderson, Caitlin Shaw, Gayle Marshall
Medicines Discovery Catapult, Alderley Edge, United Kingdom

Aims: The future of treatment for patients with neurodegenerative disease has the potential to be revolutionised using cutting-edge technologies, enabling the discovery of new targets and potential treatments that can alter the course of these illnesses and significantly improve patient care outcomes. In this study we utilised multi-omics platforms to identify biomarkers from a diverse range of human clinical samples in addition to pre-clinical samples taken from in vivo models of the disease. By applying both focused and comprehensive omics techniques using advanced proteomics, lipidomics and metabolomics profiling, we sought to identify molecular signatures to improve the understanding of the diseases and their progression, and to inform the development of more effective, patient-specific treatments.
Methods: Human plasma and cerebrospinal fluid samples were collected from clinical cohorts, and comparative profiling was conducted on preclinical samples from a relevant animal model. A comprehensive omics-based strategy using both bulk and spatial analysis was employed, examining targeted proteomic profiles using the Luminex platform, including customized multiplex assay build. Untargeted proteomics, lipidomics, and metabolomics profiling was achieved using a mass spectrometry platform. For spatial transcriptomic and lipidomic analysis of in vivo brain tissue, GeoMx Digital Spatial Profiling and Mass Spectrometry Imaging was used.
Results: Preliminary results from the transcriptomic, proteomic, lipidomic and metabolomic analyses revealed a set of candidate molecules showing differential expression across human plasma and CSF, with some overlap observed in the animal model.
Conclusions: This exploratory study demonstrates the potential of multi-omics approaches for biomarker discovery in human and animal samples. While initial findings are promising, further investigation and validation are required to elucidate the clinical relevance of the identified molecules. The integration of targeted and untargeted techniques shows potential for advancing biomarker research.

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SHIFT 02-490

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

THE RELATIONSHIP BETWEEN NEUROFILAMENT LIGHT CHAIN AND ACOUSTIC AND LINGUISTIC MARKERS OF COMMUNICATION IN PEOPLE AT RISK OF DEVELOPING ALZHEIMER'S DISEASE

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Aims: Neurofilament light chain (NfL) is a well-established biomarker for neuronal damage and neurodegeneration, with elevated levels observed in Alzheimer's Disease (AD) and individuals at risk of developing AD. Acoustic and linguistic features of speech, such as speech fluency, pitch, and language structure, are increasingly recognized as non-invasive indicators of cognitive decline. However, the relationship between speech parameters and NfL levels in at-risk populations remains underexplored. Aim is to investigate the relationship between acoustic and linguistic features of speech and plasma NfL levels in individuals at risk for AD, evaluating the potential of speech analysis as a predictive tool for early AD-related neurodegeneration.
Methods: Speech samples were acquired from 140 people at risk of AD as well as plasma NfL level quantified using a Single Molecule Array (Simoa) platform. Speech and language analysis was performed using Redenlab® analytics. Statistical correlation analysis and machine learning methods were used to explore the dataset.
Results: There is a significant association between objective markers of speech and language and plasma NfL levels. Outcomes include variations in speech fluency, pitch, syntactic complexity, and lexical richness correlating with NfL levels, which may support the use of speech analysis as a predictive tool for early neurodegeneration in AD.
Conclusions: Establishing the relationship between underlying neuropathology in at-risk individuals and meaningful clinical outcomes like speech will provide insight into the mechanisms of actions of disease as well as provide an easy to acquire, non-invasive tool for early detection.

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SHIFT 02-491

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

ASSOCIATION OF NEUROMELANIN AND IRON CONTENT WITH MRI MEASUREMENTS IN POST-MORTEM MIDBRAIN TISSUES OF PARKINSON AND ALZHEIMER SUBJECTS

Luigi Zecca[1,2], Clifford M. Cassidy[3,4], Michela Sturini[5], Lauri Tuominen[3], Fulvio Adorni[2], Victoria Cheung[3], Luigi Casella[5], David Sulzer[6,7], Gianni Pezzoli[1,8], Ioannis Isaias[8,9], Guillermo Horga[10,11], Fabio A. Zucca[2]
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Aims: In Parkinson's disease (PD) the dopamine neurons containing neuromelanin (NM) are lost in the substantia nigra (SN), resulting in decreased NM and increased Fe concentrations. In Alzheimer's disease (AD) neurons are lost in cortical regions where an increase of Fe occurs. We aimed to measure NM and Fe concentrations in human midbrain subregions of PD and AD subjects and to investigate the effect of NM and Fe on NM-sensitive magnetic resonance imaging (NM-MRI) signal, in order to evaluate the reliability of MRI in detecting the loss of dopamine neurons in PD.
Methods: We imaged NM and Fe in slices of PD (n = 4) and AD (n = 7) subjects using NM and T_2-weighted MRI sequences. Results were then compared with a precise measurement of NM and Fe concentrations in the same midbrain slices, then imaging maps were calculated for each subject.
Results: Compared to AD, the PD subjects showed increased NM-MRI values in superior colliculus and periaqueductal gray matter, and higher Fe concentration in SN. Both NM and Fe concentrations had unique significant contributions to the NM-MRI signal (mixed-effects model controlling for diagnosis, 163 grid sections, 11 specimens).
Conclusions: Our results support the use of NM-MRI to study NM in the SN and midbrain regions like superior colliculus and periaqueductal gray matter for better monitoring of neuropathological damage in patients with PD and possibly in patients at risk of developing this disease.

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SHIFT 02-497

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4 - 5 April

TRANSCRIPTOMICS-NEUROIMAGING PARKINSON'S DISEASE STRATIFICATION REVEALS DISTINCTIVE MOTOR-COGNITIVE SUBTRAJECTORIES

Sue-Jin Lin[1,2,3], Rhalena Thomas[2], Frederique Larroquette[2], Edward Fon[2], Yasser Iturria-Medina[1,2,3]
[1]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada, [2]Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Canada, [3]Ludmer Centre for Neuroinformatics, McGill University, Montreal, Canada

Aims: To advance clinical care with individualized treatments in a multifactorial disease such as Parkinson's Disease (PD), identifying subtypes of disease progression (subtrajectories) using multimodal data is a crucial step. In this study, we leveraged transcriptomics and neuroimaging data from two PD cohorts to identify disease subtypes using a multilayer contrastive trajectory inference (mcTI) method of unsupervised machine learning and clustering. We aimed to identify clinical utilities in each subtype and explore the links between subtrajectories and clinical subgroups.
Methods: In this study, 743 PD and 212 control participants from the Parkinson's Progression Markers Initiative (PPMI) and the Quebec Parkinson Network (QPN) were included. Gene expression of whole blood RNA from PPMI and regional measures of MRI from both cohorts were included. The mcTI method utilized a contrastive trajectory inference to i) define the trajectories of patients against control participants and ii) estimate disease severity based on blood and brain data. Severely impaired PDs from PPMI, defined by a combination of motor and cognitive scores, were used as a proxy to initiate the process; while the QPN cohort acted as test datasets to show clinical utilities.
Results: Four PD subtypes were identified. Multiple cognitive performance and postural instability scores significantly differed between subtypes (figure 1). In two of the subtypes, multiple cognitive domains were associated with estimated disease severity (figure 2). There was a trend showing mixed, higher postural, lower postural, and tremor-dominated subgroups in these subtypes (figure 3), partially supporting clinical observations.

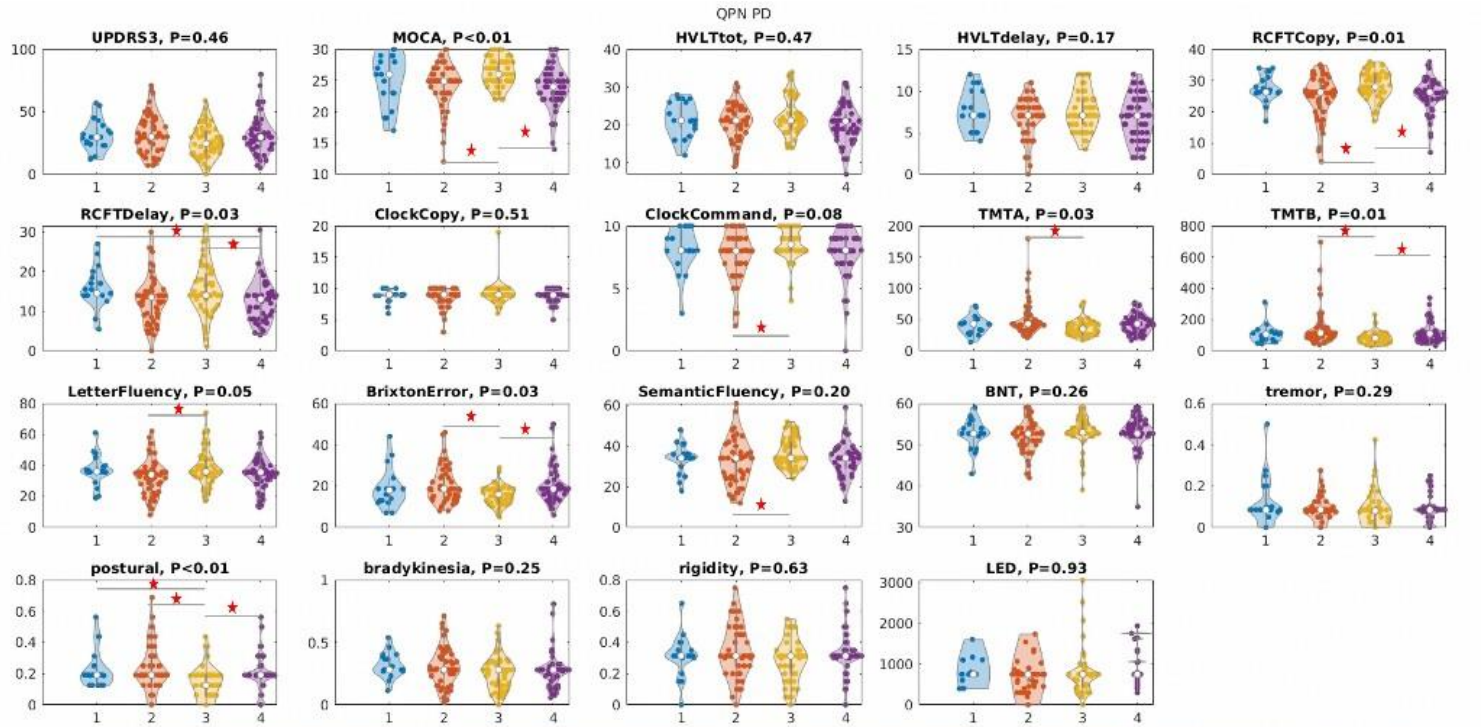

Figure 1. Violin plots showing the *distribution* of scores on the indicated test for subjects in each subtype. Results of multivariate analysis of covariance (mancovan) show that multiple clinical variables are different across subtypes. Red asterisk indicates significance in pair tests in addition to mancovan.

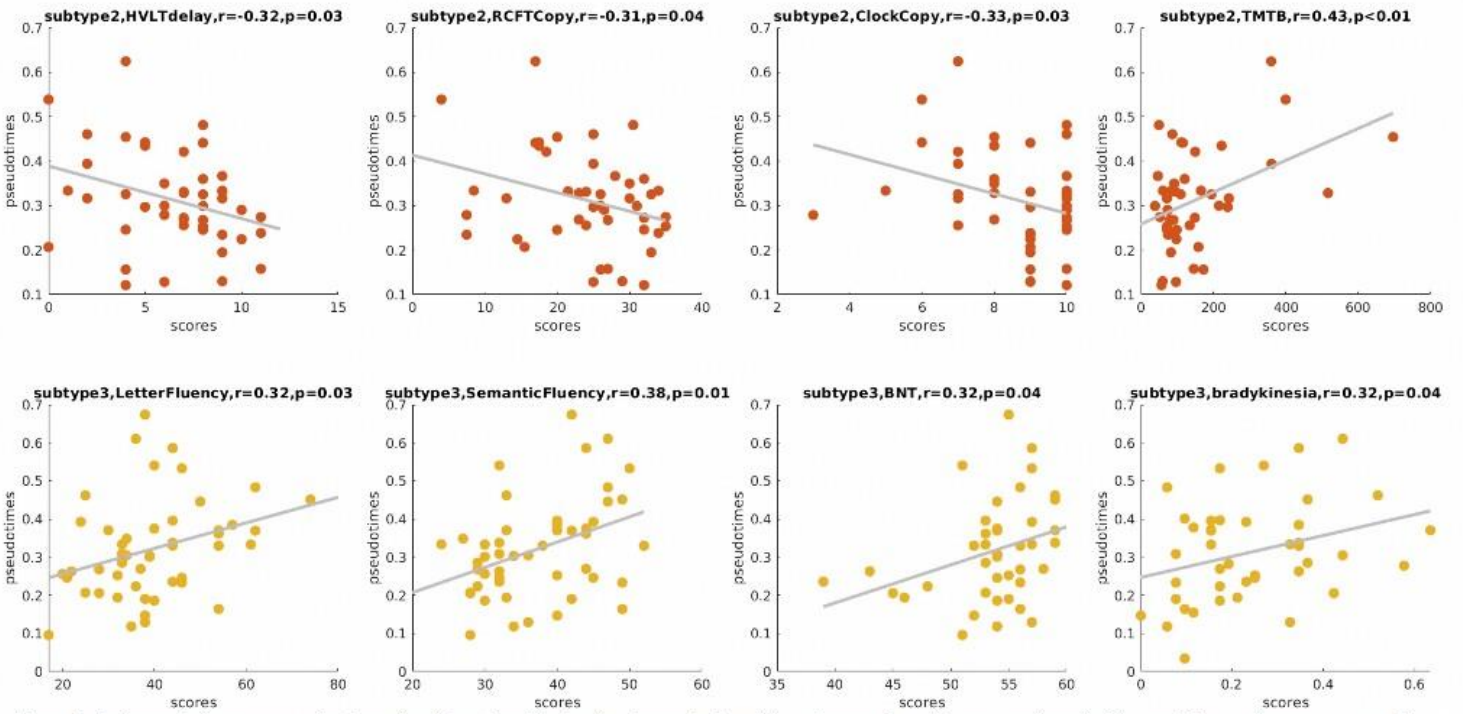

Figure 2. Estimated disease severity based on blood and brain data (pseudotimes) in subtypes 2 and 3 are correlated with cognitive and motor scores. The tested subtype, clinical data, correlation coefficient and p value are indicated in the graph titles.

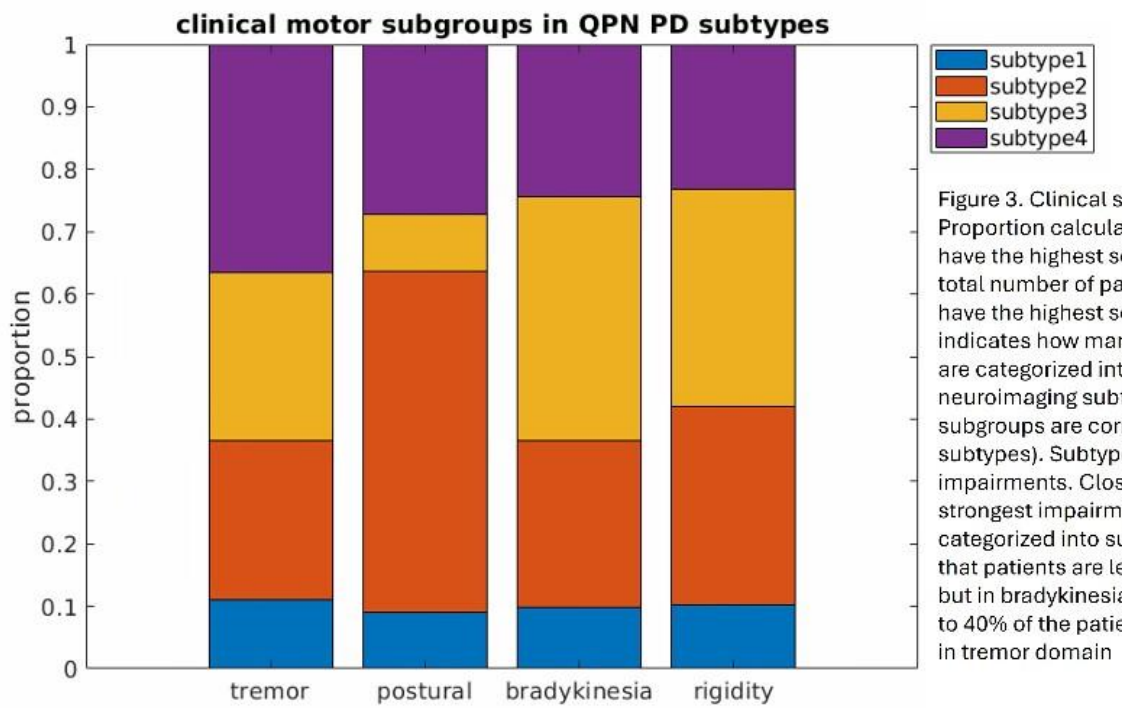

Figure 3. Clinical subgroups in mcTI subtypes. Proportion calculates the number of patients who have the highest score in a subtype divided by the total number of patients across all subtypes who have the highest score in this motor domain. This indicates how many patients of a motor subgroup are categorized into the transcriptomic-neuroimaging subtypes (i.e., whether clinical subgroups are corresponding to mcTI-derived subtypes). Subtype 1 shows a mixed motor impairments. Close to 60% of the patients have strongest impairments in postural instability are categorized into subtype 2, while subtype 3 shows that patients are less impaired in postural instability but in bradykinesia and rigidity. Subtype 4 has close to 40% of the patients have strongest impairments in tremor domain

Conclusions: The mcTI method jointly assessed blood and brain data, identifying 4 PD subtypes with different motor and cognitive characteristics. Future work includes highlighting the transcriptomic and imaging markers of each subtype to help with treatment plans.

SHIFT 02-498

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4 - 5 April

TARGETING NEUROINFLAMMATION WITH PS21HKR: IMPACTS ON COGNITIVE PERFORMANCE IN AN ALZHEIMER'S DISEASE RAT MODEL

Prajjwal Sharma
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Aims: To investigate the antiplatelet and neuroprotective activity of novel coumarin derivative PS21HKR in Alzheimer's disease.
Methods: **Method:** Recently, it was discovered that platelets, which make up 90% of the circulatory Aβ, encourage the development of AD. Therefore, we hypothesized to use a novel coumarin derivative PS21HKR, which is believed to possess anti-platelet and anti-inflammatory properties for the treatment of AD. We investigated the effects of PS21HKR on STZ induced cognitive decline and neuroinflammation. Intra-cerebroventricular streptozotocin (ICV-STZ) (3mg/Kg) induced Wistar rat models of AD were used in the study. Rats were divided into 3 groups including sham, STZ and PS21HKR group.
Results: **Result:** Behavioural studies revealed that PS21HKR mitigates the cognitive deficit associated with STZ. Anti-platelet effect of PS21HKR was confirmed by tail vein bleeding assay. Further, in-vitro studies were performed on BV2 cells including the MTT assay and determination of expression of inflammatory markers. The results suggested that PS21HKR potentially regulated the expression of pro- and anti-inflammatory cytokines.
Conclusions: **Conclusion:** Therefore, findings of this study indicate that PS21HKR has a potent neuroprotective effect by virtue of its anti-platelet and anti-inflammatory activity.

SHIFT 02-499

On-Demand Oral Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4 - 5 April

INCREASED BACH1 EXPRESSION AFTER TRAUMATIC BRAIN INJURY IS A NEUROPROTECTIVE TARGET FOR PREVENTING COGNITIVE IMPAIRMENT

Edwin Vázquez-Rosa[1], Sarah Barker[2], Emiko Miller[3], Kalyani Chaubey[1], Yeojung Koh[2], Sofia Corella[2], Salvatore Caradonna[2], Hui Liu[1], Adrian Cintrón-Pérez[4], Adora Ezepue[5], Kathryn Franke[1], Coral Cintrón-Pérez[1], Otis Attucks[6], Carmen Valcarce[6], Mitsuyo Matsumoto[7], Kazuhiko Igarashi[8], Sudarshana Sharma[9], Bindu Paul[10], Bobby Thomas[11], Andrew Pieper[12]
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Aims: Traumatic brain injury (TBI), which annually afflicts ~70 million people worldwide, results from various causes and leads to complex and often chronic neurodegeneration that prominently features oxidative stress. The antioxidant Nrf2 pathway is a principal component of the brain's natural defense from oxidative stress, and its activity is impaired in neurodegenerative diseases. Here, we hypothesized that TBI would also impair Nrf2 signaling, and if so, then selective pharmacologic inhibition of the Bach1, the transcriptional repressor of Nrf2 signaling, would confer neuroprotection in TBI.
Methods: We analyzed publicly available whole RNA sequencing data from postmortem brains of chronic traumatic encephalopathy (CTE) human subjects, a progressive neurodegenerative disorder associated with repetitive head injury, and matched normal controls to identify gene signatures

associated with dysregulation of the antioxidant response. We additionally queried Bach1 and Nrf2 expression in mouse TBI and the effect of pharmacologic Bach1 inhibition on behavior and neuropathology after TBI.

Results: Bach1 expression is increased in human CTE and in mice after TBI. Overlaying of Bach1 target genes, which were identified by combining ChIP-seq data with bulk RNA-seq data from Bach1 KO mice hippocampus, with publicly available murine TBI brain transcriptomics data (GSE44625) revealed Bach1 as a critical modulator of inflammation, oxidative phosphorylation signaling, ferroptosis, cellular response to oxidative stress, and diseases associated with cognitive deficits. We also showed that selective inhibition of Bach1 in mice after TBI increases levels of Nrf2 pathway-associated proteins, reduces protein oxidation, blocks neurodegeneration, and prevents cognitive deficits.

Conclusions: Our results provide insights into the neuropathophysiological consequences of TBI and identify Bach1 as a negative regulator of Nrf2 in TBI. Bach1 inhibition bolsters the antioxidant response and protects mice from neurodegeneration and cognitive impairment after TBI.

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SHIFT 02-500

On-Demand Oral Poster on Board - Shift 02
LYSOSOMAL STORAGE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4 - 5 April

NEURODEGENERATIVE DISEASE-ASSOCIATED PROTEIN AGGREGATION IN LEUKODYSTROPHIES

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Aims: Leukodystrophies are genetic disorders that predominantly affect the central nervous system white matter. Their pathogeneses are highly complex, with cell-autonomous and non-cell-autonomous mechanisms impacting on tissue integrity and cellular pathology. Emerging evidence also demonstrates grey matter involvement in several leukodystrophies. Here, we assessed neurodegenerative disease-associated protein aggregation in grey and white matter regions in leukodystrophies.
Methods: Post-mortem paraffin-embedded tissue of the frontal cortex and subcortical white matter, hippocampus, cerebellum and medulla oblongata was obtained from 11 genetically-proven leukodystrophy patients (3 months – 69 years of age). Diagnoses included Krabbe disease, metachromatic leukodystrophy (MLD), adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), and Alexander disease (AxD). Protein aggregation was scored using a panel of neurodegenerative disease markers.
Results: Expression of amyloid precursor protein, phosphorylated(p)-tau, alpha-synuclein and autophagy marker P62 co-varied with disease, age, brain region, and cell type. Findings included alpha-synuclein positive astrocytes, pericytes and some neurons using the 5G4 marker in a region-dependent manner in MLD. Even in MLD cases with more severe inflammation, no pSer129 positivity was found. p-Tau positivity was mainly found in AxD either as tangles, threads, around blood vessels or in astrocytes in close association with Rosenthal fibres, depending on the region. For all leukodystrophies and regions, P62 showed cell-specific immunoreactivity. No case showed immunoreactivity for pTDP-43.
Conclusions: These findings confirm disease-, age-, region- and cell type-specific neurodegenerative disease-associated protein aggregation in leukodystrophies. This highlights the complexity of their neuropathology, which includes both white and grey matter involvement and might predispose surviving patients to classic neurodegeneration later in life. Combined therapies should therefore be considered as treatment options for these debilitating disorders.

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SHIFT 02-507

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / MOBILE APPLICATIONS, SOCIAL NETWORKS
4 - 5 April

VIRTUAL REALITY BASED MUSIC INTERVENTION IN AN ACUTE GERIATRIC SETTING

Harmehr Sekhon[1], Olivier Beauchet[2], Julia Chabot[1]
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Aims: The globally aging population is resulting in greater burden on healthcare as older adults proportionately occupy more hospital care beds and have higher healthcare utilization. Music is an emerging therapy for in-patient and community dwelling older adults. It is associated with improvements in positive emotions, pain, anxiety, depression, quality of life and behavioural issues in older adult inpatients[3]. Virtual Reality (VR), an immersive 360 degree visual and audio experience can increase the scalability of non-pharmacological interventions as its immersive and engaging ability allows users to partake in diverse activities safely and even with limited mobility. The goal of this study was to assess a concert-like VR musical experience vs active control in older adult in-patients.
Methods: This pilot study is a feasibility open-label RCT (n=30) of a novel VR based music intervention vs. an active control of audio only music, in older adults with and without dementia. This study took place in a Montreal (Canada) hospital in an acute inpatient geriatric assessment unit (GAU). The object of the study was to assess feasibility, tolerability, and acceptability (primary objectives), preliminary efficacy of the VR music intervention in improving positive emotions and pain (secondary objective), and the preliminary efficacy of the VR based music intervention in improving mental wellbeing, and symptoms of anxiety and depression (exploratory objectives).
Results: This is an ongoing study with results expected in December 2024
Conclusions: If successful, this will be the first study assessing a VR Music intervention for older adult inpatients, including those with dementia. Establishing the feasibility of VR music interventions will allow for the integration of VR with older adults including those with dementia and the creation of content tailored to this population.

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SHIFT 02-508

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
4 - 5 April

DIVERSITY IN A PIVOTAL REGISTRATION TRIAL FOR AR1001 IN THE TREATMENT OF EARLY ALZHEIMER'S DISEASE

Fernando Melgar Somoza[1], Linda Pao[1], Yaneicy Gonzalez[1], Young Ho Park[2], James Rock[3], Adam Schindler[1], Jai Jun Choung[3]
[1]Melgar-Caro MedCenter and Community Research, Family Medicine/ Internal Medicine, Miami, United States of America, [2]Seoul National University Bundang Hospital, Neurology, Seongnam, Korea, Republic of, [3]AriBio Co., Ltd, San Diego, United States of America

Aims: Alzheimer's disease (AD) affects people of all races and ethnicities, yet enrolling a diverse population into AD trials has proved challenging. Obstacles to recruit diverse participants include language and cultural barriers, distrust of the medical establishment, limited site selection in locations with a diverse population, and lack of community outreach. AriBio is developing AR1001, a phosphodiesterase-5 inhibitor, for treatment of early AD. AriBio executed on a diversity plan that proposed: 1) Selecting diverse investigators and staff to augment trust in potential trial participants; 2) Overcoming language and cultural barriers by conducting the trial in research centers with access to diverse populations; 3) Utilizing community-based trial sites not just academic centers to place the study close to potential participants; 4) Providing advertising and outward facing materials sensitive to a diverse population.
Methods: Demographics from a Phase 2 study of AR1001 for mild-to-moderate AD conducted in the US with 210 patients, and demographics from a Phase 3 study ongoing in 3 regions (US/Canada, United Kingdom/European Union, and South Korea) for early AD were analyzed.
Results: In the Phase 2 trial, the trial population was 20% Hispanic-Latino and 13% African-American (AA) participants. In this Phase 3 pivotal registration trial, as of September 17th 2024, 1749 people have been globally screened. The screened population includes 53.3% female, average 73 years of age, racial and ethnic composition of 82.4% Caucasian, 10.4% AA, 8.9% Asian, 0.9% other and 30.5% Hispanic-Latino
Conclusions: This trial demonstrates that efforts to enroll a diverse population can be successful. AriBio continues to refine its recruitment strategy aimed at a trial population that more closely reflects the diversity of the AD patient community.

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SHIFT 02-509

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
4 - 5 April

VALIDATION OF HARMONISED NEUROPSYCHOLOGICAL DATA TO COGNITIVE IMPAIRMENT AND COGNITIVE DECLINE IN PRECLINICAL AND SYMPTOMATIC AD.

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Aims: Large study samples enhance understanding of clinical-pathological relationships in Alzheimer's Disease (AD) by providing measurement precision and statistical power. Harmonizing neuropsychological data is limited by different tests measuring the same cognitive domains in different studies. Harmonization can be improved with data science techniques though optimal methods are sought. We report the sensitivity to AD-related cognitive decline of composite scores harmonized from multiple neuropsychological tests using a machine learning (ML) method[1] across the AIBL, ADNI, and OASIS studies.
Methods: The harmonization method utilized longitudinal clinical/pathological data from the AIBL (N=1765), ADNI (N=1779), and OASIS (N=440) cohorts. The process involved three steps: (1) defining cognitive domains and corresponding neuropsychological tests for each cohort, (2) establishing a standardized scoring and naming convention, and (3) applying an ML harmonization approach. Test scores absent in each cohort were treated as missing and imputed using ML, enabling calculation of composite scores for episodic memory, executive function, and language. Imputation considered test data, age, gender, education, and *APOE*-ε4 status. Linear mixed models (LMMs) assessed the sensitivity of these composite scores to AD clinical status and amyloid levels, modelling score changes over time and interactions with CDR-global score and amyloid status. Differences in baseline values and slopes between clinical groups and the amyloid-negative cognitively unimpaired (CUAβ-) group were expressed as effect sizes (Cohen's d).
Results: Figure 1 shows the effect sizes for the baseline and decline of harmonized composites in amyloid-positive CU, prodromal AD, and AD dementia groups compared to CUAβ- adults.

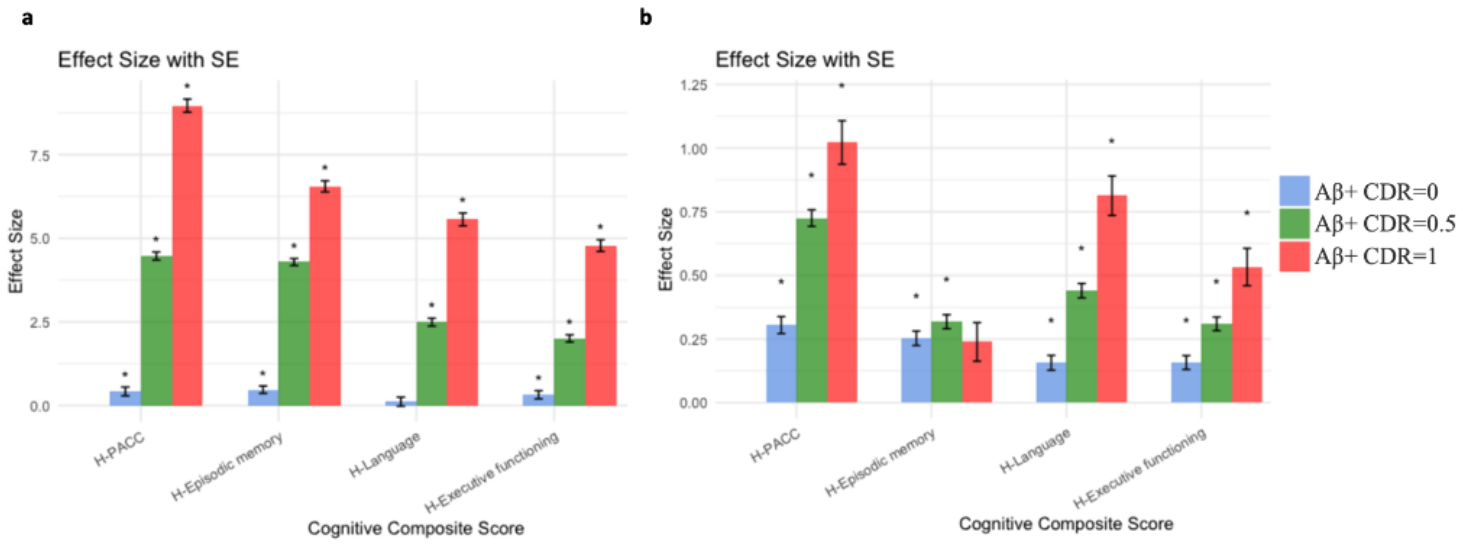

Figure 1. Statistical summary of the effect sizes for the (**a**) baseline and (**b**) rate of decline values for cognitive composite scores, stratified by CDR and Aβ status of β-amyloid-positive CU adults (Aβ+ CDR=0), prodromal AD (Aβ+ CDR=0.5), and AD dementia groups (Aβ+ CDR=1). Asterisks indicate significant differences ($p < .001$) compared to the reference group, CUAβ- adults. The effect sizes were calculated from linear mixed models (LMMs) assessed the sensitivity of the composite scores to AD clinical status and amyloid levels, modelling score changes over time and interactions with CDR-

Conclusions: The sensitivity of cognitive composites from harmonized data aligns with expected AD stages. This provides strong validation of the harmonization method and supports its use to enhance understanding of AD clinical-pathological relationships through combining data across studies.

References:[1]doi:10.1002/alz.044302

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SHIFT 02-510

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
4 - 5 April

THE AUSTRALIAN DEMENTIA NETWORK (ADNET) REGISTRY: A CLINICAL QUALITY REGISTRY FOR DATA-DRIVEN HEALTHCARE IMPROVEMENTS

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Aims: The Australian Dementia Network (ADNeT) Registry is the first nationwide clinical quality registry (CQR) established for people diagnosed with either MCI or dementia of any cause in Australia. The Registry aims to improve quality of diagnosis and post-diagnostic care.
Methods: The ADNeT Registry recruits clinics which assess cognitive disorders. Clinicians input a minimum dataset when a diagnosis of either dementia or MCI is confirmed. The Registry then invites patients, and/or caregivers to complete surveys on experiences of care and quality of life. Data are analysed, benchmarked, and reported back regularly to sites, with clinical quality indicators used to identify variations in practice.
Results: By the end of 2023, the ADNeT Registry had 64 participating clinical sites across Australia, and 4280 participants, of whom 34.3% had MCI and 65.7% had dementia, with Alzheimer's disease the most common subtype (52%). Time from referral to a first appointment (median 76 days) was the indicator with the greatest variation. Only 56% of people with dementia were referred to a post-diagnostic program. Biomarkers were used in diagnosis in <5% of cases.
Conclusions: Since 2020, the ADNeT Registry has published three Annual Reports, provided six-monthly benchmarked reports to each participating site, and secured ongoing federal funding. Clinics use Registry data to evaluate services and inform improvements. For clinicians, their time spent in Registry activities contributes towards meeting their continuous professional development requirements. ADNeT Registry data will be utilised for the evaluation of Australia's National Dementia Action Plan. Furthermore, the dataset has been augmented to monitor the efficacy and safety of emerging dementia treatments. The ADNeT Registry provides an example of how CQRs can drive local improvements in clinical practice and collect valuable high-level clinical data nationally.

SHIFT 02-511

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / OTHER
4 - 5 April

PATIENTS WITH POSTOPERATIVE DELIRIUM HAVE POOR COGNITION BEFORE SPINE SURGERY

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Aims: Postoperative delirium (POD) is common, especially in the elderly population and is associated with poor outcome. Multiple factors, such as old age, education, alcohol use disorder and depression, may be preoperative risk factors for POD. Our study is aimed to determine whether poor preoperative cognitive functions are risk factors for POD.
Methods: Participants who are 65 years old or older with spine surgery for at least 2 segments were recruited at the University of Virginia Hospital. All participants were evaluated by Katz Instrumental Activities of Daily Living (ADL), Beck Depression Inventory, State-Trait Anxiety Inventory and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) before surgery. The delirium diagnosis was performed based on confusion assessment method (CAM), which was performed twice a day for 3 days after surgery.
Results: A total of 52 participants completed the study. Eighteen participants developed delirium after spine surgery. POD incidence was 34.6%. There was no difference in ages between participants with and without POD [median (25^{th}-75^{th} percentile), 71.0 (69.0-75.0) years for participants with POD and 70.5 (68.0-73.0) years for participants without POD, P = 0.772]. There was no difference in the ADL, anxiety and depression levels in participants with or without POD (Fig. 1). However, patients with POD had lower total RBANS scores than patients without POD before the surgery (Fig. 2). This lower total RBANS score was due to the lower scores in immediate memory, language and attention.

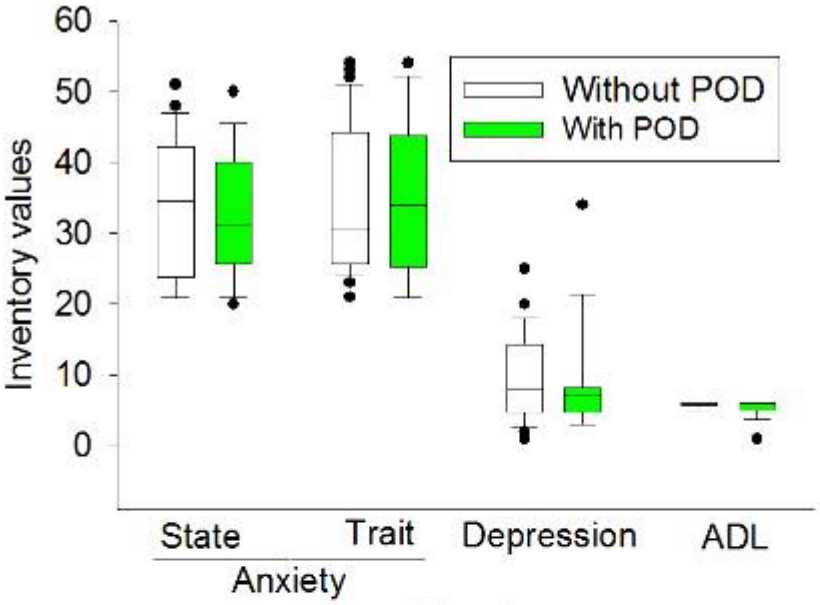

Fig. 1

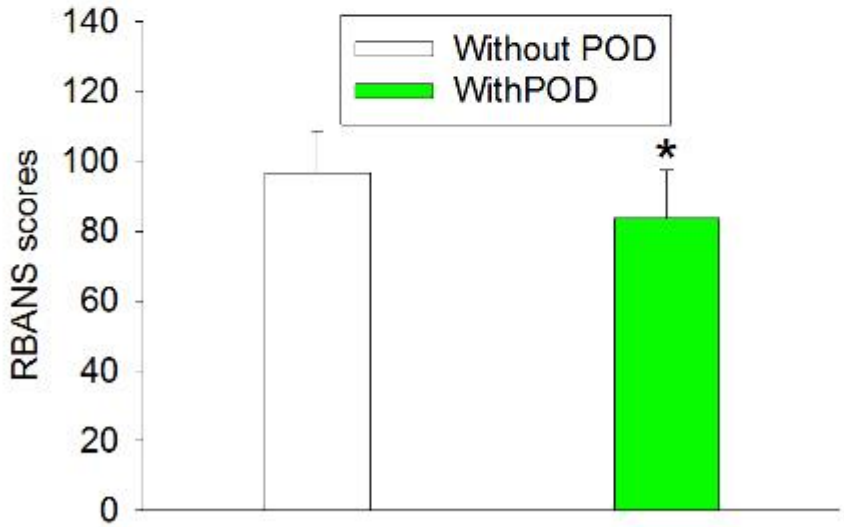

Fig. 2

Conclusions: Poor cognition before spine surgery may be a risk factor for POD in elderly patients.

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SHIFT 02-512

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / QUALITY OF LIFE
4 - 5 April

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-six people were interviewed ranging in age from 50 to 84. The independent coders identified the same examples of resilience 69% of the time. Their agreement on ratings of resilience in each life period averaged 68%. Their overall rating of resilience for interviewees agreed 73% 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 0.85.
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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SHIFT 02-513

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / QUALITY OF LIFE
4 - 5 April

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 11 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 5 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 18% 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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SHIFT 02-514

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / SUPPORT DEVICES & MONITORING
4 - 5 April

A COMPUTER SIMULATION MODEL TO PREDICT COGNITIVE IMPAIRMENT

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Aims: Modifiable factors related to cognitive impairment and neurocognitive disorders (and their avoidance) are well recognized.
Methods: We designed a system's dynamics computer simulation model to predict the onset of cognitive impairment given data across the person's entire life. The model allows for studying multiple, interacting variables and an interactive patient and family motivational tool. The simulation model aims to portray the time course for a person to develop cognitive impairment and to progress to major neurocognitive disorder. It incorporated the role of exercise, genetic load, age, quality of diet, presence of diabetes and level of hemoglobin A1C, ongoing levels of cognitive stimulation, presence or absence of micronutrients, presence or absence of other co-morbidities, overall general health index, levels of smoking and other substance use, and family history. The model is based upon available data on individual risk factors with extrapolated interaction relationships. It was built with data on the life course of 15 individuals, adjusting parameters to make correct predictions for all people. Then we entered the data from another 25 people to determine how accurate the model would be with new individuals for whom it had not been developed. We defined success as a prediction of onset within 10% of the actual date and a prediction of the slope of the trend within 20%.
Results: We had 12 successes. We then modeled an additional 19 people, asking them what they would be willing to change to alter their predictions. We then re-ran the model using the changed variables to show what difference altering these factors could make. Fifteen indicated willingness.
Conclusions: Interaction with computer simulation models can provide tools of persuasion to overcome difficulties inherent in people changing their modifiable risk factors.

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SHIFT 02-527

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
4 - 5 April

DETECTING APATHY THROUGH AUTOMATIC ACOUSTIC SPEECH ANALYSIS IN PEOPLE WITH PARKINSON'S DISEASE

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Aims: Apathy is a common non-motor symptom in people living with Parkinson's disease (PwPD) that can significantly impact the quality of life. Detecting and addressing apathy is essential for improving the health management in PwPD. This study investigates if automatic speech analysis is capable of detecting apathy in PwPD.
Methods: Data from 99 PwPD (32 female, aged 62 ± 8, UPDRS III 22 ± 9) were analyzed. All were native German speakers and completed three speech tasks: maximum vowel /a/ phonation, a reading text, and a picture description. Speech was recorded via a condenser microphone headset, and prosodic features were extracted using SIGMA, ki:elements' speech processing library. Participants also completed the Apathy Evaluation Scale (AES-S). Spearman Rank-Sum correlations between speech features and AES scores were calculated, with p-values adjusted via the Benjamini-Hochberg method. An ROC analysis identified optimal cut-offs for apathetic and non-apathetic groups (cut-off > 37).
Results: The average AES score was 30 ± 9, ranging from 18 to 59. Of the 99 PwPD, 21 were classified as apathetic and 78 as non-apathetic. The AES score significantly correlated with phonation task features, including spectral_slope_500_1500 ($r = .384$, $p < .001$), spectral_slope_0_500 ($r = .314$, $p = .024$), h1_h2_harmonic_difference ($r = .376$, $p < .001$), and harmonics-to-noise ratio ($r = -.301$, $p = .024$). The harmonics-to-noise ratio also differentiated between the two groups (AUC: 0.698, specificity: 0.538, sensitivity: 0.857).
Conclusions: In this study, 21% of PwPD exhibited apathy, which correlated with specific speech motor function parameters. Apathy was associated with changes in speech features related to phonatory control, potentially causing vocal fold tension fluctuations and vocal quality instability. These acoustic features may serve as indicators for detecting apathy in PwPD.

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SHIFT 02-530

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
4 - 5 April

EXERCISE MODULATES CLINICAL STATE, GLUCOSE METABOLISM AND PROTEOME OF CIRCULATING EXTRACELLULAR VESICLES IN PATIENTS WITH PARKINSON'S DISEASE

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Aims: Physical exercise has a potential to improve clinical state and glucose metabolism of patients with Parkinson's disease (PD), while prediabetes and type 2 diabetes contribute to the progression of Parkinson`s disease. Circulating extracellular vesicles (EVs) can contribute both to PD pathogenesis and exercise-induced adaptations. Aim of this work was to assess effects of exercise on glucose metabolism, cognitive functions, and proteome of circulating extracellular vesicles (EVs) in patients with mild-to-moderate PD.
Methods: Patients (M/F 9/8; 61.1±8.8yrs; H&Y score I-III, BMI 27.6±5.4 $kg.m^{-2}$), completed a 4-month supervised aerobic-strength training (3x1h/week). Clinical state was assessed by United-Parkinson-Disease-Rating-Scale (MDS-UPDRS; ON/OFF states). Cognitive functions (Memtrax and CogState; ACE-R), body composition (bioelectrical impedance, MRI: abdominal adiposity), muscle strength (dynamometry), resting energy expenditure and metabolic substrate preference (RER, indirect calorimetry), metabolic flexibility and insulin sensitivity (euglycemic hyperinsulinemic clamp) were measured before/after training intervention. Proteomic analysis of plasma-derived EVs, isolated by size exclusion chromatography/SEC at baseline, immediately after and 1h after a bout of 40min cycling (60-70%HRmax) on a stationary bike was performed both, before and after 4-month training by mass spectrometry.
Results: Four-month of aerobic-strength training improved body composition (reduced: BMI, p=0.007; body fat, p=0.080; visceral fat, p=0.038), reduced HbA1C, improved whole-body metabolic flexibility and muscle strength (all p<0.05). These changes were paralleled by improvements in cognitive performance (ACE-R verbal production subscore, p=0.029; psychomotor function, p=0.040; visual learning & short-term memory, p=0.009) and clinical state of patients including both motor and non-motor symptoms (MDS-UPDRS, p<0.050). Both acute and regular exercise distinctly modulated proteome of plasma-derived EVs.
Conclusions: Regular exercise improves clinical state and glucose metabolism in patients with Parkinson`s disease. Exercise-induced changes in circulating extracellular vesicles might contribute to the systemic adaptive response to training, underlying health benefits of exercise.

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SHIFT 02-531

On-Demand Oral Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
4 - 5 April

TRANSLATION OF THE CHARACTERIZING FREEZING OF GAIT QUESTIONNAIRE FROM ENGLISH TO GERMAN USING THE TRAPD PROCESS

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Aims: Freezing of Gait (FoG) is a severe symptom of Parkinson's Disease (PD) that affects mobility and quality of life. The Characterizing Freezing of Gait Questionnaire (CFoG) is a valuable tool for screening and determining the dominant triggers of FoG. Currently, it is unavailable in German. This project seeks to address this gap by creating a linguistically accurate translation of the CFoG from English to German using the TRAPD process (Translation, Review, Adjudication, Pretesting, and Documentation).
Methods: This NÖGUS-funded project uses the TRAPD process, a structured method to ensure high-quality translations. Two professional translators will translate the CFoG into German. A review team will then evaluate, compare, and discuss these translations in a workshop to ensure the accuracy, clarity, and consistency of the content. This workshop will include students and employees at a University of Applied Sciences over 18 years old, and whose first language is either German or English. Participants must also self-assess their proficiency at C1 level or higher in both languages. After the workshop, the project leader will handle the adjudication process. Next, a second workshop will be held as part of the pretest phase, involving therapists, doctors, and people with PD to ensure the translation is comprehensible and culturally appropriate. The entire process will be documented to maintain transparency and accountability.
Results: This project will be completed at the end of 2024. The entire translation process will be documented. Feedback from workshops will be incorporated into the final version of the German translation of the CFoG, making it suitable for clinical and research use.
Conclusions: This project will enhance the screening of FoG in German-speaking populations as well as the understanding of the various FoG triggers as a basis for therapeutic interventions. As such, it will contribute to improved healthcare outcomes for individuals with PD.

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SHIFT 02-540

On-Demand Oral Poster on Board - Shift 02
PRION DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

SERUM GDF-15, GFAP, AND NFL: THEIR LINK AND ROLE IN CREUTZFELDT-JAKOB DISEASE

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Aims: Creutzfeldt-Jakob Disease (CJD) is characterized by the aberrant accumulation of a misfolded prion protein in neurons, causing spongiform changes, and neuronal loss. The exact neuropathogenic mechanisms associated with the rapid neuronal death partly remain unclear, with mitochondrial dysfunction possibly giving a contribution. This study explores the serum concentrations of biomarkers of neurodegeneration, glial activation, and mitochondrial dysfunction in CJD and their associations. .
Methods: Using preliminary data, a one-tailed power analysis was performed with G*Power to determine the sample size. We assessed the serum material of 19 CJD patients; median age 68,3 years (25th-75th percentile: 61-74 years), and 81 healthy controls (HC) median age 63 years (25th-75th percentile: 54-72years). Serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP) levels were assessed with Simoa TM assay Neurology 2-Plex B Assay Kit, and serum Growth Differentiation Factor-15 (sGDF-15) with ELISA kit (Bio-Techne, USA R&D Systems, Inc.). Spearman correlation and analysis of covariance, considering age as covariate, were performed.
Results: G*Power determined that at least 15 participants are required to detect a statistically significant correlation. Significant differences were observed between CJD and HC in median sNfL levels: CJD at 137,29 (92,78-268,18) vs. HC at 10,88 (7,5-15,96) $p<0.001$. Similarly, median sGFAP levels were higher in CJD at 684,98 pg/mL (25th-75th percentile:438,41-1926,53) compared to HC at 100.89 pg/mL (25th-75th percentile: 49,93-168,76), $p<0.001$.However, no significant difference was found in sGDF-15 levels: median CJD at 970 ng/mL (25th-75th percentile: 671-355) vs. HC at 516 ng/mL (25th-75th percentile: 374-818). In CJD patients, sNfL levels showed a significant positive correlation with sGDF-15 ($p< 0,004$; $r= 0,60$).
Conclusions: Our study suggests a role of inflammation and mitochondrial dysfunction in the complex process of neurodegeneration in CJD.

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SHIFT 02-549

On-Demand Oral Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

FUNCTIONAL CONNECTIVITY DYSREGULATION IN HYPERNOSOGNOSIA WITHIN THE ALZHEIMER'S DISEASE CONTINUUM

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Aims: . Recent evidence suggests anosognosia in the AD continuum is associated with a dysregulation of the of three large-scale networks, namely the Default-Mode (DMN), the Salience (SN), and the Fronto-Parietal (FPN) Network. Here, we further investigate if this functional connectivity dysregulation shows a different trajectory across the continuum between hypernosognosia (i.e. increased awareness of cognitive function) and anosognosia (i.e. reduced awareness of cognitive function).
Methods: . Sixty patients with MCI and AD dementia underwent fMRI and neuropsychological assessment including the Anosognosia Questionnaire Dementia (AQ-D), a measure of anosognosia based on a discrepancy score between patient's and carer's judgments. Patients were classified in 3 groups according to AQD scores: hyperaware (hyAW) if AQD<-14, unaware (uAW) if AQD>14, aware (AW) if -14<AQD<14. After having applied Independent Component Analysis (ICA) to resting fMRI data, we performed comparisons between the 3 groups considering DMN, SN, and FPN functional connectivity.
Results: hyAW subjects had greater DMN functional connectivity in posterior cingulate cortex in comparison to uAW and AW subjects, and in midcingulate cortex in comparison to AW only. On the contrary, unaware subjects had greater salience functional connectivity in anterior cingulate in comparison to hyAW and in anterior cingulate, anterior insula, and basal ganglia in comparison to AW only. Unaware subjects had also grater FPN functional connectivity in inferior frontal gyrus in comparison to hyAW.
Conclusions: Conclusion. Our results confirmed that awareness in the AD continuum is associated with an imbalance of the functional connectivity of three large-scale networks, namely the DMN, SN, and FPN. In addition, we demonstrated that the recruitment of these 3 functional networks follows a gradient according to the level of awareness.

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SHIFT 02-550

On-Demand Oral Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

BRAIN NETWORK CONNECTIVITY UNDERLYING AFFECTIVE SYMPTOMS IN PRODROMAL LEWY BODY DEMENTIA.

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Aims: Mood-related neuropsychiatric symptoms (NPS) including anxiety, apathy and depression are highly prevalent and associated with poorer outcomes in Lewy body dementia (LBD). Research on the neural basis of these symptoms in LBD is limited but suggests they may reflect dysfunction in distributed neuronal networks. This study aimed to investigate this in prodromal LBD using resting-state functional MRI.
Methods: Fifty-seven participants with mild cognitive impairment (MCI), including MCI with Lewy bodies (MCI-LB, n=28) and Parkinson's disease MCI (PD-MCI, n=29), were included. Functional MRI assessed connectivity within multiple resting-state networks including default mode, dorsal attention, salience, and limbic networks. NPS were measured using the Neuropsychiatric Inventory (NPI). Principal component analysis grouped apathy and depression into a single 'affective disorder' factor. Anxiety did not load onto any NPI factor and was analysed independently. Seed-to-voxel connectivity maps were analysed in CONN to determine associations between NPS and network connectivity.
Results: In PD-MCI, affective disorder and anxiety correlated with greater connectivity between the orbitofrontal seed and medial frontal regions, including prefrontal and subgenual cingulate cortex, and weaker connectivity between the orbitofrontal cortex and the brainstem (all *FWE p*<0.001). Additionally, participants with affective disorder demonstrated greater connectivity between the orbitofrontal cortex, medial prefrontal regions and angular gyrus. MCI-LB participants with anxiety demonstrated increased connectivity within medial prefrontal areas compared to those without (*FWE p*<0.001). However, no other significant correlations were found between NPS severity and network connectivity.
Conclusions: Associations between affective symptoms, anxiety and aberrant connectivity in limbic and default mode medial prefrontal areas in prodromal LBD reflect established neural mechanisms of mood disorders. Validating these findings in larger, more diverse cohorts is essential to establish neural signatures LBD-related NPS that will support the identification of symptomatic treatment targets.

SHIFT 02-558

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

AMPLIFYING EFFICIENCY AND ACCURACY IN DEMENTIA DRUG DEVELOPMENT

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Aims: Neurodegenerative disorders, including Alzheimer's disease and related disorders (ADRD), present significant challenges for effective drug development. Despite intensive global research efforts in past decades, multiple clinical trials have failed, with substantial financial burdens and a lack of successful therapeutic outcomes. Recent FDA approvals of amyloid targeting treatments like aducanumab, lecanemab, and donanemab highlight ongoing challenges related to efficacy, cost, and patient access.
Methods: The International Neurodegenerative Disease Research Center (INDRC) convened a Delphi panel of experts from multiple fields including clinical medicine, statistics, neurobiology, psychology, computer science, genetics and pharmaceutics to explore the use of genetics, proteomics and transcriptomics in ADRD research and to identify opportunities.
Results: The multifactorial nature of ADRD, including its variable symptom progression, selective neuronal vulnerability, and regional brain impacts, further complicates clinical trials. Emerging approaches, such as the integration of proteomics and transcriptomics, offer potential to reduce variance and increase precision in randomized controlled trials by providing deeper molecular insights. However, barriers such as insufficient sample sizes, lack of diversity in datasets, and the need for standardized data protocols remain.
Conclusions: This initiative aims to enhance the discovery, validation, and regulatory adoption of novel diagnostic and therapeutic technologies, ultimately fostering more accurate, cost-effective, and personalized treatment interventions for dementia. The workgroup identifies up challenges and proposes the research questions for wider public to answer

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SHIFT 02-559

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4 - 5 April

METHYLOMIC-BASED SUBTYPING OF LATE-ONSET ALZHEIMER'S DISEASE CORTEX

Valentin Laroche[1], Rachel Cavill[2], Rick Reijnders[1], Morteza Kouhsar[3], Joshua Harvey[3], Adam Smith[3], Lachlan Macbean[4], Jennifer Imm[3], Byron Creese[5], Julia Kofler[6], Daniel Van Den Hove[1], Katie Lunnon[3], Ehsan Pishva[1]
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Aims: The aim of this study is to identify and characterize methylomic-based subtypes of late-onset Alzheimer's disease (LOAD) using genome-wide DNA methylation (DNAm) data.
Methods: We analyzed genome-wide DNAm data from three independent postmortem brain cohorts (n = 831 samples) using data-driven clustering algorithms to identify subtypes based on methylomic patterns. The clusters were validated across cohorts, and we applied epigenome-wide association studies (EWAS) to explore differentially methylated positions (DMPs). Furthermore, we integrated transcriptomic and genetic data to investigate the molecular and biological drivers of the identified subtypes. Cell-type specificity was assessed using single-cell RNA sequencing (scRNA-seq) data.
Results: Our analysis identified two distinct methylomic subtypes of LOAD (LOAD-S1 and LOAD-S2), which were confirmed through robust cross-cohort replication. LOAD-S1 was enriched in pathways related to neurogenesis, nervous system development, and oxidative stress response, while LOAD-S2 was associated with cellular responses to external stimuli, extracellular matrix organization, and amyloid-beta regulation. Genetic analysis revealed distinct risk loci for each subtype, with LOAD-S1 linked to HLA-DQA1 and CLU, and LOAD-S2 associated with BIN1, ADAM10 and MAPT. Cell-type analysis showed subtype-specific methylation signatures in microglia, neurons, and oligodendrocytes, with notable differences in microglial responses between the subtypes.
Conclusions: Our findings suggest that methylomic-based subtypes of late onset AD reflect different underlying molecular mechanisms, contributing to the observed heterogeneity in disease progression and response to treatment. Understanding these subtypes could guide personalized therapeutic strategies targeting specific molecular pathways in LOAD.

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SHIFT 02-562

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4 - 5 April

CHARACTERIZATION OF THE ASTROCYTIC RESPONSE TO THE COMBINATION OF AMYLOID-BETA AND TAU LESIONS IN PRECLINICAL MODELS OF ALZHEIMER'S DISEASE

Nathan Louvel[1], Kevin Muret[2], Gwenaëlle Aurégan[1], Sueva Bernier[1], Martine Guillermier[1], Marjorie Benfissa[1], Julien Mitja[1], Vivien Letenneur[1], Caroline Jan[1], Fanny Petit[1], Eric Bonnet[2], Alexis-Pierre Bemelmans[1], Karine Cambon[1]
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Aims: Recent evidence supports the idea that reactive astrocytes precipitate Tau pathology in Alzheimer's disease (AD). Yet the mechanisms at play are unknown.
Methods: To investigate this question, we mimicked early and advanced stages of the disease in a new AD mouse model by injecting 3-month-old APP/PS1dE9 mice with AAVs overexpressing Tau in either its soluble (TauWT) or its aggregated form (TauProAggr). We assessed Tau pathology, neuroinflammation, and hippocampal integrity by immunohistochemistry 3 months later. In parallel, we performed bulk RNAseq on sorted hippocampal astrocytes.
Results: Preliminary histological findings showed that amyloid pathology did not trigger the formation of mature Tau aggregates in APP/PS1dE9 mice injected with AAV-TauWT, nor did it exacerbate the load of aggregated Tau in APP/PS1dE9 mice injected with AAV-TauProAggr, when compared to their WT counterparts. Atrophy of the CA1 layer and the whole hippocampus was detectable in TauWT injected mice but was not exacerbated by amyloidosis. Quantification of AT8-dystrophic neurites is underway. Bulk RNAseq analysis revealed that there was some overlap between the astrocytic responses associated with soluble or aggregated forms of Tau (immune response, cytokine response and secretion, phagocytosis) in both WT and APP/PS1dE9 genotypes. However a substantial number of genes were specific to each condition, suggesting a specific and/or synergistic effect of amyloid and Tau pathologies. Additional single nuclei RNAseq on total hippocampi is ongoing.
Conclusions: Our findings show that early amyloid pathology does not exacerbate the formation of Tau aggregates in the hippocampus of our models. Yet, the astrocytes surrounding the affected neurons seem to respond differently to each combination of Tau and beta-amyloid lesions. The characterization of this astrocytic response will provide new clues about the contribution of astrocytes to AD pathology.

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SHIFT 02-565

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
4 - 5 April

IMPROVING IMAGE-BASED PHENOTYPIC PROFILING IN NEUROSCIENCE: UTILIZING IPSC-DERIVED NEURONAL MODELS FOR MORPHOLOGICAL PROFILING

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Aims: Image-based phenotypic profiling methods, such as “Cell Painting” have revolutionized drug discovery research by leveraging microscopy images of cells to extract numerical information that characterizes various morphological aspects of a cell. These methods enable the screening of numerous chemical or genetic perturbations, assigning a unique morphological profile to each cell, and clustering together conditions that induce similar profiles. Recent advancements in high content data capture, the increase in computational power and the introduction of sophisticated analysis tools like machine learning approaches have further enhanced morphological profiling, allowing screening for thousands of different conditions. These developments have facilitated the identification of mechanisms of action, prediction of compound behaviors and drug repurposing.
Methods: While the classical cell painting approach offers scalability and cost-effectiveness, it often relies on cell lines that do not accurately represent the disease-relevant cell types in neuroscience. To address this limitation, we have focused on developing a morphological profiling approach using iPSC-derived neuronal models. We have adapted classical cell painting protocols and applied an optimized data augmentation pipeline combined with machine-learning-based feature selection.
Results: With our approach we have successfully extracted essential features from neuronal cultures, generating distinct morphologic profiles that describe and separate perturbations in iPSC-derived neuronal models.
Conclusions: Incorporating iPSC-derived neuronal models into image-based phenotypic profiling provides a deeper insight into disease-relevant cellular models. Despite the high complexity at the single cell level compared to homogenous U2OS cells, morphological profiling of iPSC-derived neurons can successfully derive intricate details for targets of novel biology in neuroscience, assigning pathway information and uncovering their mechanism of action. Therefore, cell painting in neural cells has the potential of enhancing our understanding of neurological disorders and accelerating the discovery of therapeutic targets.

SHIFT 02-578

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4 - 5 April

CHARACTERIZATION OF MYELIN COMPROMISE IN RATS WITH ALZHEIMER'S-LIKE TAUOPATHY

Ai Liu, Sonia Do Carmo, Claudio A. Cuello
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Aims: Alzheimer's disease (AD) affects both grey and white matter, leading to axonal degeneration, demyelination and glial pathologies. This study investigates the impact of pathological hyperphosphorylated tau (p-Tau) on axonal damage, as well as demyelination and remyelination process in the Alzheimer's-like tauopathy rat model in vivo.
Methods: We utilized the newly generated McGill-R955-hTau transgenic (Tg) rats expressing the longest human tau isoform with the P301S mutation. Cognitive function was assessed through behavioral testing. Tau expression patterns in grey and white matter were mapped using immunohistochemistry. Axonal damage and myelin pathology were examined via electron microscopy, and oligodendrocyte marker expression profiles were analyzed through immunohistochemistry.
Results: Tg rats exhibited age-dependent progression of p-Tau levels, spreading from neuronal cell bodies in grey matter to axonal tracts and oligodendrocyte cytoplasm in white matter. This progression resulted in cognitive impairments, neurodegeneration, as well as axon and myelin loss. Ultrastructural analysis revealed extensive axonal and myelin degeneration characterized by swollen myelinated axons, empty myelin sheaths, myelin lamellae splitting, myelin balloons, and concentric membranous whorls. Myelin debris were observed in microglia and astrocytes. Following white matter demyelination, we found that oligodendrocyte progenitor cell (OPC) differentiated more efficiently in Tg rats than wild type (Wt) rats. We also found an increased level of myelin basic protein within white matter, which however did not translate into increased remyelination due to increased axonal degeneration in Tg rats compared to Wt rats.
Conclusions: Our findings suggest that axonal damage caused by abnormal tau accumulation and phagocytosis by microglia and astrocytes can lead to myelin pathology and loss. The resulting demyelination may signal OPCs to differentiate to facilitate remyelination.

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SHIFT 02-579

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4 - 5 April

DIVERSE SOMATIC GENOMIC ALTERATIONS IN SINGLE NEURONS IN CHRONIC TRAUMATIC ENCEPHALOPATHY

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Aims: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that follows repetitive head impact (RHI) in some individuals, yet little is known about its molecular pathogenesis. Previous studies of single neurons showed that private somatic mutations increase both during normal aging and in neurodegenerative disorders, and show diverse mutational patterns.
Methods: We applied two orthogonal single-nucleus whole-genome sequencing (snWGS) methods to hundreds of neurons isolated from the prefrontal cortex of 15 individuals with CTE, and 4 individuals with RHI but no CTE diagnosis, and compared mutational rates and spectra with neurons from neurotypical controls and Alzheimer's disease (AD).
Results: We found a significant elevation of somatic double-stranded single-nucleotide variants (SNVs) in CTE that resembles a pattern previously reported in AD. Furthermore, we found a strikingly large burden of small insertions and deletions (indels) and used duplex sequencing to show that these indels are mainly single-stranded, and again found a similar phenomenon in neurons from AD brain, resembling a known pattern, ID4.
Conclusions: Our results suggest that neurons in CTE brain are exposed to stereotyped mutational processes, and that these processes are shared between AD and CTE suggesting potentially common pathogenic mechanisms. Furthermore, the absence of similar changes in RHI neurons without CTE suggests that the development of CTE entails a mechanism beyond that caused by RHI alone.

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SHIFT 02-601

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / TAU CLEARANCE
4 - 5 April

EXPERTS ENVISION A VALUABLE ROLE FOR TAU-PET IN DRUG TRIALS AND CLINICAL PRACTICE

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Aims: Recent advancements in Alzheimer's disease biomarker research and drug trials prompt reflection on the value and appropriate use of tau-PET in future clinical practice and trials. We therefore conducted a survey among dementia and PET experts worldwide to investigate how they envision the future role of tau-PET in trials and clinical practice.
Methods: An online survey was distributed to dementia clinicians and researchers who were invited to participate through personalized emails, social media channels and presentations at relevant conferences. With this approach we intended to recruit participants from different countries with diverse backgrounds and expertise. We used a mix of multiple choice questions, statements with a 5-point Likert scale ("strongly disagree" to "strongly agree") and a few open questions.
Results: In total 268 dementia experts, comprising 121 researchers and 143 clinicians, covering six continents completed the survey (Figure 1). Experts anticipate an important role for tau-PET for participant selection (76-100%) and measuring endpoints (75-97%), in both anti-amyloid and anti-tau drug trials (Figure 2A). On the topic of target engagement in anti-tau trials, respondents foresee utility of tau-PET in tau immunotherapies (89%), which gradually decreases for tau aggregation inhibitors, therapies targeting intracellular tau levels and reversing post-translation modifications (Figure 2B). The vast majority of respondents (90%) fosters a positive attitude towards the added value of tau-PET in clinical practice. Experts are confident that a tau-PET scan could influence patient management in current practice (median 4 "agree" [IQR 3-4]) and this would increase when effective disease-modifying treatments are available (median 5 " strongly agree" [IQR 4-5]) (Figure 3C).

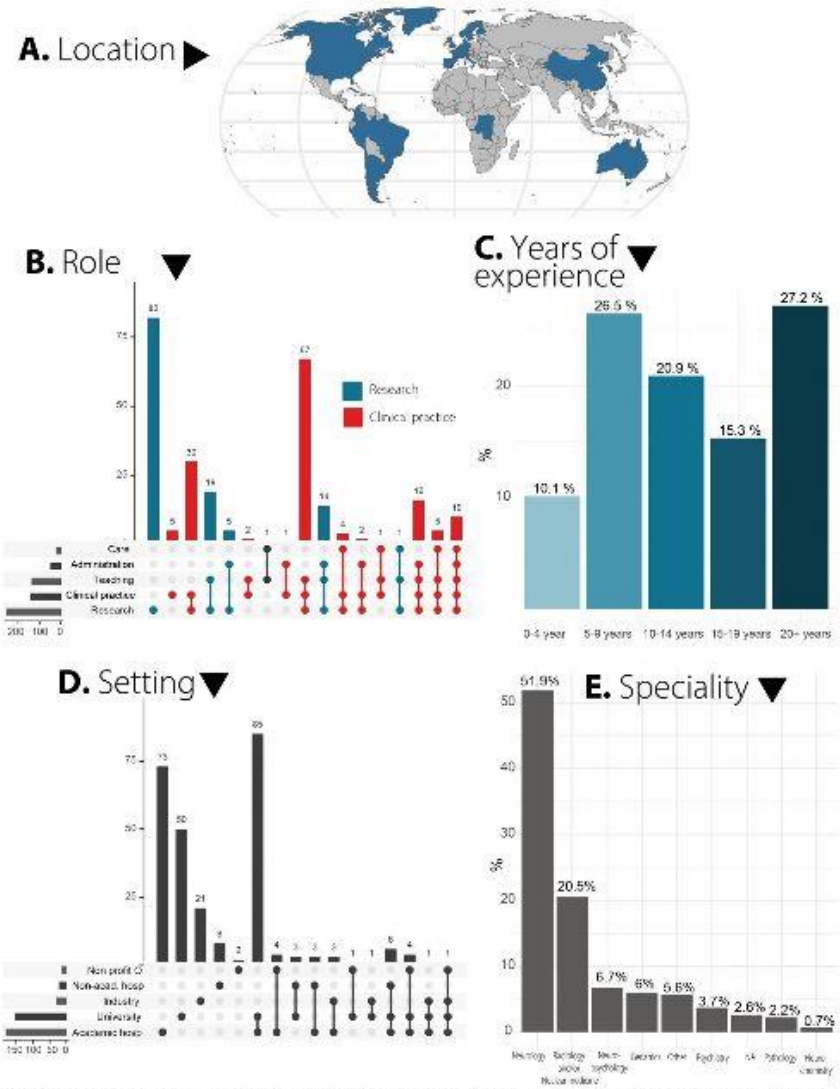

Figure 1. Respondent demographics. (A) Map displaying respondents' locations by country. (B) Upset plot illustrating the roles and tasks of the respondents: horizontal bars represent the frequency of each activity, while vertical bars show the frequency of task combinations. Colors differentiate between clinicians and researchers. (C) Bar graph showing the relative frequency of respondents by years of experience. (D) Upset plot summarizing the work setting of each respondent. (E) Bar plot showing the main professional specialty fields of the respondents. Abbreviations: Non profit O = non-profit organization; non-acad. hosp = non-academic hospital; academic hosp = academic hospital.

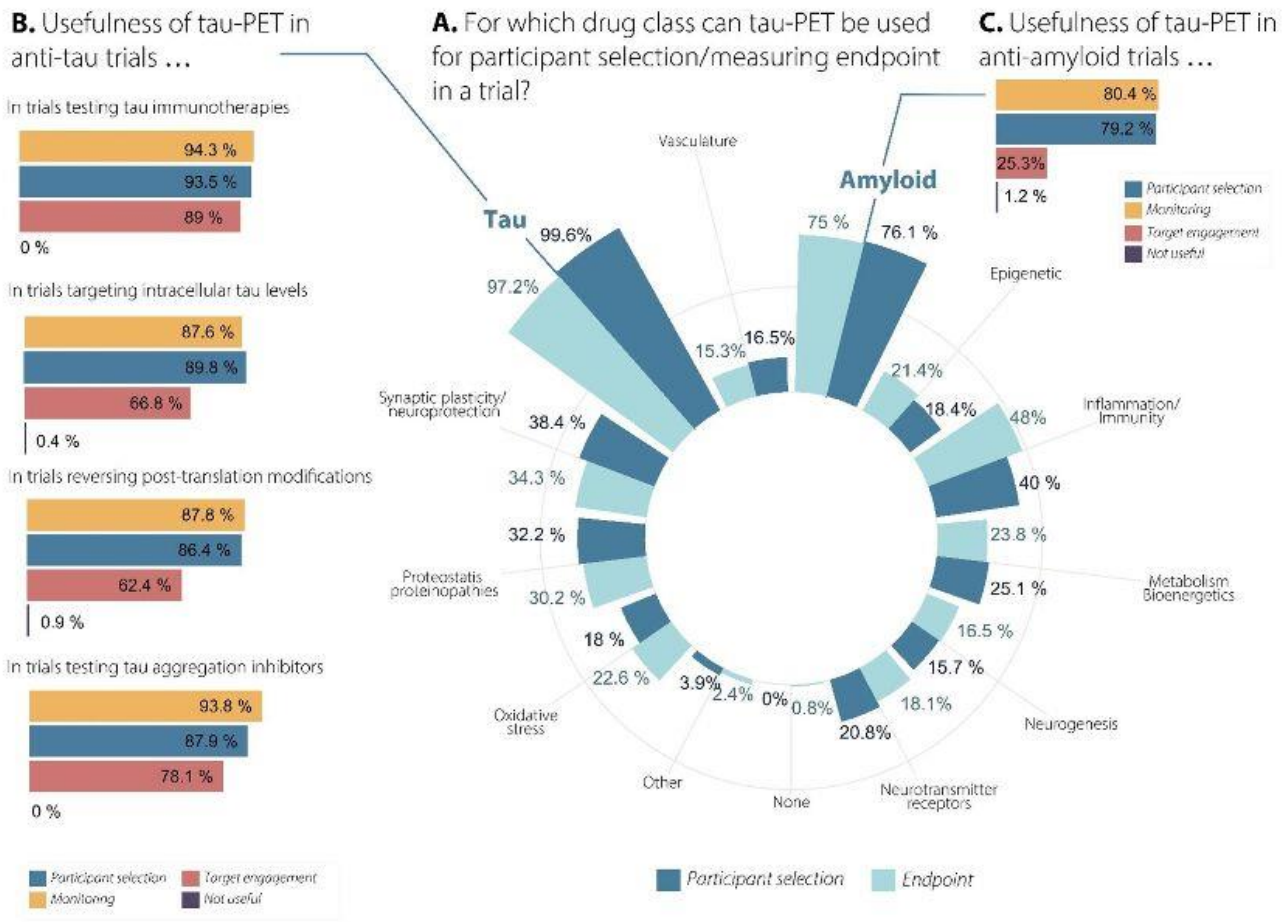

Figure 2. Summary findings on the envisioned future role of tau-PET in drug trials. (A) Circular bar plot showing proportions of respondents envisioning a role for tau-PET for participant selection and measuring endpoints across different drug classes. (B) Bar plots showing proportions of respondents envisioning a role for tau-PET for participant selection, monitoring and target engagement within four anti-tau trial classes specifically. (C) Bar plots showing proportions of respondents envisioning a role for tau-PET for participant selection, monitoring and target engagement within anti-amyloid drug trials specifically. Abbreviations: tau-PET, tau positron emission tomography.

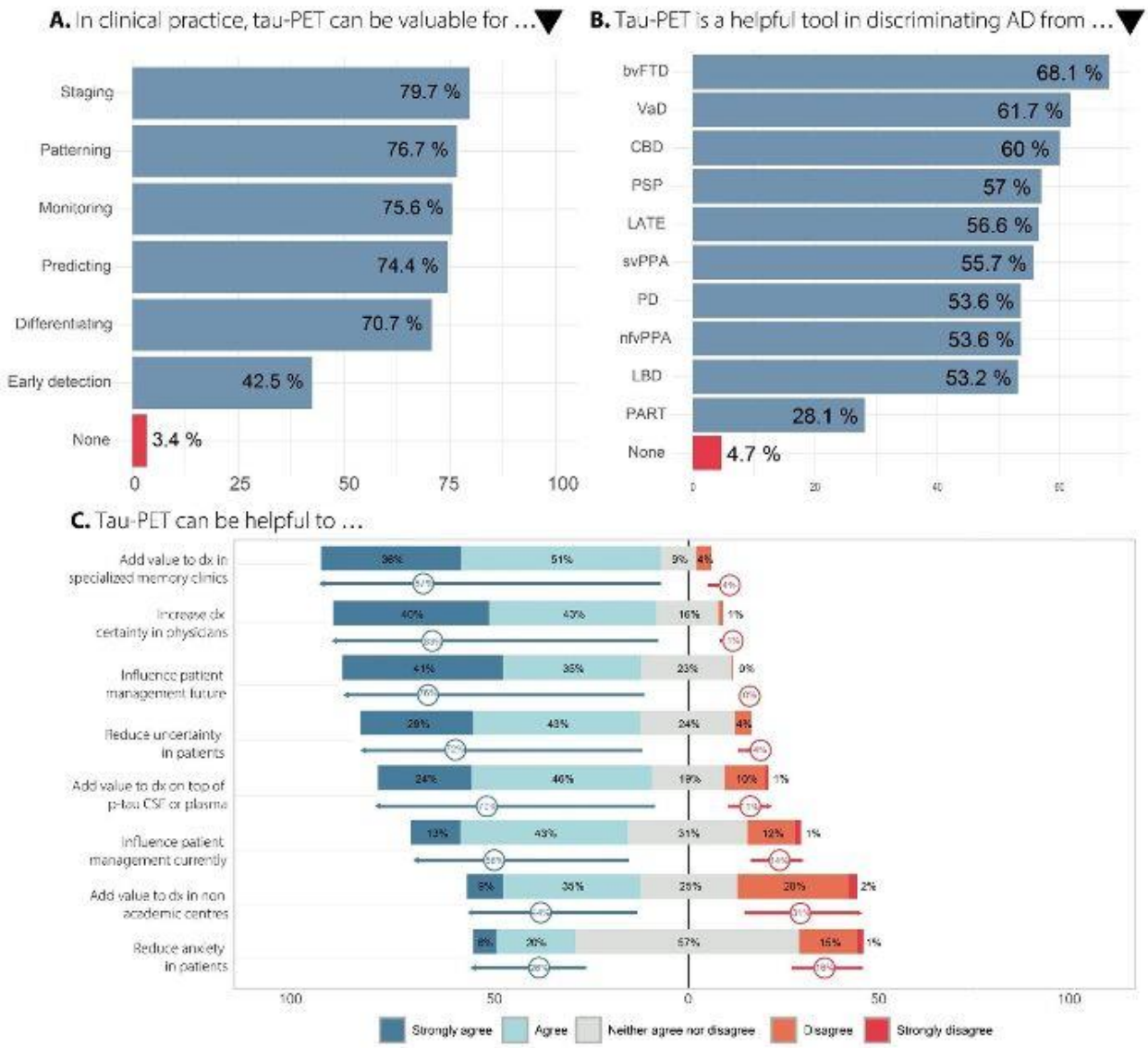

Figure 3. Summary findings on the envisioned future role of tau-PET in clinical practice.
(A) Envisioned value of tau-PET per clinical purpose. (B) Envisioned utility of tau-PET to differentiate between various neurodegenerative pathologies. (C) Proportions of responses of (dis)agreement on a Likert scale to eight statements regarding the added value of tau-PET. Arrows indicate the combined proportion of agreement or disagreement. Abbreviations: tau-PET, tau positron emission tomography; AD, Alzheimer's disease; dx, diagnosis/diagnostic; p-tau, phosphorylated tau; CSF, cerebrospinal fluid.

Conclusions: Our global survey shows that dementia experts envision an important role for tau-PET in the future, both in drug trials and clinical practice.

SHIFT 02-607

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

EVALUATION OF 120 NEURODEGENERATIVE AND INFLAMMATORY PROTEINS IN DRIED BLOOD SPOTS AND PLASMA SPOTS FOR POPULATION-WIDE BIOMARKER SCREENING WITH NULISASEQ

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Aims: Blood-based biomarker profiling holds great promise for the early detection of neurodegenerative diseases. However, standardization of sample collection and storage conditions is critical for reliable and accurate testing. Dried blood spots (DBS) and dried plasma spots (DPS) provide alternative collection methods for longitudinal, population-wide studies especially in remote areas with a lack of infrastructure and warrant further evaluation for compatibility with highly multiplexed proteomic platforms for profiling key markers of disease pathogenesis including pTaus, amyloid betas, and inflammatory cytokines.
Methods: Multiple commercially available dried blood spots and dried plasma spots collection devices were evaluated in comparison with matched whole blood and plasma from healthy and diseased subjects with the NULISAseq™ 120-plex CNS Disease Panel on the ARGO™ HT platform. Different extraction conditions and sample input volumes were tested to determine optimal conditions for detection of key neurodegenerative and inflammatory targets at high sensitivity. Pearson correlation analysis was performed to determine the concordance between matched whole blood and DBS as well as plasma and DPS.
Results: Our preliminary results show high detectability in DBS (>85%) and DPS (>90%), comparable to overall detectability in paired whole blood and plasma samples. Additionally, key CNS targets such as NFL, GFAP, pTaus (pTau-181, pTau-217 and pTau-231) showed close to 100% detectability. Overall, relative protein quantification in DBS and DPS demonstrate high correlations with matched blood and plasma respectively (r>0.8).
Conclusions: We have developed an optimized protocol for extraction of proteins from DBS and DPS followed by evaluation with the NULISAseq™ technology. Our data suggests that most targets of interest are compatible with this type of collection method and DBS/DPS can be a promising substitute for blood-based profiling with added benefits of ease of collection, storage, transportation and analysis.

SHIFT 02-608

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

DEVELOPMENT OF A HIGH-SENSITIVITY BIOPHOTONIC PLATFORM FOR THE DETECTION OF BLOOD-BASED BIOMARKERS IN ALZHEIMER'S DISEASE

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Aims: A major issue in the fight against Alzheimer's disease is the availability of an accessible diagnostic technology for plasma-based biomarker detection. Evidence suggests the abundance of plasma-based biomarkers, including amyloid-ß (Aß) and phosphorylated tau, change years before clinical symptoms arise, allowing for early diagnosis via a blood test. Our goal is to develop an inexpensive handheld guided mode resonance (GMR) biosensor for rapid, ultrasensitive, multiplexed and label-free detection of these biomarkers in plasma, aiming for detection at clinically relevant pg/mL concentrations through optimization of the GMR geometry, surface chemistry, and microfluidics.
Methods: Our sensor employs chirped GMRs that utilize wavelength-scale gratings to excite standing waves sensitive to refractive index changes. The gratings translate spectral variations into spatial information which is captured using a simple smartphone camera. We present a handheld interferometric GMR design, enhanced with surface functionalization to support antibody immobilization and reduce non-specific binding, that can be mass-produced at very low cost.
Results: We use phase noise matching and optimisation of the fringe spacing to maximise the signal-to-noise ratio and a as a result, we demonstrate that the interferometric GMR design enables the label-free sensing of 100 pg/mL for Aß *in vitro*. Our cartridge-based design also supports multiplexed detection of at least 8 biomarkers in parallel and allows for quantifiable readouts to be obtained within minutes. We also demonstrate detection of Aß(1-42) at pg/mL concentrations in diluted serum, underscoring the platform's clinical potential for quantitative plasma biomarker determination.
Conclusions: Our photonic platform offers rapid and sensitive detection of Alzheimer's disease biomarkers *in vitro* and in serum at clinically-relevant concentrations. This portable, cost-effective and scalable tool is promising for clinical translation, early-stage diagnosis and is widely applicable beyond the Aß biomarkers demonstrated here.

SHIFT 02-609

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

PRESYNAPTIC AND AXONAL LOSS SYNERGISTICALLY PREDICT LONGITUDINAL NEURODEGENERATION AND COGNITIVE DECLINE

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Aims: This study aims to investigate whether presynaptic losses measured by cerebrospinal fluid (CSF) growth-associated protein 43 (GAP-43) and axonal degeneration detected by plasma neurofilament light (NfL) have a synergistic effect on predicting longitudinal neurodegeneration and cognitive decline in Alzheimer's disease (AD).
Methods: We identified 730 Alzheimer's Disease Neuroimaging Initiative participants (233 cognitively unimpaired (CU), 387 mild cognitive impairment (MCI), and 110 AD dementia) with concurrent (interval < 1 year) CSF GAP-43, plasma NfL, and longitudinal memory and executive function data. Among them, 706 participants (225 CU, 388 MCI, 93 AD dementia) had longitudinal measurements of residual hippocampal volume (rHCV) and temporal metaROI cortical thickness, and 366 participants (108 CU, 235 MCI, 23 AD dementia) had longitudinal data of metaROI ^{18}F-fluorodeoxyglucose (FDG) standard uptake value ratio (SUVR). We investigated the interaction of baseline CSF GAP-43 and plasma NfL at longitudinal prediction of rHCV, temporal metaROI cortical thickness, metaROI FDG SUVR, memory, and executive function, controlling for age, sex, education, and diagnosis.
Results: Higher CSF GAP-43 and Plasma NfL at baseline had significant interaction (p=0.028) on predicting faster rates of temporal metaROI cortical thinning but not on longitudinal decreases of rHCV and metaROI FDG SUVR. In addition, given the same levels of CSF GAP-43, higher baseline plasma NfL was related to more rapid rates of memory decline (p=0.022) and executive function (p=0.004) over more than four years of median follow-up.
Conclusions: We found a synergistic effect between presynaptic dysfunction and axonal degeneration on predicting longitudinal cortical thinning and cognitive decline. These findings provide novel insights into understanding the association of presynaptic and axonal loss with subsequent neurodegeneration and cognitive decline in elderly adults.

SHIFT 02-610

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

LINKING P-TAU217 IN AN AT-RISK POPULATION TO OBJECTIVE MARKERS OF SPEECH AND LANGUAGE

Alveena Siddiqui[1,2], Jessica Alber[3,4], Thayabaran Kathiresan[1], Peter Snyder[3,4], Adam Vogel[1,2]
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Aims: Early identification of Alzheimer's Disease (AD) is an important clinical challenge. Plasma p-tau217 has emerged as a promising biomarker for AD showing high specificity and sensitivity. In parallel, subtle alterations in speech and language may precede overt cognitive symptoms in AD, making them valuable for early detection. The relationship between speech and language impairments and the underlying neuropathology of AD, particularly the correlation with p-tau217, has not been extensively studied. To explore the relationship between speech and language features and plasma p-Tau217 levels in individuals at risk of or in the initial stages of AD. We are aiming to enhance our understanding of how communication changes reflect underlying tau pathology and contribute to the development of more precise and earlier diagnostic tools for AD.
Methods: Blood biomarkers including genetic status and plasma p-tau217 and speech were acquired in 140 individuals at risk of AD. Speech and language was analyzed objectively using acoustic and linguistic protocols. Statistical correlation analysis as well as machine learning methods were used to explore data.
Results: Preliminary data suggest an association between speech and language features and elevated p-tau217 level. Full analysis will provide better insight into the use of speech and language markers in addition to blood biomarkers for early AD detection.
Conclusions: There is a link between underlying pathology and measurable behaviors like speech in at risk individuals. Communication outcomes may serve as a proxy of pre-clinical status or as a meaningful clinical outcome in clinical trials.

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SHIFT 02-611

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

A PRELIMINARY INVESTIGATION OF BRAIN DERIVED (BD) TAU AS A BIOMARKER OF ACUTE AND CHRONIC TRAUMATIC BRAIN INJURY.

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Aims: Across the spectrum of traumatic brain injury (TBI), fluid-based biomarkers are valuable diagnostic and prognostic tools. Brain-derived (BD) tau is an emerging neurodegenerative marker that recognizes tau derived exclusively from the brain. This pilot study assessed BD-tau as a plasma biomarker in two distinct TBI cohorts alongside glial fibrillary acidic protein (GFAP) neurofilament light chain (NfL) and phosphorylated (p)-tau-217.
Methods: Under IRB approved protocols, participants with a history of multiple TBIs and self-reported cognitive complaints ("chronic-mixed"), severe TBI patients admitted to the intensive care unit ("acute-severe," GCS 3-8) and cognitively intact controls were included in the study. Plasma BD-tau, GFAP, NfL and ptau-217 from a single time-point were measured by the Simoa-Quanterix platform. Groups were statistically analyzed by non-parametric tests.
Results: There were 22 chronic-mixed (40±8.5yrs, 19% female), 34 acute-severe (46±21yrs, 21% female) and 8 controls (38±6.1yrs, 13% female) participants. Across all biomarkers (BD-tau, GFAP, NfL, p-tau-217) expression was significantly higher in the acute-severe group (4d post-injury) compared to controls (Mean±SD: 121.4±119.1 vs. 7.4±2.1 pg/mL; 13080±11522 vs. 118.0±57.3 pg/mL; 194.7±215.3 vs. 5.8±1.4 pg/mL; 0.75±0.9 pg/mL vs. 0.21±0.06 pg/mL, respectively). No significant differences were observed between the chronic-mixed group (10.6±6.7yrs post-injury; 7.7±2., 97.5±32.6, 7.1±2.8, 0.36±0.7 pg/mL, respectively) and controls. In the acute-severe group, BD-tau, GFAP and NfL levels were significantly higher in patients with unfavorable 6-month outcome (GOS-E≤2) compared to favorable outcome (GOS-E≥5), adjusting for age/sex/GCS. P-tau-217 was not significant.
Conclusions: Plasma BD-tau performed similarly to hallmark injury biomarkers GFAP and NfL in both the chronic-mixed and acute-severe TBI cohorts and outperformed ptau-217 as a prognostic marker in the acute-severe group. Future studies are warranted to determine the potential for BD-tau as a plasma biomarker for acute neuronal damage or chronic TBI-associated neurodegeneration.

SHIFT 02-612

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4 - 5 April

SCALABLE, ULTRA-SENSITIVE QUANTIFICATION OF BLOOD-BASED BIOMARKERS FOR EARLY ALZHEIMER'S DISEASE DETECTION AND MONITORING

Jason Wan, Robert Lin
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Aims: The need for an accessible, sensitive, and accurate tool for Alzheimer's disease diagnostics is an increasingly urgent public health challenge with critical societal implications. Current diagnostic methods such as PET scans and biomarker testing in cerebral spinal fluid are invasive, expensive, and not easily accessible. These shortcomings limit their use, particularly in settings without specialized capabilities. Here we present results from the development of a widely accessible, novel absolute quantitation immunoassay focused on Alzheimer's Disease blood-based biomarkers.
Methods: We utilized novel chemistry and a proprietary background reduction technique to combine traditional PLA with digital PCR (dPCR) to create a highly sensitive and absolutely quantitative assay platform. Reference material was used to demonstrate the LLOD and LLOQ of the assays. Samples were diluted by 20% and 30% to simulate small changes in biomarker levels and quantified by the assays. Levels of p-Tau 217 and Aβ42 from 20 serum/plasma samples were quantified using the platform to demonstrate the real-world performance of the platform.
Results: We demonstrated two prototype assays – p-Tau 217 and Aβ42 – that both achieved sub-pg/mL quantitation using dPCR, demonstrating superior sensitivity without the need for reference material. The digital output enabled the detection of subtle differences in biomarker levels, which are difficult for traditional systems to measure but crucial for longitudinal monitoring and disease staging. Lastly, all human samples were shown to be above LLOQ, showing the assays' compatibility with real patient samples.
Conclusions: Taken together, the improved sensitivity, consistency and ability to detect small changes suggest this technology has the potential to revolutionize Alzheimer's disease by bringing a scalable and accurate diagnostic tool to a wide range of clinical settings.

SHIFT 02-614

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

A MULTI-MODAL BLOOD-BASED BIOMARKER PANEL REVEALS ALTERED LYSOSOMAL IONIC CONTENT IN ALZHEIMER'S DISEASE

Souvik Modi, Shareefa Thekkan, Dhivya Venkat
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Aims: Lysosomal storage disorders (LSDs) and adult neurodegenerative disorders like Alzheimer's disease (AD) share various clinical and pathophysiological features. Lysosomal ionic homeostasis is recognized as a key feature of many LSDs, but it has not been clinically linked with AD pathology. The aim is to develop a multi-parametric platform that is better equipped to comprehensively phenotype lysosomal ion homeostasis in AD, which is essential to the development of disease-modifying therapies.
Methods: Esya's multiparametric platform incorporates 1) Two-ion probes that ratiometrically measure concentrations of ions such as H^+ and Ca^{2+} with single lysosome resolution from CD14+ monocytes, 2) ApoE4 carrier status and 3) A protein panel comprising biomarkers related to AD pathology, screened from 120 diverse CNS-related proteins using Nucleic acid Linked Immuno-Sandwich Assay (NULISA). AD prediction scores were calculated using logistic regression with lasso regularization.
Results: We developed the 2-Ion Index, measuring pH to Ca^{2+} ratio in lysosomes, quantifies ion homeostasis disruption in AD. We observed significant deacidification and Ca^{2+} loss in monocyte lysosomes. Using NULISA, we identified four new biomarkers for AD (REST, S100A12, S100B, and PDGFRB) in addition to biomarkers of the A/T/N/I pathway (e.g., Aβ42, pTau217, pTau231, NfL, and GFAP). Lysosomal ionic status correlates with AD pathological markers in plasma, suggesting potential for a multi-modal biomarker panel. Our multi-parametric models demonstrated high accuracy (AUC 85.4-98.5%), with efficient logistic regression performing best (AUC 96.8 ± 0.6%). These findings indicate the promise for developing a comprehensive AD evaluation tool.
Conclusions: Our multi-parametric approach, combining lysosomal ions with plasma biomarkers, shows promise for a comprehensive blood-based AD evaluation panel. This non-invasive platform could aid in AD diagnosis, progression, monitoring, and complement lysosome-targeted drug development efforts.

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SHIFT 02-615

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

PROTEOMIC ANALYSIS OF CORTEX-DERIVED EXTRACELLULAR VESICLES IN THE CONTEXT OF TAUOPATHIES

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Aims: The aim of this study is to characterize the proteomic content of brain-derived extracellular vesicles (EVs) from the interstitial fluid (ISF) of patients diagnosed with 3R tauopathies (Pick's disease) and 4R tauopathies (progressive supranuclear palsy), as well as non-demented controls. The goal is to differentiate between these tauopathies based on their proteomic profiles, with a focus on hyperphosphorylated tau accumulation.
Methods: Extracellular vesicles were isolated from the freshly frozen frontal cortex post-mortem tissue of patients with 3R tauopathies (n=5), 4R tauopathies (n=10), and non-demented controls (n=4). The proteome of these EVs was analyzed and correlated with hyperphosphorylated tau accumulation, characterized through histology. Key proteins such as glial, mitochondrial, and microtubule-associated proteins were examined to determine their relationship with tau inclusions.
Results: The proteomic content of extracellular vesicles from tauopathy patients strongly correlates with pathological tau accumulation in the cortex. The proteomic features allow for accurate differentiation between 3R and 4R tauopathies, with variations in the abundance of glial, mitochondrial, and microtubule-associated proteins. These features correlate significantly with the number of hyperphosphorylated tau inclusions, allowing for a 100% accurate prediction of 3R or 4R tau pathology.
Conclusions: This study highlights the significance of characterizing the brain-derived extracellular vesicles' proteomic content in the context of tauopathies. The findings demonstrate the potential for using EV protein signatures to develop more precise diagnostic tools and targeted therapeutic strategies for specific types of tauopathie

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SHIFT 02-616

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

PREANALYTICAL FACTORS IMPACTING BIOMARKER USE IN CHARACTERIZING NEURODEGENERATION: FINDINGS OF THE ADRC BIOFLUID BIOMARKERS BEST PRACTICES WORKGROUP

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Aims: The workgroup was tasked by the NACC and ADRC Biomarker Steering Committee to update the previous NIA-ADRC working guidance documents from 2014 to support standardization of clinical and scientific inquiry across the 37 ADRCs. The team is integrated with other similar international efforts at standardization and gained additional insights from the SABB and from thorough review of the primary literature. The focus of the updated working documents included preanalytical processing, storage and study methods critical to standardized quantification of biomarkers in multicenter studies and for integration of data across studies to advance the understanding of underlying pathologies.
Methods: The current Workgroup was formed in 2023 and utilized the following approach for revising the NIA-2014 guidelines: Detailed questionnaires were distributed to the ADRC network to identify assays currently in research use needing standardization. Literature and non-published resources were

analyzed to identify preanalytical factors shown to affect assay results. Literature support was documented and the need for further information was noted for biomarker assays in use.
Results: 37 ADRC centers were surveyed for data on biomarker use and instrumentation. Biomarkers in widespread use for research purposes beyond ATN included 18 biomarkers in CSF and blood, including novel Tau assays (BDTau, MTBR Tau), Neuronal Pentraxin 2, Neurogranin, TDP-43, YKL-40 and sTREM2 in CSF. Vascular and neuroinflammation biomarkers were represented as well. Instrument use included 7 distinct assay types. Data specific to preanalytical concerns for each biomarker, as available, were also collected and presented in the recommendations.
Conclusions: The Biofluid Biomarkers Best Practice Workgroup found and highlighted the need for further study of preanalytical factors in many commonly studied biomarkers to support multicohort data integrations. These findings will support standardization efforts at the ADRCs and for dementia research worldwide.

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SHIFT 02-617

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4 - 5 April

NEUROFILAMENT LIGHT AS A BIOFLUID BIOMARKER AND ITS PATHOLOGICAL CORRELATES IN BRAIN IN PRECLINICAL MODELS AND A HUMAN COHORT

Sarah Vanherle[1], Jana Hardy[1], Art Janssen[1], Pablo Botella Lucena[1], Bieke Janssen[1], Yanyan Wang[1], Rose Bruffaerts[2], Riet Vangheluwe[3], Ilse Dewachter[1]
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Aims: Alzheimer's Disease (AD) is marked by the accumulation of extracellular amyloid beta (Aβ) peptides and intracellular hyperphosphorylated tau, which lead to the formation of Aβ plaques and neurofibrillary tangles (NFTs), respectively. Alongside neurodegeneration, which occurs in the later stage of AD, these hallmarks define the ATN framework. Over the last decade, there has been growing interest in blood-based (BB) biomarkers to follow up the disease progression. Detailed study of pathological correlate of biofluid biomarkers will reciprocally increase insight in disease mechanisms and will increase the utility and use of biofluid biomarkers.
Methods: This study aims to investigate the relation between neurofilament light (NfL) and pathological processes in the brain of mice with progressive amyloid and tau pathology, using 5xFAD and TauP301S mice, respectively. For this, immunohistochemical stainings of the brain of these mice and biomarker measurements in blood were performed at different pathological stages. Furthermore, we validate these relations in a human cohort.
Results: Immunostaining revealed a gradual increase of NfL with age in different brain regions, correlating with increasing amyloid and tau pathology. These changes correlate with the NfL concentrations in blood and brain homogenates of these models. Super-resolution microscopy also showed irregularities of NfL organization in the area close to the amyloid plaques and partial colocalization between tau pathology and NfL. In the human cohort, AD patients show increased NfL serum levels, compared to healthy and mild cognitive impairment (MCI) subjects.
Conclusions: This research seeks to understand the pathological mechanisms in AD and other neurodegenerative diseases linked to elevated blood NfL, increasing its potential as a biomarker for disease monitoring.

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SHIFT 02-624

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4 - 5 April

LONGITUDINAL INVESTIGATION OF LOCUS COERULEUS NOREPINEPHRINE SYSTEM INTEGRITY AND COGNITIVE PERFORMANCE ACROSS THE ALZHEIMER'S SPECTRUM

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Aims: Noradrenergic neurons of the locus coeruleus (LC) play a critical role in the pathophysiology of Alzheimer's disease (AD). LC imaging with MRI is a promising in-vivo method to study the integrity of this system in AD. Here we investigate longitudinal change in LC integrity across the AD spectrum and its correlation to different cognitive measures.
Methods: Participants (n=387) were enrolled in the TRIAD cohort at McGill University and completed detailed clinical assessment and MR imaging using TSE sequence for LC imaging, PET imaging of amyloid and tau (using [^{18}F]MK6240), and cognitive assessments. The LC was segmented and divided into rostra-caudal sections using our, FDA approved, automated algorithm. LC contrast was assessed relative to a pontine reference region. An LC integrity metric was created using logistic regression to predict AD status from the pattern of LC signal across sections. Linear mixed effect models related LC integrity to cognitive measures and time.
Results: Contrast in the middle LC section decreased over time (t_{458}=-2.37, p=0.018) but there was no group-by-time interaction. LC integrity was positively correlated to most cognitive domains in tau-positive participants even when controlling for illness severity and amyloid and tau burden. LC integrity did not correlate to cognitive measures in tau-negative participants.
Conclusions: Loss of LC integrity may impair cognition in AD independent of other measures of illness severity. We did not see clear evidence that this was most pronounced for any cognitive domain. Using a strict definition of healthy aging (tau-negativity), LC integrity may not be linked to cognition.

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SHIFT 02-628

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4 - 5 April

FREE-WATER IMAGING IN PROGRESSIVE SUPRANUCLEAR PALSY

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Aims: Progressive supranuclear palsy (PSP) is a rare neurodegenerative movement disorder characterised by falls, postural instability, oculomotor dysfunction and cognitive decline. The diagnosis and measurement of disease in PSP currently relies on clinical criteria with no objective biomarkers available. Advanced MRI techniques such as free-water diffusion imaging have shown microstructural changes associated with neurodegeneration. In this study we investigated the potential of free-water diffusion imaging as a suitable biomarker of disease in PSP.
Methods: We used a bi-tensor free-water (FW) model to measure diffusivity in several sensorimotor and transcallosal white matter tracts in a cohort of 16 subjects with PSP. We investigated the correlation between FW and free-water corrected fractional anisotropy (fwFA) with clinical disease severity as measured by the PSP rating scale (PSPRS).
Results: We found significant negative correlations between the PSPRS and FW values in both the sensorimotor and transcallosal tracts of the dorsal (r=-0.57, p=0.023 and r=-0.50, p=0.049) and ventral (r=-0.54, p=0.032 and r=-0.56, p=0.025) premotor areas, as well as in the transcallosal primary sensory cortex (r=-0.54, p=0.032) and supplementary motor area (r=-0.53, p=0.034). However, none of these results survived multiple comparisons correction using the false discovery rate. No significant correlations were found between the PSPRS and fwFA.
Conclusions: These findings suggest that FW may be a more sensitive measure than fwFA in PSP, particularly in white matter tracts of the premotor and supplementary motors areas. However, the negative correlations with the PSPRS exhibited here are in contrast to previous research which report that FW is positively associated with clinical disease severity in neurodegenerative diseases. Therefore, further investigation into the relationship between FW and other measures of disease severity in PSP is needed.

SHIFT 02-629

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4 - 5 April

ASSOCIATION BETWEEN COGNITIVE FUNCTION AND CEREBELLAR ATROPHY IN ALZHEIMER'S DISEASE

Deborah Van Rossem[1], Nuno Pedrosa De Barros[2], Annemie Ribbens[2], Sara De Witte[1], Sebastiaan Engelborghs[1]
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Aims: Recent research has highlighted the importance of cerebellar atrophy in AD. In this work, we evaluated the relationship between the volume of different cerebellar subregions and cognitive function in different stages of AD.
Methods: 134 subjects from routine clinical care at UZ Brussels were included in this study. The population included 49 individuals with Subjective-Cognitive-Decline (SCD), 23 with Mild-Cognitive-Impairment (MCI), and 62 with dementia due to AD. T1-weighted MR images were collected for all participants and processed with icobrain dm. Deep-learning-based segmentation of the cerebellar gray matter and white matter from icobrain were then combined with an atlas-based approach for identifying the different cerebellar lobules. The association between regional cerebellar volumes and Mini-Mental-State Examination was assessed using Pearson correlation.

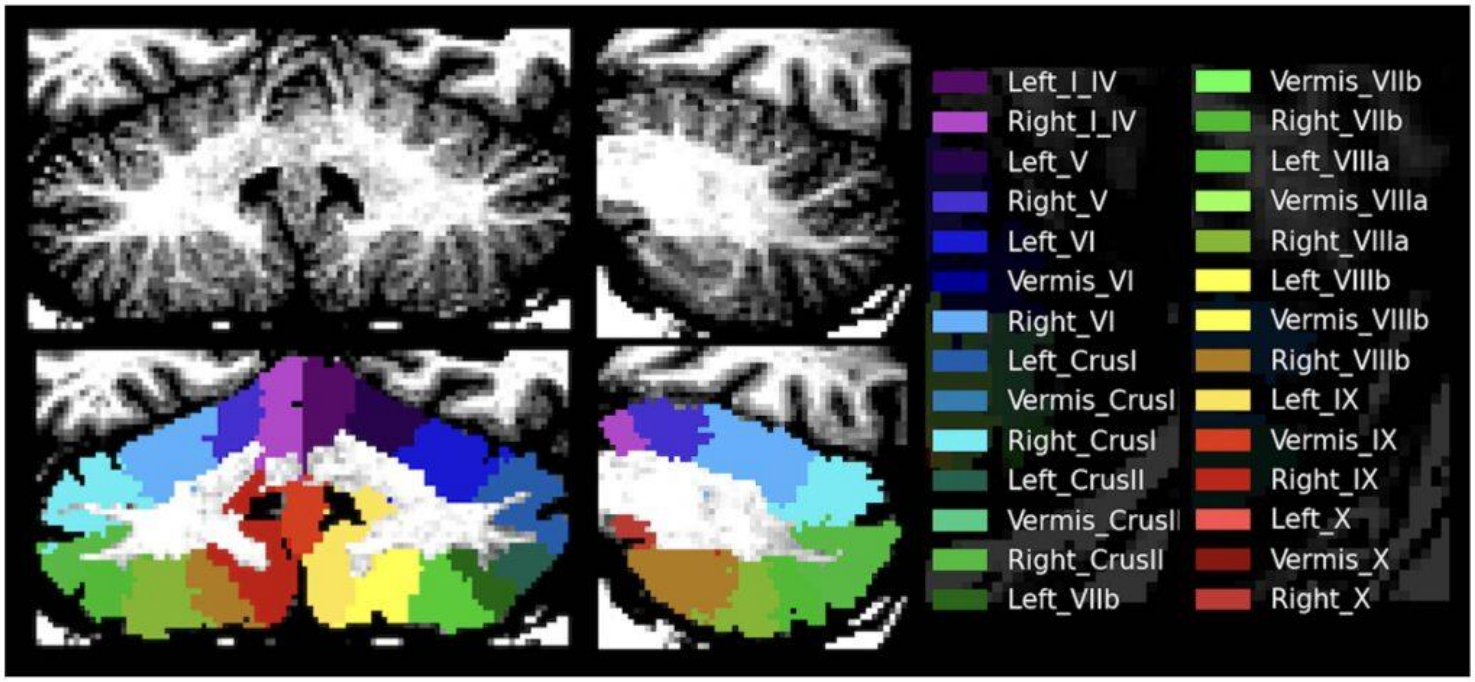

Figure 1 - *Segmentation of different cerebellar lobules.*

Results: Pearson correlation results are shown in Table 1. For both MCI and dementia groups, significant associations between MMSE and the global cerebellar grey matter volume were observed. The MCI group showed the strongest correlations, with the left Crus II region having one of the highest associations with MMSE scores, a region associated with social mentalizing. In the dementia group, the

right VIIb and left X subregions which are associated, respectively, with cognitive flexibility and attention, showed some of the strongest associations with MMSE. No significant associations were found for the SCD group.

***Table 1** - Pearson correlation between different cerebellar regions and MMSE for different diagnostic groups.*

	SCD-Mixed		MCI-AD		Dementia-AD	
	Pearson Correlation	*p(2-tailed)*	*Pearson Correlation*	*p (2-tailed)*	*Pearson Correlation*	*p (2-tailed)*
Whole cerebellum	-.188	.503	.484	.027*	.266	.057
Grey matter	-.222	.426	.481	.022*	.285	.041*
Left Crus II	-.316	.251	.442	.045*	.236	.092
Left VIIb	.054	.848	.275	.228	.198	.160
Right VIIB	-.257	.354	.296	.193	.299	.031*
Left VIIIa	-.147	.601	.184	.424	.083	.558
Right VIIIa	-.362	.184	.221	.335	.232	.098
Left VIIIb	-.191	.496	.252	.270	.034	.811
Right VIIIb	-.303	.273	.143	.537	.036	.799
Left X	-.295	.286	-.093	.687	.387	.005*
Right X	-.228	.414	.380	.090	.254	.069
Posterior cerebellum	-.357	.192	.514	.017*	.300	.031*
Left Cerebellum	-.373	.171	.559	.008*	.295	.034*
Right Cerebellum	-.365	.181	.515	.017*	.285	.040*

Conclusions: The results of this study highlight the importance of cerebellar atrophy in the cognitive function of AD patients. Interestingly, the strongest associations were found in the MCI group, which may suggest a compensatory role of the cerebellum in cognition that may become less effective in the later stages of AD. Further research is needed to improve our understanding of the role of the cerebellum in AD and other dementia types.

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SHIFT 02-637

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
4 - 5 April

POST-MORTEM VALIDATION OF IN VIVO 18KDA TRANSLOCATOR PROTEIN (TSPO) PET AS A MICROGLIAL BIOMARKER

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Aims: Neuroinflammation is a feature of many neurodegenerative diseases, and can be quantified *in vivo* by PET imaging with radioligands for the translocator protein (TSPO, e.g. [^{11}C]-PK11195). TSPO radioligand binding correlates with clinical severity and predicts clinical progression. However, the cellular substrate of altered TSPO binding is controversial and requires neuropathological validation.
Methods: We used progressive supranuclear palsy (PSP) as a demonstrator condition, to test the hypothesis that [^{11}C]-PK11195 PET reflects microglial changes. We included people with PSP-Richardson's syndrome who had undergone [^{11}C]-PK11195 PET in life. In *post-mortem* brain tissue from the same participants we characterised cell-type specific TSPO expression with double-immunofluorescence labelling and quantified microgliosis in eight cortical and eleven subcortical regions with CD68 immunohistochemistry.
Results: Double-immunofluorescence labelling for TSPO and cell markers showed TSPO expression in microglia, astrocytes, and endothelial cells. Microglial TSPO expression was higher in donors with PSP compared to controls, while this was not the case for astrocytic TSPO expression. There was a significant positive correlation between regional [^{11}C]-PK11195 binding potential *ante-mortem* and the density of *post-mortem* CD68+ phagocytic microglia, as well as microglial TSPO expression.
Conclusions: We conclude that [^{11}C]-PK11195 binding *in vivo* is driven by microglia and can be interpreted as a biomarker of microglia-mediated neuroinflammation in tauopathies[1]. [1]Medrvix https://doi.org/10.1101/2024.07.15.24309178

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SHIFT 02-641

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
4 - 5 April

TAU SEEDING COMPETENCY AND HUMAN AD TAU STRAIN IDENTIFICATION: INSIGHTS FROM BIOCHEMICAL AND BIOPHYSICAL ANALYSIS

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Aims: The specific biochemical characteristics of seed competent Tau strains, defined as a replicating and propagating pathological conformation, remains unknown. Here, our first objective is to develop chromatographic strategies for isolating Tau competent seeds from Alzheimer's Disease (AD) brains. Then, by a combination of biochemical and biophysical assays we aim at mapping the seeding competency characteristics and determine the shared features between AD cases.
Methods: For Tau seeds isolation, 9 AD brains were homogenized in aqueous buffer, and the resulting lysates were injected in a size exclusion column (SEC) to collect high molecular weight (HMW) Tau, which was then injected in an anion exchange column (AIEX). Following each step, the seeding activity was evaluated via a cell-based assay. Biochemical and biophysical features such as size and morphology were assessed via super resolution microscopy, atomic force microscopy and SEC; the oligomeric content and phosphorylation status were determined by single molecule arrays.
Results: We have isolated both non-bioactive and bioactive HMW Tau from every AD case tested (n=9). Moreover, the elution pattern off the AEIX column is identical between cases, suggesting shared conformations of bioactive species. Interestingly, both HMW Tau species are populated with aggregates of similar spherical morphology, ranging from 1 to 100nm. Then, we have shown that the bioactive species are more phosphorylated than the non-bioactive counterpart. Finally, we determined that the bioactive species are exceedingly rare (<0.1% of all tau) and, correspondingly, exceedingly potent.
Conclusions: This work brings new evidence that aggregate status, while necessary, is not a sufficient feature to mediate Tau seeding competency and that bioactive seeds share common characteristics suggesting the presence of an AD Tau strain that could be used as a therapeutic target.

SHIFT 02-642

On-Demand Oral Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
4 - 5 April

ALLEVIATION TAUOPATHY BY PP2A-DEPHOSPHORYLATION AND NEUROPROTECTIVE ANTI-INFLAMMATION VIA PIEZO1 IN ALZHEIMER'S DISEASE MODEL

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Aims: Piezo1 is a mechanical senstive ion channel which has been recently recognized to mitigate Alzheimer's Diseases (AD) pathological signatures such as Aβ clearance and microglial neuroinflammation. However, the impact of Piezo1 channel in tauopathy remains elusive, partly due to the complex neuroglia interactions mediating tau pathogenesis. This study aims to investigate how Piezo1 modulate neuroimmune axis in tau phosphorylation and indentify factors regarding to these transformations.
Methods: Neuron-glia interactions in AD environments were closely mimicked by ultilizing a 3D human AD minibrain, including Aβ accumulation, neuroinflammation, oxidative stress, tauopathy, and neuronal loss. Piezo1 channel was regulated via an agonist, Yoda1 for the convenience of mechanism study.
Results: We observed that Piezo1 activation transformed neurotoxic M1 microglia to the phagocyted state, which subsequently reduced miroglial CXCL1 production, an inflammatory cytokine responsible for tau hyperphosphorylation (Fig. A,B). Piezo1 also mitigated tau phosphorylation by inhibiting STAT3-mediated A1 astrocytic neuroinflammation and reducing the production of IL-8 and CCL2 (Fig. C). We examined tau-related kinases and phosphatases and found an increase in PP2A and a decrease in CDK5 in neurons, indicating the roles of Piezo1 activation in promoting tau dephosphorylation and limiting tau phosphorylation via protein kinases, respectively (Fig. D, E).
Conclusions: Taken together, our discovery highlights the beneficial roles of Piezo1 in alleviating tauopathy by regulating central immunity and promoting tau dephosphorylation. We envision that targeting Piezo1 is a promising therapeutic strategy for mitigating tauopathy-mediated neurodegeneration.

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SHIFT 02-650

On-Demand Oral Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4 - 5 April

IN SITU PROTEOMICS PROFILING OF PTDP43 PATHOLOGY-ASSOCIATED PROTEOMES IN HUMAN BRAIN TISSUE WITH LATE DISEASE

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Aims: The cytoplasmic mislocalization of the RNA-binding protein TDP-43 is a hallmark of limbic-predominant age-related TDP-43 encephalopathy (LATE), often occurring with AD. While pTDP-43 aggregates are believed to play a pivotal role in neurodegeneration, their aggregation composition and the mechanism of their formation, toxicity, and spread across the brain regions remain poorly understood.
Methods: We have employed the Microscoop (Syncell), a novel opto-proteomic spatial biology platform, in combination with mass spectrometry-based proteomics to interrogate the composition of pTDP-43 aggregates in situ. This platform enables precise labeling, identification, and quantification of pTDP-43-associated proteins in formalin-fixed paraffin-embedded (FFPE) postmortem human brain tissue with high spatial resolution. The Microscoop platform integrates advanced AI algorithms for ROI selection with high-precision and scalable protein photolabeling, followed by streptavidin pulldown of biotinylated proteins and subsequent LC-MS/MS analysis.
Results: Our analysis identified both known and novel interactors of pTDP-43 aggregates in human FFPE tissue with LATE. GO analysis showed significant enrichment in terms such as "Regulation of synaptic plasticity," "Regulation of amyloid fibril formation," and "Endosome organization." A protein-protein interaction network was generated using the STRING database to visualize the connectivity of these interactors. Further, KEGG analysis also identified the "Synaptic vesicle cycle" pathway among proteins with differential abundance between the photolabeling group and controls. Validation through co-immunofluorescence in human postmortem brain confirmed the associations of these proteins with pTDP-43 lesions, providing a novel insight into the molecular mechanisms driving TDP-43 pathology.
Conclusions: This work establishes the use of the Microscoop platform for FFPE tissue and provides comprehensive profiling of TDP-43 pathology in human LATE brain tissue, leading to a better understanding of mechanisms driving TDP-43 proteinopathy and informing potential therapeutic development.

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SHIFT 02-651

On-Demand Oral Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4 - 5 April

PRENATAL NEURODEVELOPMENT AS BRAIN RESERVE IN GENETIC FRONTOTEMPORAL DEMENTIA

Alexander Santillo[1], Luke Harper[1], Niklas Mattsson-Carlgren[1], David Cash[2], Olof Lindberg[3], Oskar Hansson[1], Harro Seelar[4], Raquel Sanchez-Valle[5], Robert Laforce[6], Caroline Graff[3], Daniela Galimberti[7], Rik Vandenberghe[8], Alexandre De Mendonça[9], Pietro Tiraboschi[10], Johannes Levin[11], Sandro Sorbi[12], Marcus Otto[13], Florence Pasquier[14], Simon Ducharme[15], Isabelle Le Ber[16], Elisabeth Finger[17], Carmela Tartaglia[18], James Rowe[19], Matthis Synofzik[20], Barbara Borroni[21], Jonathan Rohrer[2]
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Aims: Age at onset (AAO) in familial Frontotemporal Dementia (FTD) is highly variable. The presence of a prenatally derived anatomical variant, the right paracingulate sulcus (PCS) is associated with later AAO and faster disease progression after onset in sporadic behavioural variant FTD (bvFTD). Here we quantify PCS frequency and examine associations between PCS presence and disease onset and progression in familial bvFTD.
Methods: C9orf72, GRN, and MAPT mutation carriers and healthy controls underwent structural MRI and yearly clinical assessment as part of the Genetic FTD Initiative (GENFI). MRI data were evaluated for hemispheric PCS presence. General linear models were performed with covariates mean family AAO and sex to investigate AAO and linear-mixed effects models were used to investigate disease progression according to the CDR® plus NACC FTLD in mutation carriers.
Results: 113 C9orf72, 100 GRN, and 88 MAPT mutation carriers and 273 controls were included. Similar PCS frequencies were observed between carriers and controls. Further analyses were conducted in 114 C9orf72, 47 GRN, and 35 MAPT symptomatic carriers. Right PCS presence was not significantly associated with AAO in the entire cohort (b = -0.22 p = 0.85) or in individual genetic groups; C9orf72 (b = -0.85, p =0.57), GRN (b= 3.4, p =0.27) or MAPT (b = -0.78, p =0.72). Disease progression with respect to PCS presence was similar in the entire cohort and individual genetic groups.
Conclusions: With reservation due to underpowering, right PCS presence may be associated with a later AAO in GRN but not C9orf72 or MAPT mutation carriers. Data from the ALLFTD study will be

added.

SHIFT 02-652

On-Demand Oral Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4 - 5 April

TDP-43 CITRULLINATION: SCRATCHING THE SURFACE ON A NOVEL MODIFICATION INVOLVED IN AD AND RELATED DEMENTIA_

Maj-Linda Selenica, Christopher Saunders, Patricia Rocha-Rangel, Peter Nelson, Daniel Lee, Maj-Linda Selenica
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Aims: TDP-43 (transactive response DNA binding protein of 43 kDa) proteinopathies are a continuum of neurodegenerative disorders, and recent consensus multi-center neuropathological studies have unraveled the profound impact of TDP-43 pathology in cognitive decline and neurodegenerative changes associated with Limbic-predominant age-related TDP-43 encephalopathy (LATE) and Alzheimer's disease (AD). We have recently reported on a novel post-translational modification (PTM) of TDP-43, citrullination, that requires the irreversible conversion of arginine (R) to citrulline (citR) moiety. This modification depends on the activity of peptidyl arginine deiminases (PADs), where PAD2 and PAD4 are expressed in the brain. This study aimed to uncover the role of citrullination on TDP-43 structural modifications and its functional impact related to AD+ LATE pathogenesis.
Methods: We uttilzied biochemical and structural methods to uncover the impact of citrullination on protein function in health and disease.
Results: Immunohistochemical and biochemical analysis demonstrated increased regional PAD4 and PAD2 expression in disease tissue, while we identified 11 citR epitopes on recombinant TDP-43 and IP/LC-MS analyis identify citR293 in cortex of TDP43 mouse models. Our citR-specific antibodies provided the first evidence for induced epitope-specific citR TDP43 levels in brain regions from AD and LATE-NC cases. Staging analysis revealed the epitope-specific TDP-43 citrullination profile, and identified citR epitopes associated with early stages of pathology. Aggregation and structural studies demonstrated the impact of citR on TDP-43 structu and how it contributed to novel citR TDP-43 conformers. Intriguingly, citR TDP-43 conformers were represent in the neuropathological profiles associated with AD/LATE-NC stages. Biochemical analysis and electron microscopy protein imaging revealed citR-dependent TDP-43 phase separation and impairment of protein-RNA interactions.
Conclusions: Our studies suggest that activation of the PADs and citrullination affect TDP-43 protein properties and function, contributing to the neuropathology of TDP-43.

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SHIFT 02-656

On-Demand Oral Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / GENETICS, EPIDEMIOLOGY
4 - 5 April

MUNICIPALITY-SPECIFIC INCIDENCE OF AMYOTROPHIC LATERAL SCLEROSIS AND PARKINSON'S DISEASE 2010-2018

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Aims: To investigate whether the reported high worldwide prevalence correlations between Parkinson's Disease (PD) and Motor Neuron Diseases,[1] suggested to indicate common causative factors, are similarly reflected in more granular data on incidence.
Methods: Municipality-level 2010-2018 incidence data of PD and amyotrophic lateral sclerosis (ALS) were investigated in North Karelia in easternmost Finland. The number of annual new PD cases were obtained from the National Social Security Institute (KELA) and ALS data from a previously published cohort.[2] Incidence was calculated as new cases per 100,000 person-years at risk during the study period in population at least 18 years of age (1,218,970 total; 18,564 – 555,911 / municipality), available from governmental open sources.
Results: Municipality-specific ALS incidence varied between 0 and 21.5 in men and 0-11.2 in women whereas PD incidence varied between 60.2 and 210.6 in men and 40.6-104 in women (figure 1). The incidences of both disorders were high in both sexes in the northernmost municipality, Nurmes. Otherwise, ALS occurred more commonly in the western and central municipalities in both sexes (with outliers: 9.5 for women in the easternmost Ilomantsi and the 21.5 hotspot for men in southestern Tohmajärvi) while PD occurred most frequently in the southwestern and northeastern municipalities.
Conclusions: These municipality-specific incidence data suggest only limited common incidence patterns for ALS and PD. REFERENCES: James and Georgopoulos. *Neurosci Insights*. 2022: DOI: 10.1177/26331055221117598 Hanhisuanto, Solje, Jokela and Sipilä. *Neuroepidemiology*. 2023. DOI: 10.1159/000531238

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SHIFT 02-663

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4 - 5 April

DEVELOPMENT OF AAV-ENCODED RNAI AND PEPTIDE APTAMER TO INTERFERE WITH PIZEZO1 MECHANOSENSOR FUNCTIONS

Seung Min Shin[1], Fan Fan[2], Hongwei Yu[1]
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Aims: Piezo1 is expressed in CNS capillaries, impacting blood flow control. Piezo1 is also expressed in CNS neurons and glial cells, guiding functional phenotypes of neurons and glial cells and participating in the pathogenesis of various neurological diseases. However, molecular mechanisms of Piezo1 in CNS physiology and pathophysiology remain largely unclear, primarily due to a lack of in vivo manipulation tools. This study aims to develop AAV-encoded RNAi and inhibitory peptide aptamer (iPA) tools to interfere with Pizezo1 mechanosensor functions.
Methods: Molecular cloning, immunoblot, and calcium imaging
Results: We designed an AAV plasmid in which the U6 promoter drives Pizezo1shRNA. Two Pizezo1shRNAs against rat Piezo1 were designed, and Piezo1 silencing effects were determined in NG108-15 cells in vitro tests by transfection. Results show that Pizezo1-shRNA1 induces >85% reduction of Piezo1 protein level after transfection into NG108 cells, compared with sham- and scramble-transfected cells. Fura-2 ratiometric microfluorimetry calcium imaging shows that responses of intracellular calcium ($Ca_i^{2+)}$ increase to Yoda1 stimulation are significantly reduced in Piezo1-shRNA1 transfected cells. By targeting intrinsically disordered regions of human PIEZO1 protein, we defined an intrinsically disordered peptide from the intracellular loop linking transmembrane domain 34 and outer helix near the PIEZO1 pore, anchor domain, and Yoda-binding region. This 25 amino-acid (aa) peptide, named PZ1iPA, is enriched with positively charged amino acids and conserved between humans and rodents. AAV-encoded PZ1iPA (GFP fusion) expression into HeLa cells and NG108 cells dramatically inhibits Yoda1-evoked Ca_i^{2+} increases. It is expected that AAV-mediated PZ1iPA expression will provide a sustained block of Piezo1 without abrogating protein per se, providing specific functional interference.
Conclusions: Collectively, we successfully developed AAV-encoded RNAi and peptide aptamer tools to interfere with Pizezo1 mechanosensor functions for investigating Piezo1 block-associated cerebrovascular and neurodegenerative phenotypes.

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SHIFT 02-664

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4 - 5 April

CEREBRAL SMALL VESSEL DISEASE ALTERS INFLAMMATION IN THE RETINA AND LEADS TO VISUAL DEFICITS

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Aims: Diagnosis of Alzheimer's disease (AD) via MRI is costly and can be limited by regional availability. With recent advancements diagnosis of AD and the effect of AD pathology on the retina is becoming well characterized. However, the prevalence of vascular contributions to cognitive impairment and dementia (VCID) and its effects on the retina are less well known. With the retina being a highly vascularized tissue and the considerable overlap of AD with VCID, it is imperative to understand the effect of VCID on vision.
Methods: We induced hyperhomocysteinemia (HHcy) in 6mo old wild-type mice. HHcy is a risk factor for VCID and has been well characterized in our lab. After 14 weeks on diet, mice underwent the Visual-Stimuli 4-arm Maze (ViS4M) to identify visual and cognitive abnormalities. Eyes were either fixed in 4% PFA for 24hrs or flash frozen for RNA extraction. The fixed retina was flat mounted and stained for vessels, GFAP, and IBA-1 and the flash frozen retina was used for RNA isolation and NanoString analysis.
Results: On the ViS4M, the mice on the HHcy diet showed impaired alternation and sensitivity to blue and white stimuli, suggesting visual and cognitive changes. Gene expression changes showed more significant downregulation of neuroinflammatory genes due to HHcy. Analysis of glial cells and the vasculature in the retina indicated reduced vascular coverage by microglia and fewer vessels due to HHcy.
Conclusions: The high prevalence of VCID with AD along with the impact of AD pathology on the eye makes it critical to understand the effect of VCID on the retina. In our model of HHcy induced VCID, we determined that HHcy does impair both cognition and vision and affects vessels within the retina.

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SHIFT 02-666

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / GENETICS, EPIDEMIOLOGY
4 - 5 April

GENETIC COVARIANCE ANALYSIS OF ALZHEIMER'S DISEASE AND STROKE IMPLICATES PHLPP1 AS A SHARED LOCUS IN INDIVIDUALS OF AFRICAN ANCESTRY

Nicholas Ray[1], Brian Kunkle[2], Farid Rajabli[2], William Bush[3], Rufus Akinyemi[4], Jonathan Haines[5], Giuseppe Tosto[6], Scott Williams[3], Allison Caban-Holt[7], Goldie Byrd[7], Jeffery Vance[8], Margaret Pericak-Vance[8], Christiane Reitz[9]
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Aims: Neuropathological and neuroimaging studies indicate that cerebrovascular disease (CVD) is a major risk factor for Alzheimer's disease (AD) with a significant subset of AD cases also presenting vascular disease. The molecular mechanisms underlying the correlation between CVD and AD remain unclear. To elucidate the mechanistic relationship between the two phenotypes, the current study examined the genetic correlation between stroke and AD in individuals of African ancestry.
Methods: Capitalizing on the results from recent genome-wide association studies (GWAS) on AD (2,844 cases; 6,521 controls; Ray et al., 2024) and stroke (3,961 cases; 20,030 controls; Mishra et al., 2022) in individuals of African ancestry, genetic correlation analysis was conducted using LAVA, which partitions the genomes based on LD structure and estimates local genetic covariance within each resulting partition to detect regions of shared genetic association between traits of interest.
Results: Genetic covariance analysis identified a locus shared between AD and stroke on chromosome 18q21.33 that includes the *PHLPP1* gene ($\rho = .77$, $P = 2.41\times10^{-6}$). Examination of the LD structure and genetic association patterns identified an identical disease-associated haplotype exerting an effect in the same direction in both traits. *PHLPP1* is strongly expressed in the brain, is differentially expressed in AD cases vs controls, and has a moderately high AD risk score of 3.27 according to Agora (agora.adknowledgeportal.org).
Conclusions: Pleckstrin Homology domain Leucine-rich repeat Protein Phosphatases (PHLPP) are regulators of multiple cellular processes involved in neurodegenerative diseases including memory formation, neuronal survival, and neuronal glucose metabolism. Identification of shared etiological mechanisms between AD and CVD in diverse populations will aid in elucidating the underlying etiologic mechanisms and inform the development of more effective and personalized treatment and prevention strategies for both disorders.

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SHIFT 02-669

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

PEAK WIDTH OF SKELETONIZED MEAN DIFFUSIVITY ON MRI DIFFERENTIATES CEREBRAL AMYLOID ANGIOPATHY FROM NON-AMYLOID CEREBRAL SMALL VESSEL DISEASE IN NON-DEMENTED OLDER ADULTS

Lene Pålhaugen[1,2], Julia Gundersen[1,2], Sandra Tecelão[1], Jonas Jarholm[1,2], Bjørn-Eivind Kirsebom[1,2,3,4], Atle Bjørnerud[5,6], Per Selnes[1,2], Tormod Fladby[1,2]
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Aims: Cerebral amyloid angiopathy (CAA) is frequently seen in Alzheimer's disease (AD) patients and increases the risk for amyloid related imaging abnormalities. Peak width of skeletonized mean diffusivity (PSMD) measures disrupted white matter microstructure based on MRI diffusion tensor imaging, and occipital PSMD was previously reported to be increased in CAA patients compared to controls and cases with non-amyloid small vessel disease (SVD). Here, we compare global and regional PSMD in healthy controls (HC) and preclinical cases with probable CAA, SVD and predementia AD.
Methods: We used the Boston 2.0 criteria on cases from the Dementia Disease Initiation cohort to define a subgroup with probable CAA (n=17). SVD cases (n=108) had increased WMH load and normal levels of CSF Aβ42/40 ratio, p-tau181 and total tau. AD cases (n=75) had reduced Aβ42/40 ratio and increased p-tau181 or total tau. HC individuals (n=68) had normal cognition, low WMH load and normal levels of Aβ42/40 ratio, p-tau181 and total tau. We performed cross-sectional comparisons of global PSMD and PSMD by lobe between the groups, using linear regression models and age/sex as covariates.
Results: CAA cases had increased global (b=-0.498, p=0.025), frontal (b=-0.513, p=0.022) and temporal lobe (b=-0.590, p=0.007) PSMD compared to SVD. Compared to AD, temporal lobe PSMD was also increased at a trend level (b=-0.436, p=0.051). Global and all lobar PSMDs were increased in CAA compared to HC.
Conclusions: We found increased global, frontal and temporal lobe PSMD in cases with probable CAA compared to SVD, with the largest effect in the temporal lobe. Temporal lobe PSMD was also increased in probable CAA cases compared to AD cases at a trend level. As such, temporal lobe PSMD is a promising early-stage marker of CAA.

SHIFT 02-670

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

ASSOCIATIONS OF MARKERS OF ENDOTHELIAL FUNCTION WITH BLOOD-BASED BIOMARKERS OF ALZHEIMER'S DISEASE IN INDIVIDUALS OF ADMIXED ANCESTRY

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Aims: Cardiovascular health is a major risk factor for cognitive decline and dementia, including Alzheimer's disease (AD). Despite a higher risk of cardiovascular disease and dementia, individuals of Hispanic and African ancestry are vastly under-represented in AD research, and therefore the relationship between cardiovascular health and AD in diverse populations is largely unknown. To address this, we examined the associations between biomarkers of cardiovascular function, AD, and genetic ancestry.
Methods: AD biomarkers include Aβ42/40 and p-tau/Aβ42 ratios. CVD biomarkers include VEGF, PlGF, bFGF, VCAM-1, and ICAM-1. Biomarkers were collected from 256 admixed individuals sampled from Puerto Rico and Peru as well as African Americans from the continental US. Including age and sex as covariates, mixed effects regressions were modeled separately predicting both AD biomarker ratios by all 5 VCID biomarkers, degree of African ancestry, and *APOE*.
Results: Aβ42/40 ratio was associated with VEGF ($\beta = -1.97\times10^{-5}$, $P = .002$), bFGF ($\beta = -2.10\times10^{-4}$, $P = .02$), VCAM-1 ($\beta = 1.53\times10^{-5}$, $P = 9.02\times10^{-4}$), ICAM-1 ($\beta = -3.72\times10^{-5}$, $P = .01$) and degree of African ancestry ($\beta = 0.01$, $P = .04$). Similarly, p-tau/Aβ42 ratio was associated with VEGF ($\beta = 0.01$, $P = .001$), bFGF ($\beta = 0.18$, $P = 5.21 \times 10^{-5}$), VCAM ($\beta = -0.005$, $P = .02$), and ICAM ($\beta = 0.02$, $P = .02$). No significant associations were observed for PlGF.
Conclusions: Cardiovascular markers VEGF, bFGF, ICAM-1, and VCAM-1 are associated with both the p-tau/Aβ42 and Aβ42/40 ratios, the latter of which is also modulated by degree of African ancestry. These markers are valuable measures of cognitive health in admixed individuals and could inform the design of clinical trials for biomarker development across diverse populations.

SHIFT 02-671

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4 - 5 April

VASCULAR CLUSTERIN AGGREGATION IN THE HUMAN BRAIN CORRELATES WITH STAGES OF ALZHEIMER-RELATED NEUROFIBRILLARY CHANGES AND AMYLOID PHASES

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Aims: Vascular dementia often occurs alongside neurodegenerative diseases like Alzheimer's disease (AD). The two diseases do not only share risk factors such as aging, ApoE genotype, diabetes, and hypertension, but also show overlap in cerebrospinal fluid and blood biomarkers. Clusterin (CLU) is such a biomarker that forms aggregates in both the brain parenchyma and in the cerebral vasculature along with beta-amyloid, but current data on vascular CLU aggregates is limited. The goal of the present study was therefore to investigate the regional distribution of vascular CLU in the human brain in relationship to different stages of AD-related neurofibrillary changes and amyloid phases.
Methods: We investigated the distribution of CLU-positive vessels in the human brain using immunohistochemistry. Numbers of CLU-positive vessels in the frontal, parietal and occipital lobes were correlated with transentorhinal, limbic and neocortical Braak stages of AD-related neurofibrillary changes, amyloid phases and ApoE genotype.
Results: Numbers of total CLU-positive vessels showed a significant, but weak correlation with Braak's neurofibrillary stage ($r=0.3$, $p=0.01$, $n=76$), and a stronger significant correlation with Thal's beta-amyloid phase ($r=0.452$, $p<0.001$, $n=71$). No effect of the ApoE4 genotype was found compared to the ApoE3 genotype.
Conclusions: Our data indicate that vascular CLU aggregation is a common finding in AD brains. The stronger correlation of vascular CLU aggregation with the amyloid phase than with the neurofibrillary pathology supports the presence of some common mechanisms that facilitate aggregation of CLU and beta-amyloid in AD.

SHIFT 02-673

On-Demand Oral Poster on Board - Shift 02
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4 - 5 April

A DRUG SCREENING PLATFORM TO TARGET THE AGGREGATION OF THE HUMAN AORTIC MEDIAL AMYLOID PEPTIDE MEDIN

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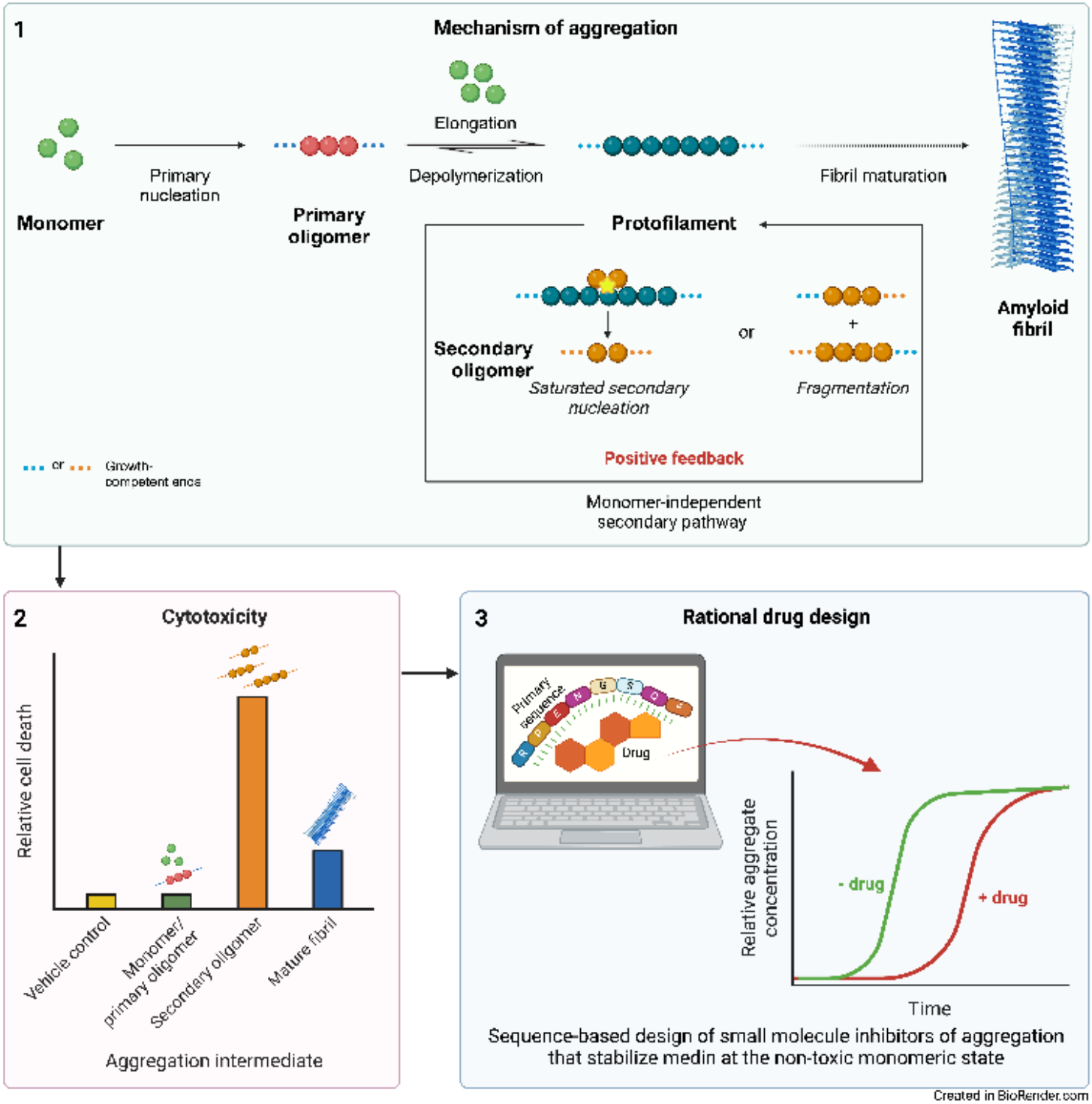
Aims: Medin, a proteolytic fragment of lactadherin, forms highly common localized amyloids in the upper body vascular media of aged individuals. Medin co-aggregates with Aβ in cerebral amyloid angiopathy (CAA). Cerebrovascular medin deposits correlate with cognitive decline, suggesting their potential role in blood-brain barrier (BBB) disruption in CAA. We developed a therapeutic screening platform to discover aggregation inhibitors that can stabilize medin at a non-toxic state.
Methods: Aggregation kinetics data of recombinant human medin, monitored under physiological conditions *in vitro* using thioflavin T, were fitted to a kinetic model to determine the dominant mechanism and kinetic parameters of aggregation. Cytotoxicity of monomers, oligomers and fibrils was compared using murine b.End3 brain endothelial cells to model BBB. Then, a deep learning sequence-based drug design strategy helped identify small molecule inhibitors of aggregation.
Results: Medin aggregates proliferate almost equally by primary nucleation and secondary pathways, and grow rapidly by a fast elongation rate even at submicromolar concentrations. Amongst monomers, oligomers and fibrils of medin, oligomers are the most cytotoxic, and intrinsically disordered monomers are the least. Therefore, a panel of 30 small molecule inhibitors stabilising medin monomers was developed by a sequence-based drug design strategy. Initial kinetic screening identified a compound that increases the half-time of medin aggregation by ~1.5-fold. Further screenings, kinetic characterizations and cell viability analyses are under way. **Figure 1. Compound screening platform integrating kinetic and cell viability analyses to discover medin aggregation inhibitor.**



Conclusions: We established a screening platform for discovering small molecules stabilizing medin in its monomeric native state by combining structural, kinetic and cell viability analyses. The pipeline is general, as it can also be applied to test the effects of co-aggregating proteins, such as Aβ, on modulating medin aggregation.

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On-Demand Oral Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4 - 5 April

PHOSPHORYLATION AT SERINE-262 AND SERINE-356 DETECTS EARLY-STAGE PRE-FIBRILLAR SOLUBLE TAU ASSEMBLIES IN ALZHEIMER'S DISEASE

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Aims: The degree of tau neurofibrillary tangle (NFT) pathology in Alzheimer's disease (AD), assessed according to the Braak staging at autopsy and by tau positron emission tomography (PET), is a stronger indicator of cognitive outcomes. Despite their several advantages, these two major diagnostic methods for protein aggregates lack sensitivity for the pre-fibrillar species of tau that form earlier in the aggregation process. Recent evidence from clinical trials has shown that AD patients with little to no brain NFT pathology recorded stronger clinical therapeutic benefits than those with advanced pathology, suggesting that targeting pre-NFT species might be a viable therapeutic and biomarker strategy. However, biochemical understanding and biomarker methods for pre-fibrillar tau aggregates are lacking.
Methods: In this study, we applied an integrative biochemical approach to identify a minimal peptide (~amino acid 258-368) sequence that makes the core region of soluble tau assemblies (STAs) – physiological buffer-soluble, low-order tau aggregates in AD (including oligomers, protofibrils, and tangle-free filaments. Moreover, we uncovered the novel aggregation-relevant phosphorylation sites serine-262 and serine-356.
Results: Moreover, we uncovered the novel aggregation-relevant phosphorylation sites serine-262 and serine-356. In neuropathological assessments, antibodies against serine-262 and serine-356 almost exclusively stained granular (i.e., pre-fibrillar) tau aggregates in pre-NFTs whilst antibodies against phosphorylation at threonine-202/205 and threonine-231, outside the STA core, stained the entire spectrum of tau aggregates in pre-NFTs and mature NFTs. Furthermore, we developed a cerebrospinal fluid assay that differentiated STAs in AD from non-AD tauopathies, and correlated with NFT burden and

cognitive decline independently of amyloid-beta deposition
Conclusions: Together, our findings inform about the status of early-stage tau aggregation, reveal aggregation-relevant phosphorylation epitopes in tau, and offer a novel diagnostic biomarker and targeted therapeutic opportunities for AD.