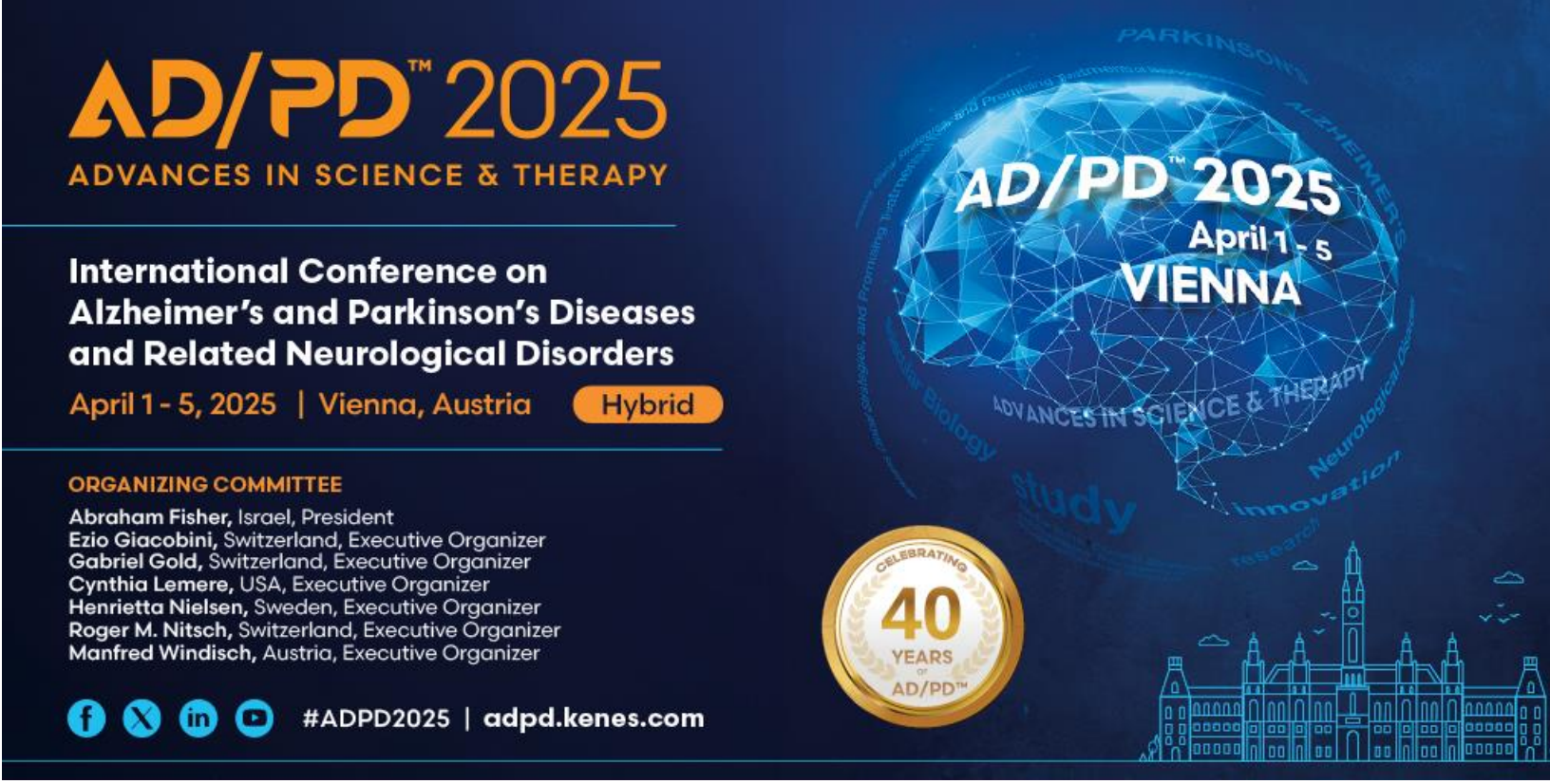

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Virtual E-Posters

Virtual EP – 001

Virtual E-Posters and Oral On-Demand
VIRTUAL E-POSTERS IN ONLINE GALLERY AND MOBILE APP ONLY

LOCALISATION OF AMYLOID PRECURSOR PROTEIN TO THE ENDOPLASMIC RETICULUM REDUCES BRAIN AMYLOID PLAQUE FORMATION

Karnika Gupta[1], Pierre Parutto[2], David Gershlick[3], David Klenerman[4], Giovanna Mallucci[2], Edward Avezov[2]
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Aims: Amyloid precursor protein (APP) processing by secretases is a central event in the pathogenesis of Alzheimer's disease (AD), with amyloid-β (Aβ) peptide accumulation leading to neurodegeneration. An incomplete understanding of APP processing in subcellular compartments has constrained the development of Aβ-lowering strategies. To date, approaches inhibiting APP secretases lack specificity and lead to prohibitive side effects. Antibody-based approaches aimed to eliminate Aβ plaques have proved efficacious, with limited disease-modifying effect. Thus, in the search for an earlier and more effective intervention in amyloidogenesis, we aim to direct intracellular Aβ precursor's fate as a viable strategy.
Methods: We mapped the kinetics of APP cleavage to Aβ with subcellular resolution, measuring secretase activity in the organelles visited by APP as it traverses through secretory pathway. In the Endoplasmic Reticulum (ER) and on plasma membrane, secretase activity was markedly lower than in the Golgi and endosomes. Based on these insights, we explored a therapeutic strategy focusing on redirecting APP to the ER to reduce amyloidogenic processing. Employing a combination of real-time organelle-specific secretase activity and AI-designed, organelle-targeted nanobody specific to the APP luminal domain, this approach was tested in cell lines and a transgenic mouse model of AD-related amyloidogenesis (5xFAD).
Results: Nanobody-induced prolonged ER residency of APP significantly decreased total levels of Aβ40 and Aβ42 peptides and their aggregates in cells. Targeted relocalisation of APP to the ER in 5xFAD mice led to a marked reduction in Aβ plaque formation and associated neuropathology without inducing ER stress or other toxic effects.
Conclusions: Thus, redirecting APP to the ER can mitigate Aβ pathology via the selective modulation of APP processing. These results underscore the therapeutic potential of manipulating protein localisation to influence disease at a molecular level.

Virtual EP - 002

Virtual E-Posters and Oral On-Demand
VIRTUAL E-POSTERS IN ONLINE GALLERY AND MOBILE APP ONLY

EFFECT OF GUT MICROBIOTA ON BRAIN BETA-AMYLOID BURDEN MEASURED BY 18F-FLORBETABEN PET IN MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

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Aims: This study investigated changes in the gut microbial composition of individuals with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and their relationship with positron emission tomography (PET) amyloid accumulation.
Methods: In total, 17 cognitively normal individuals without amyloid-beta (Aβ) accumulation ($Aβ^-$NC) and 24 with Aβ-positive mild cognitive impairment ($Aβ^+$MCI) who underwent ^{18}F-florbetaben PET and fecal bacterial 16S ribosomal RNA gene sequencing were enrolled. The taxonomic compositions of the $Aβ^-$NC and $Aβ^+$MCI groups were compared. The abundance of taxa was correlated with the standardized uptake value ratio (SUVR), using generalized linear models.
Results: There were significant differences in microbiome richness (ACE, $p = 0.034$ and Chao1, $p = 0.024$), alpha diversity (Shannon, $p = 0.039$), and beta diversity (Bray–Curtis, $p = 0.018$ and Generalized UniFrac, $p = 0.034$) between the $Aβ^-$NC and $Aβ^+$MCI groups. The global SUVR was positively correlated with the genus Intestinibacter ($q = 0.006$) and negatively correlated with the genera Roseburia ($q = 0.008$) and Agathobaculum ($q = 0.029$).
Conclusions: In this study, we identified significant changes in the gut microbiota composition that occur in individuals with MCI due to AD. In particular, the correlation analysis results between PET amyloid burden and gut microbial abundance showed that amyloid deposition is associated with a reduction in specific taxa involved in butyrate production.

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Virtual EP - 003

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THE MEMORY-IMPAIRING ABETA OLIGOMER ABETA*56 ISOLATED FROM ALZHEIMER'S DISEASE-MODELING MICE EXHIBITS HOLLOW SPHEROID STRUCTURES

Peng Liu[1], David Boyer[2], Ian Lapcinski[1], Han Seung Lee[1], David Eisenberg[2], Karen Ashe[1]
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Aims: Abeta*56 is a water-soluble, memory-impairing beta-amyloid (Abeta) oligomer that is stable in sodium dodecyl sulfate (SDS). Studies from independent research groups revealed a connection between Abeta*56 and cognitive dysfunction and aging in mice, dogs, and humans. Abeta*56 is recognized by anti-oligomer A11 antibodies but not by anti-protofibril mAb158 or anti-fibril OC antibodies. This suggests that Abeta*56 represents a type of Alzheimer's disease (AD)-relevant oligomers that possess structural motifs distinct from those associated with fibrils and fibril-like assemblies targeted by FDA-approved Abeta immunotherapies. However, the structural characteristics of Abeta*56 remain unknown.
Methods: We isolated Abeta*56 using our newly developed four-step sequential purification procedure. To avoid fibrillar Abeta assemblies, we used brains of Tg2576 AD-modeling mice at ages prior to neuritic plaque formation. We first enriched Abeta*56-containing aqueous brain homogenates using non-denaturing size exclusion chromatography, then isolated Abeta*56 and other Abeta entities using an immunoaffinity matrix, and finally separated Abeta*56 using semi-denaturing SDS-polyacrylamide gel electrophoresis followed by electro-elution. We identified Abeta*56 particles using negative-stain transmission electron microscopy (TEM). We performed two-dimensional (2D) and three-dimensional (3D) classification of the particles using CryoSPARC.
Results: TEM micrographs showed that Abeta*56 exhibited circular and oval structures with denser rims than centers but no fibrils or fibril-like structures. Multiple rounds of 2D classification on 1,109 negative-stain particles revealed approximately fourteen 2D classes of ovoid-shaped particles. *Ab initio* model and 3D classification revealed four groups of 3D particles resembling hollow spheroids with approximate diameters of 8, 10, 14, and 18 nm.
Conclusions: Our findings indicate that Abeta*56 adopts novel structures distinct from previously reported Abeta assemblies. The averaging of particles into distinctly-sized classes indicates there exist discrete populations of oligomers that can allow high-resolution cryoEM structure determination.

Virtual EP - 004

Virtual E-Posters and Oral On-Demand
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DISEASE STAGE AND BRAIN REGIONS SPECIFIC CHARACTERIZATION OF AMYLOIDOSIS-ASSOCIATED PROTEINS IN POSTMORTEM HUMAN BRAINS

Wangchen Tsering, Jennifer Phillips, Stefan Prokop
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Aims: Alzheimer's disease (AD) is characterized by neuronal loss, Aβ deposits in the form of plaques, and intracellular aggregates of tau protein in the form of neurofibrillary tangles (NFT). The amyloid cascade hypothesis, one of the leading hypotheses of AD pathogenesis, suggests that Aβ aggregates are directly neurotoxic, triggering downstream neurodegeneration. However, direct evidence supporting the neurotoxicity of Aβ aggregates in vivo is lacking. If Aβ is directly neurotoxic, why does Aβ in diffuse plaques not elicit harmful responses while neuritic plaques are associated with neurodegenerative changes? Recent proteomic and transcriptomic studies suggest that there are many biologically active proteins that co-accumulate with amyloid plaques, which are termed amyloidosis-associated proteins (AAP). Most of AAP are signaling molecules, and some, such as APOE and Clusterin, are previously shown to be involved in AD pathophysiology. We evaluated the spatiotemporal distribution of diffuse plaques and neuritic plaques, and spatiotemporal accumulation of several AAP in postmortem human AD brains of different AD neuropathological changes.
Methods: We used immunohistochemistry (IHC) and IF on post-mortem brain tissue specimens to assess the disease stage and brain region specific distribution of NP and amyloidosis-associated proteins in cases with low, intermediate and high AD neuropathological changes from different brain regions. In addition, we also use spatial biology to analyze protein level differences in different Aß plaque sub-types.
Results: We identified brain region and disease stage specific differences in the distribution and ratio of NP and other Aß-deposits and correlated these findings with local microglia activation and co-depositing, amyloidosis-associated proteins.
Conclusions: Characterization of neuritic plaque and co-depositing, amyloidosis-associated proteins in different brain regions and AD stages will guide effective therapeutic treatment for AD.

Virtual EP - 005

Virtual E-Posters and Oral On-Demand
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APP/PS1 MOUSE DERIVED PLATELET HOMOGENATES CONVEY STRUCTURAL AND FUNCTIONAL HIPPOCAMPAL DYSFUNCTIONS IN HEALTHY YOUNG MICE

Heike Mrowetz[1], Kathrin Kniewallner[1], Adam Schroer[2], Gregor Bieri[2], Saul Villeda[2], Ludwig Aigner[1,3]
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Aims: Alzheimer's disease (AD) is a neurodegenerative disease that is associated with progressive and irreversible memory loss and cognitive decline. There is increasing notion that platelets might contribute to the pathogenesis of AD. Indeed, platelets of AD patients show significant structural and molecular changes compared with those of healthy individuals. However, it is completely unknown if and to what extent platelets in AD are causal in some of the pathological aspects of AD. The aim of this study was to investigate whether platelets from aged APP/PS1 mice, a genetic model of AD pathology, can convey structural and functional deficits in young healthy mice.
Methods: Platelet homogenates derived from 22-month-old mice (WT and APP/PS1) were injected via the tail vein into 3-month-old WT animals over a four-week period. Behavioral tests were conducted to evaluate cognitive function. Brain tissue was used for immunohistochemistry.
Results: Transfusion of old AD platelet homogenate results in structural hippocampal changes in healthy young mice. The hippocampal expression of pCreb as well as NeuN is reduced, and a higher expression of Casp3 can be observed, indicating neuronal loss. At the same time an increase of DCX-positive neuronal progenitor cells outside the granular layer is observed. Additionally microglia numbers and soma sizes increase, representing an increased microgliosis. Administration of WT platelet homogenate did not lead to any structural changes compared to the saline-treated control. Furthermore results the administration of platelet homogenate in functional deficits, as is evidenced by an increase in the number of committed errors observed in the RAWM.
Conclusions: Platelet factors derived from aged APP/PS1 mice convey structural and functional hippocampal dysfunction in healthy young mice.

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Virtual EP - 006

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PHOSPHO-EPITOPES WITHIN THE CORE REGION OF SOLUBLE TAU ASSEMBLIES IN ALZHEIMER'S DISEASE AND NON-AD TAUOPATHIES: IMMUNOHISTOLOGICAL ANALYSES

Eric Abrahamson[1,2], Anuradha Sehrawat[3], Xuemei Zeng[3], Tara Lafferty[3], Lan Shao[1], Thomas Karikari[3], Milos Ikonomovic[1,2,3]
[1]University of Pittsburgh, Neurology, Pittsburgh, United States of America, [2]VA Pittsburgh Healthcare System, Pittsburgh, United States of America, [3]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America

Aims: To assess disease and cell specific distribution of pSer262 and pSer356 phospho-epitopes in the core regions of soluble tau assemblies (STA) in comparison to phospho-epitopes outside the STA core region.
Methods: Immunohistochemical and multifluorescence methods were used to assess the labeling patterns of antibodies directed to pSer262, pSer356, pSer202/pThr205, or pThr231 in relation to early tau pathology forms using sections of hippocampus from Alzheimer's disease (AD) and frontal cortex from cases with corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), or Pick disease.
Results: In AD hippocampus, pSer262 and pSer356 antibodies stained punctate/granular tau aggregates in pretangles while pSer202/pThr205 and pThr231 antibodies stained tau in pretangles as well as classic neurofibrillary tangles (NFT), neuritic components of plaques, and neuropil threads. Co-distribution of pSer262-pSer202/pThr205 and pSer356-pSer202/pThr205 was observed within pretangles but not in classic NFT. In sections of middle frontal gyrus from PSP and CBD cases, tufted astrocytes and astrocytic plaques, respectively, were robustly labeled with the pSer202/pThr205 antibody. pSer356 co-distributed with pSer202/pThr205 immunofluorescence in tufted astrocytes in PSP, however in CBD, pSer356 immunoreactivity was limited to clusters of puncta/granules that did not co-distribute with pSer202/pThr205 immunoreactivity. Pick bodies and ballooned neurons were robustly pSer202/pThr205 immunoreactive and moderately labeled with the pSer356 antibody in dual immunofluorescence preparations. pSer262 immunoreactivity was rare to none in PSP and CBD cases, and was very weak in Pick bodies.
Conclusions: Antibodies to phosphorylated epitopes within the STA region of tau distinguish hippocampal pretangles in AD and may be novel biomarkers for detecting early stages of neurofibrillary pathology development in AD. These epitopes are either less prominent or partially masked in 4R tauopathies and Pick disease and require further study.

Virtual EP - 007

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OMEGA-3 FATTY ACID EPA SUPPLEMENTATION RESTORES GUT MICROBIOTA BALANCE IN THE APP-PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

Barbara Altendorfer[1], Heike Mrowetz[1], Ariane Benedetti[2], Alina Bretl[1], Diana Bessa De Sousa[1], Anja Ladek[3], Andreas Koller[3], Andrea Trost[3], Ludwig Aigner[1]
[1]Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg, Austria, [2]Institute of Experimental Neuroregeneration, Paracelsus Medical University, Salzburg, Austria, [3]University Hospital of the Paracelsus Medical University, Research Program For Experimental Ophthalmology And Glaucoma Research, Department Of Ophthalmology And Optometry, Salzburg, Austria

Aims: Microglia-driven neuroinflammation is a key characteristic of Alzheimer's disease (AD). Dietary omega-3 polyunsaturated fatty acids (PUFAs) have been shown to exert anti-inflammatory effects and to improve microglial function in the diseased brain. Further, omega-3 PUFAs have the potential to shape the gut microbiota and thereby influence microglial cells via the gut-brain axis. In a short-term pilot experiment, we aimed to decipher whether the omega-3 PUFA eicosapentaenoic acid (EPA) modulates the gut microbiome and thereby microglia and AD pathology.
Methods: APP-PS1 mice (RRID: MMRRC_034829-JAX) (TG) and non-transgenic littermates (WT), 13-14 months old, were fed a diet supplemented with 0.3% EPA or control chow for 3 weeks. The hippocampus and blood plasma was used for quantification of eicosanoids. Platelets were isolated to assess platelet activation. Primary microglia were isolated of one hemisphere to perform a phagocytosis assay. Brain and retinal tissue were used for immunohistochemistry. Fecal pellets were analyzed for gut microbiota composition.
Results: Microbiome analysis revealed elevated abundance of *Bacteroidetes* in the TG mice, indicating genotype specific gut microbiota dysbiosis. EPA supplementation decreased the percentage of *Bacteroidetes* and increased bacteria of the phyla *Firmicutes* in APP-PS1 and WT mice. The ratio of *Firmicutes* to *Bacteroidetes*, which was shown to decline in ageing and AD, was significantly increased by EPA-diet. However, other AD characteristics such as increased platelet activation, higher hippocampal levels of pro-inflammatory eicosanoids (5-HETE, PGD2, TXB2), microgliosis in the cortex, astrogliosis in the cortex and retina, and increased microglial phagocytosis of amyloid peptide ex vivo, were not affected by the short-term EPA supplementation.
Conclusions: Short-term EPA supplementation counteracted gut microbiota dysbiosis in APP-PS1 mice; future experiments will determine whether long-term EPA treatment could also influence AD pathology in the brain of APP-PS1 mice.

Virtual EP - 008

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MEDITERRANEAN VS. WESTERN DIET EFFECTS ON THE PRIMATE CEREBRAL CORTICAL PRE-SYNAPTIC PROTEOME: RELATIONSHIPS WITH THE TRANSCRIPTOME AND MULTI-SYSTEM PHENOTYPES

Thomas Register[1], Eloïse Berson[2], Brett Frye[1], Jacob Negrey[1], Suzanne Craft[3], Thomas Montine[2], Carol Shively[1]
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Aims: The purpose of this study was to determine the effects of Mediterranean vs. Western Diets on the cortical presynaptic proteome and relationships with the adjacent transcriptome and extensive phenotypes in female cynomolgus monkeys.
Methods: Monkeys consumed Mediterranean vs Western diets for ~31 months during which they were evaluated for behaviors, longitudinal brain imaging, biomarker collections, and brain collection at the end of the in vivo portion of the study. The presynaptic proteome of approximately 3.6 million synapses isolated from the lateral temporal cortex was assessed using synaptometry time of flight (SynTOF) mass spectrometry, adjacent cortex was evaluated by RNAseq.
Results: Six presynaptic proteins (DAT, Aβ42, calreticulin, LC3B, K48-Ubiquitin, SLC6A8) were elevated in the presynaptic proteome by the Mediterranean compared to the Western diet ($p<0.05$). Transcriptomics from adjacent cortex predicted SynTOF markers. The *SPATA22* transcript was positively correlated with three SynTOF markers (LRRK2, TMEM230 and Aβ40) (all $p<0.05$), while *TFAP2C* was positively correlated with SynTOF markers pTau, CD47, PARKIN and GAD65 (adjusted $p<0.02$). The multi-system phenotypes significantly predicted 26 SynTOF markers. MRI-determined changes in white matter were positively associated with GFAP (adjusted $p<0.01$), while hepatosteatosis was positively correlated with Aβ42, DAT and K48-Ubiquitin (adjusted p's<0.05) in the presynapse, suggesting relationships between liver health and the presynaptic proteome. SynTOF markers were also associated with behavioral and physiological measures of psychosocial stress.
Conclusions: These observations demonstrate that diet drives cortical presynaptic protein composition, that transcriptional profiles predict the presynaptic proteome, and that presynaptic proteins were closely associated with peripheral metabolism, stress responsivity, neuroanatomy, and behavior. These data demonstrate that brain phenotypes and brain-body interactions are influenced by common dietary patterns, suggesting that improving diet quality may be an effective means to maintain brain health.

Virtual EP - 009

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COMPLEMENT C3 REDUCTION IN YOUNG INDUCIBLE KNOCKOUT MICE PREVENTS COGNITIVE DECLINE DURING AGING

Brijendra Singh[1], A.F Batista[2], Emma Spooner[1], Takaomi Saido[3], M. Carroll[4], Cynthia Lemere[2]
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Aims: Germline C3 deletion previously protected cognition and hippocampal synapses in aged APP/PS1dE9 mice despite increased amyloid plaques. To assess if global C3 reduction in adult amyloid mice could be protective, we crossed C3-inducible conditional mice with APPNL-G-F/NL-G-F knockin mice.
Methods: C3fl/fl;Rosa26-Cre-ERT2 (C3iKO) mice were crossed with C3fl/fl;APPNL-G-F/NL-G-F mice to generate APP;C3iKO mice, injected with tamoxifen (TAM, n = 16) or corn oil (CO, n = 15) at 3.6 months. Serum was collected 30 days post-treatment and at study termination to measure C3 levels. Behavioral testing was conducted at 15 months, followed by brain tissue analysis via ELISA, immunofluorescence, qPCR, and RNAseq.
Results: Serum C3 levels were reduced by ~85% post-TAM and ~70% at study end. TAM-injected APP;C3iKO mice performed significantly better on cognitive tests compared to CO-treated mice. C3 and C1q levels were significantly reduced in the brain, with no differences in amyloid load. Iba1 immunoreactivity was reduced in the hippocampal CA3 region of TAM-injected mice, while no differences in GFAP were seen. However, plaques were associated with fewer CD68 positive microglia and GFAP positive astrocytes. Additionally, presynaptic markers (SYN and Bassoon) and postsynaptic markers (PSD95 and Homer1) were elevated in the CA3 and CA1 subregions of the hippocampus. TAM injected also reduced mRNA levels of C3, TNF-α, IL-10, CX3CR1, and IL6. RNAseq identified 1071 differentially expressed genes (569 upregulated, 502 downregulated), with many related to synaptic signaling functions (Bassoon, Homer1, Syn2, SYNPO, and SNAP25).
Conclusions: Global C3 reduction in adult APP-KI mice mitigated inflammation, preserved synaptic integrity, and improved cognition.

Virtual EP - 010

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AB AND TAU OLIGOMERS AFFECT SYNAPTIC VESICLE RELEASE THROUGH PRESYNAPTIC APP

Erica Acquarone[1], Ana Paola Costa[2], Jonhatan Van De Loo[1], Damian Williams[3], Hong Zhang[1], Agnieszka Staniszewski[1], Luciano D'Adamio[4], Daniela Puzzo[5], Laura Mcintire[2], Luana Fioriti[6], Andrew Teich[1], Ottavio Arancio[1]
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Aims: APP is a key transmembrane protein present at synapses throughout life. When APP is absent, memory and long-term potentiation (LTP) are protected from the damaging effects of Aß and tau oligomers. However, it is unclear whether APP in pre- or post-synaptic neurons is more crucial in this process, particularly at the hippocampal CA3-CA1 synapse.
Methods: To clarify the role of APP, a combination of gene editing, electrophysiology, behavioral testing, and biochemical analysis was employed. APP was selectively knocked out either in pre-synaptic or post-synaptic neurons to examine how each affects the response to Aß and tau oligomers.
Results: Deleting APP from post-synaptic neurons did not prevent Aß and tau oligomers from disrupting LTP or memory. On the other hand, removing APP from pre-synaptic neurons reproduced and blocked the harmful effects of Aß and tau, indicating that pre-synaptic APP is responsible for mediating the toxicity. In the absence of pre-synaptic APP, there were changes in neurotransmitter vesicle availability and an increase in the rate of vesicle refilling after depletion, which depended on calcium regulation. In full APP knockout mice, disruptions in intracellular calcium homeostasis were observed, likely linked to reduced levels of calcium-handling proteins like the inositol 1,4,5-trisphosphate receptor, ryanodine receptor, and SERCA3 pump.
Conclusions: These findings suggest that Aß and tau oligomers impair synaptic function and memory primarily through interactions with pre-synaptic APP. This effect is likely mediated through altered neurotransmitter vesicle dynamics and disruptions in calcium signaling.

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MAPPING MEMORY ENCODING USING GENETICALLY ENCODED REPORTERS OF SYNAPTIC POTENTIATION IN 5XFAD MICE.

Francesca Chiara Latini[1], Ajesh Jacob[1], Giorgia Ribbeni[1], Tommaso Gosetti Di Sturmeck[1], Marco Mainardi[2], Antonino Cattaneo[1]
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Aims: Our aim is to provide a cartography of physiologically induced synaptic potentiation following learning-related paradigms and elucidate differences in synaptic potentiation during progressive stages of Alzheimer's disease (AD).
Methods: We use SynActive (SA), a genetic tool which allows the expression of a protein of interest specifically at synapses subjected to activity- or learning-dependent potentiation by exploiting regulatory sequences from the Arc mRNA (Gobbo et al. 2017) combined with GFP Reconstitution Across Synaptic Partners (GRASP; Choi et al., 2018). The post synaptic moiety of split GFP is placed under the control of SA regulatory elements, conferring GFP reconstitution only at potentiated synapses to obtain SA-GRASP. We employed two pairs of AAVs, encoding: (a1) tetracyclin-responsive element (TRE3g)-controlled presynaptic half of GRASP; (a2) presynaptic label (mTurquoise-2) and the reverse tetracyclin-responsive transactivator (rtTA); (b1) TRE3g- and SA-controlled postsynaptic half of GRASP; (b2) postsynaptic label (tdTomato) and rtTA. We performed stereotaxic injections in the hippocampi of 5xFAD mice, and their WT littermates, delivering AAVs a1-a2 to the CA3, b1-b2 to the CA1. To handle the data generated, we have designed a semi-automated pipeline for image analysis of CA1 apical dendrites.
Results: Using this technique, we have been able to determine the spatial distribution of learning-associated CA3-CA1 potentiated synapses following a contextual fear conditioning associative learning protocol. We have observed the distribution of synaptic potentiation along the dendritic tree of CA1 hippocampal neurons in 5 and 8 months old 5xFAD mice, elucidating differences to their WT littermates and with disease progression.
Conclusions: These results offer the first cartography of CA3-CA1 potentiated synapses during learning, highlighting variations during AD progression. Our method enhances understanding of memory formation mechanisms and emphasizes the need to explore these in memory-related diseases for targeted therapies.

Virtual EP - 012

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SPORADIC ALZHEIMER'S DISEASE IN A DISH – THE IMPACT OF DNA REPAIR ON PATIENT-DERIVED CEREBRAL ORGANOIDS

Anna Myhre[1], Emily Karabeika[1], Oline Hovland[1], Fatma Ibrahim[1], Gøril Grøntvedt[1,2], Sigrid Sando[1,2], Magnar Bjørås[3,4], Katja Scheffler[1,2]
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Aims: DNA damage caused by oxidative stress is a key marker for sporadic Alzheimer's disease (AD). DNA glycosylase OGG1 is repairing oxidative base lesions, and loss of its activity has been implicated in AD patients. However, its exact role in AD remains elusive. Our objectives are to investigate whether OGG1 contributes to the development and progression of AD and to evaluate the therapeutic use of an OGG1 inhibitor.
Methods: Self-organized cerebral organoids were generated from hiPSCs derived from blood samples from sporadic AD patients and healthy controls and treated with the OGG1 inhibitor TH5487. Cell survival was analyzed before and after the treatment by using Presto Blue assay. Differences in gene expression of oxidative stress markers, neuronal and inflammatory genes were analyzed using qPCR. Protein expression was analyzed by immunofluorescence microscopy, using antibodies for neuronal markers, DNA damage, AD pathology and inflammatory genes.
Results: We find that cerebral organoids from sporadic AD patients reflect the pathology associated with the disease. Preliminary data show that treatment of cerebral organoids with the OGG1 inhibitor affect cell survival and the DNA damage response. Moreover, neuronal as well as astrocyte marker expressions are differently modulated in healthy controls compared to AD patients following treatment.
Conclusions: Sporadic AD patients-derived cerebral organoids are useful to study disease pathology as an alternative to animal models. OGG1 contributes to AD pathology and modulating its activity might be a promising approach for AD therapy.

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CONCENTRATION-DEPENDENT EFFECT OF APOE ON AMYLOID-BETA CLEARANCE BY HUMAN ASTROCYTES

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Aims: The imbalance between the production and clearance of amyloid beta peptide is implicated in Alzheimer's Disease pathogenesis. Isoforms of apoE are known to affect the deposition of amyloid beta peptides, with pathogenic apoE4 resulting in more amyloid burden compared to wildtype apoE3 or protective apoE2. Despite this connection, the underlying molecular details of how apoE impacts amyloid beta clearance remain unclear. Reports also conflict about whether apoE enhances or impedes amyloid beta clearance. Here, we aim to test the hypothesis that these conflicting observations are due to apoE lipidation- and isoform-specific differences in its interaction with amyloid beta in different aggregated states.
Methods: We used fluorescence correlation spectroscopy and fluorescence polarization to structurally characterize the complexes formed between apoE and amyloid beta, carefully accounting for the lipidation of apoE and the aggregation state of amyloid beta. We then quantified the aggregation-state-specific uptake of amyloid beta by human cortical astrocytes, revealing a strong dependence on apoE concentration.
Results: We observed an enhancement of amyloid beta uptake at low concentrations of apoE and a reduction of amyloid beta uptake at high concentrations of apoE. We believe these observations are primarily influenced by direct interactions between apoE and amyloid beta, as well as apoE's interaction with cellular surface receptors such as heparan sulfate proteoglycans. Interestingly, uptake depends on apoE's lipidation state but not isoform.
Conclusions: These findings help clarify the concentration- and lipidation-dependent role of apoE in Alzheimer's pathology and emphasize the therapeutic potential of modulating apoE lipidation to enhance the amyloid beta clearance by glial cells.

Virtual EP - 014

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EXPLORING THE SYNERGISTIC EFFECTS OF ERINACINES ON MICROGLIAL REGULATION AND ALZHEIMER'S PATHOLOGY UNDER METABOLIC STRESS.

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Aims: *Hericium erinaceus* mycelium and its constituents, erinacines A and S, have shown neuroprotective effects in APP/PS1 transgenic mice; however, the precise mechanisms by which they modulate microglial phenotypes remain unclear. Our study is the first to explore the effect of erinacines on microglia morphology and the underlying mechanisms using a novel primary mixed glia cell model and advanced bioinformatic tools. Furthermore, we emphasize the clinical relevance by evaluating erinacines in a metabolically stressed APP/PS1 mouse model, which more accurately reflects the complexities of human Alzheimer's disease (AD), where metabolic syndrome is a common comorbidity.
Methods: at primary mixed glial cultures were used to simulate the spectrum of microglial phenotypes, particularly the transition from immature to mature states. Microarray sequencing, along with Connectivity Map, ConsensusPathDB, and Gene Set Enrichment Analysis, identified pathways influenced by erinacines. The therapeutic efficacy was further evaluated in metabolically stressed APP/PS1 mice.
Results: Erinacines significantly promoted the development of a ramified, neuroprotective microglial phenotype. Bioinformatics revealed potential modulation of microglia via histone deacetylase inhibition, actin filament dynamics, and synaptic structure modification—pathways not previously linked to erinacines in AD. Importantly, erinacines significantly lower fasting blood glucose and insulin levels while reducing amyloid-beta plaque burden, suppressing hyper-activated glial responses, and enhancing neurogenesis in the metabolically stressed APP/PS1 mice.
Conclusions: Our findings demonstrate the dual action of erinacines in modulating microglia morphology and phenotype while providing neuroprotection in a model that closely mimic the complexities of human Alzheimer's disease. Additionally, this study provides the foundation for understanding the potential mechanisms of action of erinacines, highlighting their promise as a novel treatment approach for Alzheimer's, particularly in cases complicated by metabolic dysfunction.

Virtual EP - 015

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HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED ASTROCYTES FROM ALZHEIMER´S DISEASE PATIENTS SHOW A PRO-INFLAMMATORY AND SENESCENT PHENOTYPE

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Aims: Alzheimer's disease (AD) is characterized by a complex pathology, not fully resolved yet. This fact, together with the lack of reliable models, has impeded the development of effective therapies. Glial cell dysfunction has been proposed to be involved in AD pathogenesis, but this cannot be properly modeled using the available animal models, so we hypothesized that cells derived from AD patients can serve as a better platform for studying the disease. In this sense, human pluripotent stem cells (hPSC) allow the generation of different types of neural cells, which can be used for disease modeling, identification of new targets and drugs development.

Methods: We have generated hiPSC-derived astrocytes from AD patients and cognitively unimpaired age-matched individuals and evaluated their metabolism and phenotype employing confocal imaging, immunofluorescence, flow cytometry, RT-qPCR and functional assays.
Results: Astrocytes from AD patients showed increased expression of reactive markers. In addition, these astrocytes derived from AD patients showed significant metabolic alterations associated with a pro-inflammatory and senescent phenotype which in turn impair their neuronal support as measured in coculture assays.
Conclusions: Our preliminary data suggest that astrocytes derived from AD patients present an intrinsic pro-inflammatory and senescent phenotype which compromise their functionality. Elucidating the mechanisms inducing these processes and their functional consequences should help for a better understanding of role that astrocytes play in AD, by direct functioning and also through their interactions with neurons and the other glial cells. This should lead to potential therapeutic targets for future AD treatments. This study was supported by Instituto de Salud Carlos III (ISCiii) of Spain (grants PI21/00915-PI24/00274 to AG and PI21/00914-PI24/00308 (to JV), collaborative Ciberned PI2022/01 (AG and JV), Sumaira Foundation TSFSPARK202303 (to JAGL) and IBIMA-Bionand Innovative Funds INN24_02 (JAGL).

Virtual EP - 016

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A NODAL REGULATOR ORCHESTRATES REACTIVE GLIOSIS AND NEURODEGENERATION

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Aims: Reactive gliosis is a hallmark of neuropathology and offers a potential target for addressing numerous neurological diseases. We seek to identify nodal regulators of astrocyte behaviors that respond to multiple pathological stimulations. Such nodoal regulators are expected to control a cohort of effector genes responsible for adaptive or maladaptive functions of astrocytes.
Methods: We conducted experiments with bioinformatics, in vitro glia-neuron cocultures, astrocyte-conditioned medium, proteomics, and in vivo mouse genetics. Molecular, cellular, histological, and behavioral analyses were performed.
Results: Our results show that GADD45G is a nodal regulator of reactive gliosis and neurodegeneration. Its expression in astrocytes is sufficient to induce robust astrogliosis, microgliosis, synaptic loss, compromised animal behavior, and exacerbated Alzheimer's disease (AD). On the other hand, GADD45G reduction in astrocytes promotes synaptogenesis and rescues mouse AD pathology. At the molecular level, GADD45G associates with and controls the MAP3K4 and neuroimmune signaling pathways. Such pathway interactions control profound molecular changes including many factors that regulate both cell-autonomous and cell-nonautonomous reactive gliosis and glia-neuron interactions.
Conclusions: Our results discover that GADD45G is a nodal regulator of astrocyte behavior under pathological conditiones including AD. GADD45G could serve as a promising therapeutic target for AD and potentially for numerous other neurological disorders in which reactive gliosis may play an important role.

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Virtual EP - 017

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MILD CORTICAL INFARCT INCREASES NEUROINFLAMMATION, ELEVATES PLASMA BIOMARKERS, AND ALTERS HIPPOCAMPAL SYNAPTIC FUNCTION IN MALE 5XFAD MICE

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Aims: Vascular dysfunction is one of the most common comorbidities reported in Alzheimer's disease (AD) patients and is thought to exacerbate neuroinflammation and cognitive decline. Previously, we found that diet-induced hyperhomocysteinemia in amyloidogenic mice was associated with worsened cognitive performance and impaired synaptic plasticity. However, this model is complicated by concurrent peripheral dysfunction, which limits its ability to report on CNS-specific alterations. For the present study, we therefore characterized the effects of localized cortical infarcts in 5xFAD mice, as this represents a milder, more CNS-relevant model of vascular injury.
Methods: Male WT and 5xFAD mice (8-9 months old) received a 60 min tandem CCA/distal MCA occlusion localized to the anterior region of a single hemisphere. Seven days later, mice underwent behavioral testing (spontaneous open field activity, rotarod, and frailty index), followed by euthanasia for preparation of cortical tissue and acute brain slices for electrophysiology between 13- and 30-days post-infarct. Plasma samples were also analyzed for assessment of AD-relevant biomarkers.
Results: As expected, 5xFAD mice had elevated plasma NFL and GFAP. Extracellular field recordings in hippocampal area CA1 revealed alterations in several synaptic measures, with 5xFAD animals having smaller EPSPs and reduced Late LTP compared to WT. Additionally, injured hemispheres from both groups had smaller fiber volley responses compared to non-injured, suggesting the cortical infarct may have led to distal effects on adjacent hippocampal neurons. These differences also correlated with increased neuroinflammation and enhanced infiltration of CD3+ peripheral cells in injured cortex.
Conclusions: Overall, this work indicates that mild vascular injuries in the cortex of male 5xFAD mice can alter synaptic function in distal hippocampal regions and induce peripheral immune responses such as infiltration of CD3+ lymphocytes into the CNS.

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ASSOCIATION OF FRAILTY INDEX WITH CORTICAL THICKNESS ATROPHY IN UNCONTROLLED TYPE 2 DIABETES: A FOCUS ON HBA1C

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Aims: Type 2 diabetes (T2D) is linked to neurodegenerative changes, with uncontrolled T2D accelerating cortical atrophy. Hyperglycemia, reflected by elevated HbA1c levels, drives brain atrophy, and uncontrolled T2D is associated with faster cortical thinning than controlled T2D. Both hyperglycemia and diabetes are also linked to frailty, a syndrome of reduced physiological reserve. This study investigates whether cortical atrophy in uncontrolled T2D is driven primarily by hyperglycemia or if frailty plays an independent role. We further examined how baseline frailty and HbA1c influence cortical thickness changes over time (2014–2019).
Methods: Using data from the UK Biobank, participants aged 55 and older with uncontrolled T2D (HbA1c >7% per American Diabetes Association(ADA) criteria) were selected alongside age- and sex-matched non-diabetic controls. The cross-sectional analysis included 441 individuals, and the longitudinal analysis involved 37 participants. Frailty was assessed using a phenotype adapted from the Cardiovascular Health Study. Brain regions with atrophy in uncontrolled T2D compared to non-diabetics were identified through linear regression models. HbA1c and frailty contributions to atrophy were analyzed using ANCOVA, adjusted for age and sex.
Results: Cross-sectional analysis revealed significantly higher HbA1c levels in frail compared to non-frail individuals ($p < 0.001$, power=1.00). Frailty was marginally associated with atrophy in the left insula ($p = 0.078$) and right caudal middle frontal gyrus ($p = 0.057$), while hyperglycemia significantly contributed to atrophy in the right caudal middle frontal gyrus ($p = 0.025$). Longitudinally, frailty's impact was limited, with significant effects in the right insula ($p = 0.044$, power=0.56). Age consistently predicted cortical changes, particularly in the right caudal middle frontal gyrus ($p = 0.008$) and right inferior parietal lobule ($p < 0.001$).
Conclusions: These findings highlight the interplay between frailty, hyperglycemia, and cortical atrophy in uncontrolled T2D, suggesting potential targets for intervention.

Virtual EP - 019

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UTILIZING FOSB IMMUNOHISTOCHEMISTRY TO LOCALIZE NEURONAL HYPEREXCITABILITY IN APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Unprovoked seizures are estimated to be ~8 times more common in Alzheimer's Disease (AD) patients than in age matched controls. Epileptiform discharges strongly correlate with accelerated cognitive decline, yet they can be completely asymptomatic. Understanding the link between AD pathology at the cellular level and neuronal hyperexcitability would require identification of the brain focus where the epileptiform discharges are generated. We aimed to localize the epileptic focus by immunohistochemical staining of brain slices with FosB, marker of long-term neuronal activity.
Methods: We used 4-week- to 13-month-old transgenic (TG) and wild-type (WT) mice from lines 5xFAD and APPSwe/PSEN1dE9 (APdE9). We focused on dentate gyrus of the hippocampus where our pilot study revealed the most robust ΔFosB signal in APdE9 mouse brain. Coronal sections of 35 µm were stained with anti-dFosB. Imaging was done with Zeiss Image r.M2, comparative analysis was done using ImageJ, and statistics were done with SPSS, Microsoft Excel, and GraphPad Prism9.
Results: Whereas FosB expression at 6 weeks, 8 months, or 13 months of age did not differ between genotypes in APdE9 male mice, there was an increase in TG male mice at 12 weeks compared to WT littermates. In APdE9 female mice the FosB expression was significantly increased at all ages (6, 9, and 12 weeks). It seems that in female mice the FosB expression is elevated earlier than in male mice. Interestingly, in our mouse colony female TG mice tend to die of epilepsy before 12 weeks of age.
Conclusions: FosB provided useful tool to locate the specific cells responsible for the hyperexcitability leading to epileptiform spiking in AD. The results help identifying new therapeutic target to decrease network hyperexcitability that may aggravate AD disease progression via epileptiform activity.

Virtual EP - 020

Virtual E-Posters and Oral On-Demand
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SOMATOSENSORY AND MOTOR EVOKED POTENTIALS IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

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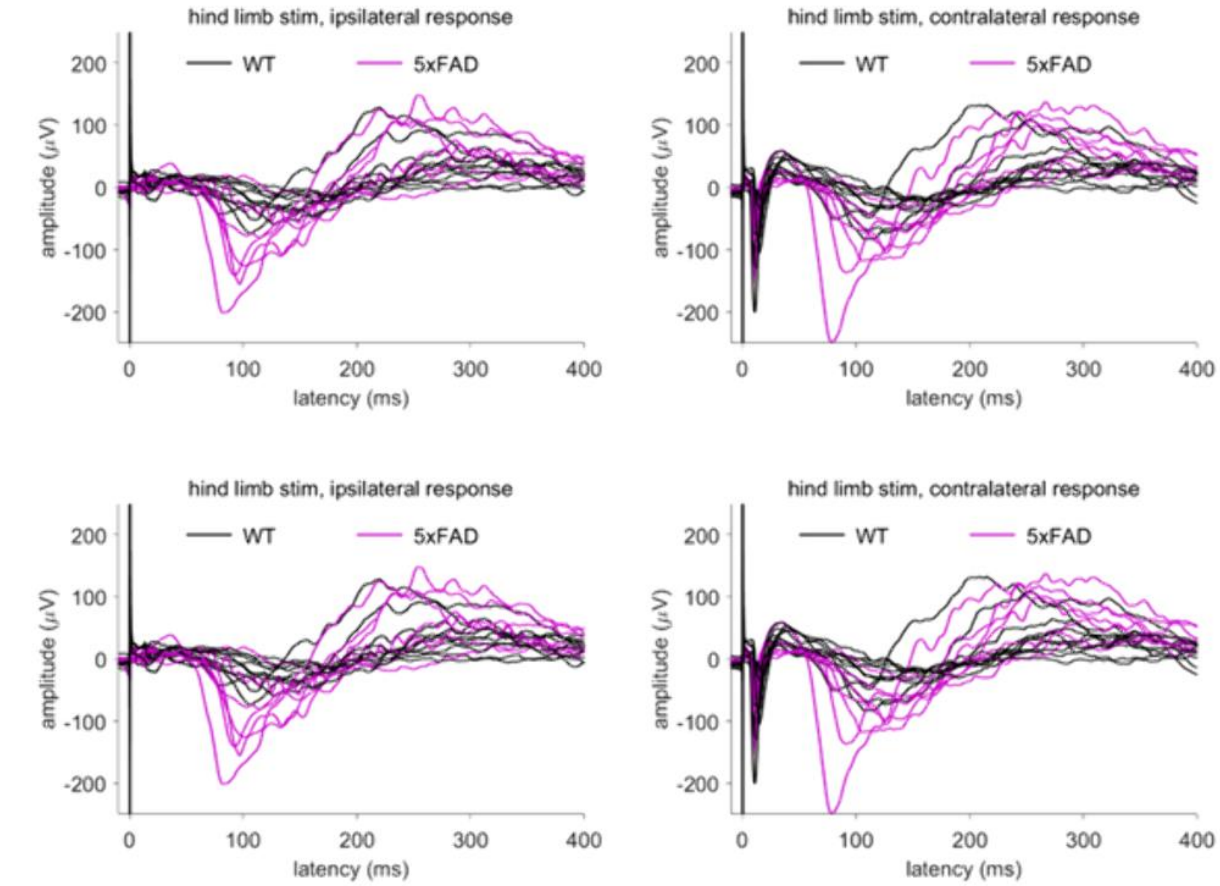
Aims: Alzheimer's disease (AD) is mainly characterized by cognitive deficits. Although motor deficits are also recognised in patients, they are less widely studied. Here, we use electrophysiological somatosensory (SSEPs) and motor evoked potentials (MEPs) to investigate motor dysfunction in the 5xFAD Alzheimer's mouse model, a model that also presents impaired motor function in old age[1] and fine motor deficits (unpublished data by our group).
Methods: 9-month-old transgenic 5xFAD mice and wild-type (WT) littermates (n = 24) received cortical screw implants for stimulation and evoked-related electroencephalographic measurements. Under 1.5% isoflurane anesthesia SSEPs were collected by stimulating the hindlimbs and forelimbs while recording from cortical screws. MEPs were collected by stimulating across the motor cortex, across the atlas bone, across the thoraco-lumbar transition of the spine and across the sciatic nerve (using either the EEG screws or subdermal needles) while recording activity from the hindlimb and forelimb.
Results: Preliminary analysis showed that limb stimulation consistently produced contralateral responses. Early responses (~10ms) were not different across groups. A prominent SSEP response at ~100ms was significantly larger in 5xFAD mice compared to WT for hindlimb but not for forelimb stimulation. Stimulation of the motor cortex yielded less consistent distal responses, without a statistically significant outcome. Stimulation across spinal and sciatic levels produced consistent distal responses for which analysis is ongoing.



Conclusions: SSEP and MEP stimulations of hindlimb and forelimb can assess bidirectional signal transmission deficits in WT and 5xFAD mice. In conjunction with ongoing histological examination of the corresponding ascending and descending pathways and motor behavioral experiments , this approach can provide complementary insights into the origins of motor deficits in AD.

Virtual EP - 021

Virtual E-Posters and Oral On-Demand
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THE APPLICATION OF LOCAL FIELD POTENTIAL IN PRECLINICAL ALZHEIMER'S DISEASE MODELS

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Aims: Alzheimer's disease (AD) is the most common cause of dementia, characterized by a continuous decline in cognitive, behavioral, and social abilities, ultimately impairing a person's capacity for independent functioning. Although current diagnostic biomarkers facilitate early detection, they do not provide an easy and minimally invasive approach to predict disease progression or monitor AD patients over time. Here, we aim to investigate the use of local field potentials in preclinical models.
Methods: In this study, we examined the hippocampal local field potentials (LFPs) in both genetically modified and chemically induced Alzheimer's disease (AD) models.
Results: We tracked the 5xFAD mouse model for over a 12-month period, observing aberrant power and modulation in several oscillation bands as the condition advanced. Significantly, phase-amplitude coupling (PAC) began to deteriorate at the 4-month mark and was almost completely lost by the 12-month mark. Histopathological observations such as amyloid plaques and gliosis were noted at 4 months, while cognitive impairments became apparent between 6 and 12 months. To substantiate the predictive value of in vivo electrophysiological assessments for drug efficacy, we administered FPS-ZM1, a potent RAGE-specific antagonist, to the 5xFAD mice as a positive control. Additionally, by analyzing LFPs in the scopolamine-induced model, we deepened our understanding of EEG pattern changes associated with the metabolism of drugs within the body.
Conclusions: Taken together, our results suggest that PAC decoupling could serve as a valuable biomarker for monitoring the progression of Alzheimer's disease (AD) in animal models. Given that PAC decoupling occurs significantly earlier than the onset of cognitive and behavioral impairments, it offers a promising new approach to predict clinical outcomes related to AD progression and therapeutic efficacy.

Virtual EP - 022

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DATURA METEL AGGRAVATES HEPATO-PREFRONTAL CORTICAL DAMAGE IN ALCOHOL COCKTAIL-EXPOSED MALE SPRAGUE DAWLEY RATS

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Aims: This study is aimed at evaluating the effects of *Datura metel* and alcohol cocktail on the hepato-prefronto-cortical axis.
Methods: Thirty-five male Sprague Dawley rats were divided randomly into five (5) groups (A-E). Group A (Control group) animals received distilled water, Group B received DM (300 mg/kg Bwt), Group C received Alcohol (700mg/kg), Group D received DM and Alcohol (300mg/kg DM+700mg/kg ALC) while Group E received DM and alcohol (150mg/kg *DM* +350mg/kg ALC) for 2 weeks respectively. Tissues from the liver and prefrontal cortex were collected for morphological, histological, and Immunohistochemical studies.
Results: There was a significant increase in body weight in control rats compared to other experimental groups. H&E stains revealed a mild attenuation in the cytoarchitecture of the liver and Prefrontal cortex (PFC) with increased necrosis, apoptosis, vacuolation, and neuronal death in the experimental rats. There was increased microglial activity in groups B, C, D, and E while the NeuN antibody displayed normal neuronal arrangement in group A when compared to experimental rats. Serum liver function biomarkers (alkaline phosphatase, alanine transaminase, aspartate aminotransferase) were statistically significantly higher in Groups C and D compared to Group A.
Conclusions: It is possible to conclude that combining *Datura metal* and alcohol hurts the liver and Prefrontal cortex of experimental rats.

Virtual EP - 023

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HEPARAN SULFATE MODIFIED PROTEINS AND THEIR IMPACT ON PRESENILIN-MEDIATED PATHOLOGY

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Aims: The involvement of heparan sulfate(HS)-modified proteins in Alzheimer's disease (AD) has been implicated by the capacity of an APOE3 variant (Christchurch) that reduces heparan sulfate binding to suppress cognitive decline in individuals with *PSEN1*-mediated AD. We have examined if reduction of heparan sulfate biosynthesis affects neuron loss, apoptosis, autophagy and mitichondrial abnormalities in *Drosophila* with knockdown of *presenilin*. We also assessed the effects of reducing HS-mediated signaling on metabolic pathways using RNAseq-based gene expression analysis of human Hep3B cells bearing a knockout of *EXT1,* an essential HS co-polymerase.
Methods: Knockdown of *presenilin/PSEN1* in *Drosophila* neurons produces cell loss, behavioral deficits, mitochondrial abnormalities and elevated apoptosis. These phenotypes were evaluated in *presenilin* KD animals compared to those with simultaneous RNAi-mediated knockdown of *sfl*/*NDST1*, a HS-specific sulfotransferase. RNA isolated from Hep3B +/+ and EXT1 -/- cells in quadruplicate, processed for transcriptome analysis.
Results: Modest RNAi-mediated knockdown of *sfl/NDST1* rescues *presenilin*-deficit mediated mitochondrial abnormalities, neuron loss, apoptosis, and behavioral abnormalities. Significant expression changes in genes affecting glycolysis, fatty acid oxidation, as well as fatty acid and cholesterol biosynthesis were apparent in Hep3B *EXT1 -/-* cells. Overall, the gene expression profiles are indicative of increased glycolysis, elevated fatty acid catabolism, decreased fatty acid and cholesterol biosynthesis, increased autophagy flux and mitochondrial biogenesis. Seahorse measures of oxygen consumption rates confirmed increases in mitochondrial function/cell in *EXT1 -/-* cells.
Conclusions: Modest reduction of heparan sulfate modification dramatically suppresses a range of phenotypes in adult *Drosophila* with knockdown of *presenilin*. Metabolic changes mediated by inhibiting HS biosynthesis in a human cell line counter metabolic abnormalities described for neurodegenerative diseases. Heparan sulfate-modified proteins play a critical role in AD pathogenic processes and modest inhibition of HS biosynthesis can ameliorate those deficits.

Virtual EP - 024

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SENSORY FUNCTION AS AN EARLY MARKER OF COGNITIVE DECLINE IN AGING

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Aims: Recent studies have identified midlife hearing loss and late-life vision impairment as modifiable risk factors for dementia. However, the extent to which these sensory deficits are linked to cognitive decline, as well as the underlying neurobiological mechanisms, remains insufficiently understood. This study used data from 472 healthy adults aged 36 to 100 years to investigate the relationships between visual and auditory functions and cognitive performance throughout the aging process, and to explore the associated brain mechanisms.
Methods: Vision and hearing were assessed using the NIH Toolbox Visual Acuity Test and the Words-in-Noise Test. Cognitive functions were evaluated through cognitive tests, and functional brain connectivity was estimated with functional magnetic resonance imaging. We used robust regression and Support Vector Machine techniques to explore how sensory functions predict cognitive performance. A model-free sliding window approach investigated the relationships between sensory performance, cognitive function, and age. Connectome-based Predictive Modeling identified brain regions and connections linking sensory functions with cognitive processes in aging.
Results: Robust regression analysis demonstrated that hearing and vision were significantly associated with working memory, episodic memory, executive function, and language abilities after controlling for age and sex. Prediction analysis using leave-one-out cross-validation and a non-parametric permutation scheme confirmed the stability and validity of these relationships. Additionally, we observed that the coupling coordination between sensory functions and cognition gradually decreased with aging. Functional connectivity of the fronto-parietal and medial temporal lobe regions was identified as the link in the relationship between sensory and cognitive performance.
Conclusions: This study elucidates the intricate relationship between visual and auditory functions and cognition, along with their underlying neural mechanisms in aging, and proposes that sensory performance could serve as an early marker for predicting cognitive decline and dementia.

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BIOLOGICAL AGE MEDIATES THE EFFECT OF EDUCATION ATTAINMENT ON COGNITIVE FUNCTION IN NHANES

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Aims: Higher educational attainment is positively associated with cognitive function in older adults, but the biological mechanisms underlying this relationship remain unclear. This study aims to investigate whether biological age, as measured by PhenoAge, mediates the association between education and cognitive function.
Methods: We used data from the 2011-2014 National Health and Nutrition Examination Survey (NHANES) cohorts to investigate the mediation effect of PhenoAge, a composite biomarker of biological aging that reflects multiple physiological pathways, including chronic kidney disease, cardiovascular disease, oxidative stress, and inflammation, on the relationship between educational attainment and global cognition scores. Mediation analysis was conducted to estimate both the direct and indirect effects of education on cognitive function, with PhenoAge representing the biological aging pathway.
Results: Mediation analysis revealed that biological age significantly mediated the effect of education on cognitive function, accounting for 13% of the total effect. Individuals with delayed biological aging (PhenoAge < chronological age) showed stronger direct effects of education on cognition, while the mediation effect of PhenoAge was more pronounced in those with accelerated aging (PhenoAge > chronological age).
Conclusions: Our findings suggest that biological age is an important mediator in the relationship between educational attainment and cognitive function. Individuals with accelerated aging may experience a diminished cognitive benefit from education, highlighting the need to consider biological aging in efforts to preserve cognitive health.

Virtual EP - 026

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PROGNOSTIC VALUE OF GUT MICROBIOME FOR PROGRESSION FROM NORMAL COGNITION TO MILD COGNITIVE IMPAIRMENT WITHIN 4 YEARS: RESULTS FROM THE ALZBIOM STUDY

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Aims: A growing body of evidence suggests that dysbiosis of the gut microbiome is associated with the pathogenesis of Alzheimer`s disease (AD) and can be used as a diagnostic measure. However, longitudinal changes of gut microbiome and its prognostic significance in cognitively healthy elderly individuals (HCs) for the development of mild cognitive impairment (MCI) are still unknown. In the present study we investigated the ability of taxonomic and functional gut microbiome data to predict the progression from normal cognition to MCI on the basis of clinical classification at 4 years follow-up (4yFU).
Methods: In the present study we investigated intestinal microbiome in 100 HCs participating at the AlzBiom study over a follow-up of 4 years (4yFU). At the end of the 4yFU, 29 HCs developed MCI, 57 HCs remained cognitively stable and 14 HCs dropped out of the study. Gut microbiome was measured using shotgun metagenomics. Statistical models were built with features that best discriminated between MCI converters and cognitively stable HCs using an ANOVA like test.
Results: The best taxonomic model for discrimination of MCI converters from cognitively stable HCs included 38 genera, yielding an area under the receiver operating characteristic curve (AUROC) of 0.72 at baseline, 0.70 at 1yFU, and 0.58 at 4yFU. The best functional GO (Gene Ontology) model included 14 features with an AUROC of 0.84 at baseline, 0.78 at 1yFU, and 0.75 at 4yFU.
Conclusions: We identified novel gut microbiome algorithms able to accurately predict MCI conversion in cognitively healthy elderly individuals within a 4 years follow-up. Gut microbiome represents an innovative prognostic supplement in AD.

Virtual EP - 027

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DESCRIBING FIRMICUTES AND BACTEROIDETES DISTRIBUTION IN RELATION TO AGE, SEX, AND APOE-E4 ALLELE STATUS IN AIBL AND WAMS COHORTS

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Aims: Alzheimer's disease (AD) is a neurodegenerative condition marked by cognitive decline and impairment in daily functioning. Emerging research suggests that gut microbiota may contribute to disease progression via the gut-brain axis. Alterations in gut microbiota have been demonstrated in AD patients, while changes associated with the preclinical stage are still under investigation.
Methods: This cross-sectional study investigated the gut microbiota composition among older adults in the Australian Imaging, Biomarkers, and Lifestyle (AIBL) and Western Australian Memory Study (WAMS) cohorts to understand microbial patterns associated with AD risk (age, sex, and APOE). Participants included 123 individuals (55% female, mean age is 75 years), 17% with apolipoprotein E (APOE-ε4 allele), the major genetic risk factor for AD. Single-point faecal samples were analysed using shotgun metagenomic sequencing to characterise gut microbiota composition. Analysis (ANOVA and T-test) revealed that Bacteroidetes was the dominant phylum, followed by Firmicutes, consistent with age-related microbial composition trends in older populations.
Results: The Firmicute/Bacteroidetes (F/B) ratio, a marker of gut health, appeared to decrease with age (0.956 for <65yrs, 0.935 for 65-75yrs, and 0.846 for >75yrs), though this trend was not statistically significant. Though insignificant, a higher (F/B) ratio was seen in male and non-carriers. The most abundant 10 phyla, classes, and order distribution showed no statistically significant difference against demographic variables except phylum Verrucomicrobia against gender ($p = 0.008$) and age categories ($p=0.05$). Alpha diversity, representing species richness within samples, showed no significant associations with age, sex, or APOE-ε4 status but showed a decreasing trend in advancing age and the presence of APOE-ε4.
Conclusions: These findings provide a basic understanding of gut microbiota in an aging Australian cohort, with Bacteroidetes and Firmicutes as the prevalent phyla.

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Virtual EP - 028

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THE ORAL MICROBIOME-BRAIN AXIS: DECODING THE ORAL MICROBIOME SIGNATURE ON COGNITIVE FUNCTION IN OLDER ADULTS: A CROSS-SECTIONAL STUDY ANALYSIS FROM THE MIND TRIAL

Robin M Voigt-Zuwala[1], Darbaz Adnan[1], Phillip Engen[1], Ankur Naqib[1], Stefan Green[1], Shohreh Raeisi[1], Michelle Villanueva[1], Klodian Dhana[2]
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Aims: Objective: The oral microbiome is a community of microorganisms that reside in the oral cavity. Alterations in the microbiota community have been associated with an increased risk of Alzheimer's disease (AD). This study aimed to evaluate the association between oral microbiome niches and cognitive function in older adults.
Methods: Methods: This study used data from the MIND trial, a randomized clinical trial on the effect of MIND diet on cognition, and 143 provided fasting saliva, buccal and lingual samples. Global cognition was evaluated using a cognitive battery, brain structure was evaluated using MRI, and serum was analyzed to determine the levels of systemic inflammation and AD biomarkers. The oral microbiome was assessed including microbiome composition (α and β diversity) and linear regression analysis was used to evaluate the relationship between microbiome and cognition, and Spearman's rank correlation test was used to examine associations between taxa and systemic inflammation, cholesterol, AD biomarkers, brain structure, and diet.
Results: Results: Analysis revealed niche-specific differences (saliva, buccal, lingual), as well as the microbiome composition differences (α and β diversity) based on cognitive function. There was higher abundance of anaerobic pro-inflammatory bacteria in participants with a lower cognitive Z Score than in those with a higher cognitive Z Score, including *Parvimonas, Treponema, Filifactor, Eubacterium_yurii_group, Lentimicrobium, Phocaeicola, Dialister, Tannerella, Anaeroglobus, Fretibacterium, and Peptococcus, and Family_XIII_UCG-001*. In contrast, *Gemella* was lower in individuals with lower cognitive Z scores than in those with higher cognitive Z scores.
Conclusions: Conclusion: Outcomes suggest: (1) oral microbiota may be a biomarker for cognitive function and (2) oral microbiota might influence cognitive function. Further research is required to assess whether the oral microbiome plays a role in AD development and progression.

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Virtual EP - 029

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SIGNIFICANT REDUCTION OF PATHOLOGICAL PROTEIN LEVELS IN TRANSGENIC MICE MODELS FOR AD BY A RHENIUM COMPLEX: PRELIMINARY RESULTS

Marina Sagnou[1], Barbara Mavroidi[1], Archontia Kaminari[2], Rebecca Noel[3], Antonio Shegani[4], John Pirmettis[4], Minas Papadopoulos[4], Elisa Konofagou[3], Maria Pelecanou[1]
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Aims: There is currently no cure for Alzheimer's Disease (AD). Poor brain penetration of many potential disease-modifying agents is precluding their advancement in clinical trials. In this work, a patented complex of rhenium (Re) **Re-1**, structural analogue of the multifaceted 2-phenylbenzothiazole pharmacophore with remarkable brain penetration *in vivo* and anti-amyloid properties (*J. Med. Chem*. 2019, 62, 2638) is evaluated for its effect on brain levels of major proteins related to the pathophysiology of AD in two transgenic mouse models the 5xFAD and 3xTg-AD.
Methods: The 5xFAD mice (5 in each group) received **Re-1** (10 mg/Kg, i.p. once a week) for 11 weeks from the age of 2 to 5 months. The mice were sacrificed, the brain was dissected out, half cut into slices and half lysed for estimation of protein expression with western blotting. The 3xTg-AD mice (10 in each group) received **Re-1** (10 mg/Kg, i.p, once every two weeks) for a period of 5 months. The brain was dissected out, treated for cryosectioning and immunostained with OC for amyloid fibrils and HT7 for tau for fluorescent imaging.
Results: In the brains of 5xFAD mice **Re-1** was shown to reduce β-amyloid plaques, in microscopic observation, reduce APP, Aβ-5mers, by 25%, 60% respectively, and increase IDE (Aβ degrading enzyme) by 70%. In the 3xTg-AD mice, **Re-1** demonstrated reduced β-amyloid fibril accumulation and, most importantly, reduced tau accumulation.
Conclusions: Reduction of levels of APP, Aβ oligomers, and tau, simultaneously, by small molecules *in vivo* is very rare in the AD literature. Our results, although preliminary in terms of number of animals used, dosage variation, further biochemical analysis of brain homogenates, are statistically sound and unveil the outstanding potential of Re-1 against AD.

Virtual EP - 030

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MINIMIZING RISK OF AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) IN ALZHEIMER'S PATIENTS ON ANTI-AMYLOID MONOCLONAL ANTIBODY THERAPY THROUGH LOWER DOSE TITRATION

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Aims: To prevent amyloid-related imaging abnormalities (ARIA) in Alzheimer's disease (AD) by implementing a slower dose titration of anti-amyloid monoclonal antibody (MAB) therapy, taking into account co-morbid cerebral amyloid angiopathy (CAA).
Methods: CAA affects 80% of Alzheimer's disease (AD) patients. Though CAA is known for hemorrhagic changes, ischemic microvascular changes are common, underrecognized, and often visible in AD neuroimaging. Both conditions are driven by abnormal processing and deposition of amyloid β (Aβ). Solubilized Aβ is cleared via transport across the blood-brain barrier (BBB) into smooth muscle cells of the cerebral vasculature where degradation occurs, through perivascular drainage, neuronal and glial uptake, and enzymatic breakdown. In CAA, Aβ40 and Aβ42 deposits accumulate in cerebral vasculature smooth muscle cells, from arterioles to arteries, compromising BBB integrity. When MABs solubilize Aβ in AD immunotherapy, they overwhelm clearance pathways, accelerating Aβ deposition in smooth muscle cells and promoting CAA, perivascular inflammation, and impaired clearance. This compromises the BBB, leading to fluid leakage or ARIA with edema (ARIA-E), and eventually red blood cell extravasation and hemorrhage (ARIA-H). While apolipoprotein E (APOE) aids Aβ clearance, the ε4 allele is less efficient, increasing amyloid burden and related risks, including ARIA. ε4 carriers face a greater risk for AD, ARIA, and support BBB repair. CAA-related inflammation (CAA-ri) mimics ARIA-E clinically, radiographically, and neuroimmunologically. ARIA-E may be an iatrogenic form of CAA-ri, potentially treatable with high-dose steroids.
Results: Slower MAB dose titration reduces ARIA risk. In one study of Alzheimer's patients (95% ε4 carriers) receiving aducanumab, no ARIA was observed over an 8-month period, when ARIA risk is highest.
Conclusions: Slower MAB dose titration, considering the high comorbidity of CAA with AD, offers an effective, straightforward approach to reducing ARIA risk in Alzheimer's treatment.

Virtual EP - 031

Virtual E-Posters and Oral On-Demand
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MOLECULAR DOCKING AND TWO-SAMPLE MENDELIAN RANDOMIZATION: COMPUTATIONAL APPROACHES TO IDENTIFICATION AND CHARACTERIZATION OF REPURPOSED DRUGS FOR TREATMENT OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive and functional decline. Masitinib has demonstrated potential in AD clinical trials, primarily through its interaction with immune cells. Yet its precise targets remain unclear. This study aims to identify and characterize the target of masitinib through molecular docking and two-sample Mendelian randomization.
Methods: We identified overlapping genes as candidates and performed molecular docking to determine their binding affinity with masitinib. Following this, we conducted a two-sample Mendelian randomization (MR) analysis to evaluate the causal relationship between candidate gene expression in the brain (exposure) and AD or cognitive function (CF) (outcome) in European Ancestry (EUR). Colocalization analysis was used to identify shared causal variants.
Results: Two candidate genes, epidermal growth factor receptor (*EGFR*, also known as Erb-B1) and tyrosine-protein kinase FYN (*FYN*), were identified as potential drug targets, showing strong binding affinities with masitinib (EGFR: -12.4 kcal/mol; FYN: -7.8 kcal/mol). MR analysis found that higher EGFR expression in the cortex had a significant causal effect on AD [$P = 1.56 \times 10^{-8}$, odds ratio (OR) = 1.09] or cognitive decline [$P = 1.34 \times 10^{-3}$, OR = 0.98]. Similar results were observed in an independent Finnish population AD GWAS (genome-wide association study) as a replication study. Sensitivity analyses did not show evidence of heterogeneity or horizontal pleiotropy. Colocalization analysis identified a known AD-risk variant, rs74504435, in the *EGFR* gene as the shared causal variant.
Conclusions: The study demonstrates that the therapeutic effects of masitinib on AD are closely associated with its inhibition of EGFR expression in the brain, highlighting that combining molecular docking and MR with publicly available genetic data as a promising approach for drug clinical trial research.

Virtual EP - 032

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NIR-LED PULSED TRANSCRANIAL PHOTOBIOMODULATION(TPBM) ON MCI ELDERLY IMPROVES COGNITIVE FUNCTIONS AND EEG PATTERNS

Nam-Heon Kim[1], Daekeun Kim[1], Paolo Cassano[2,3], Seung Wan Kang[1,4]
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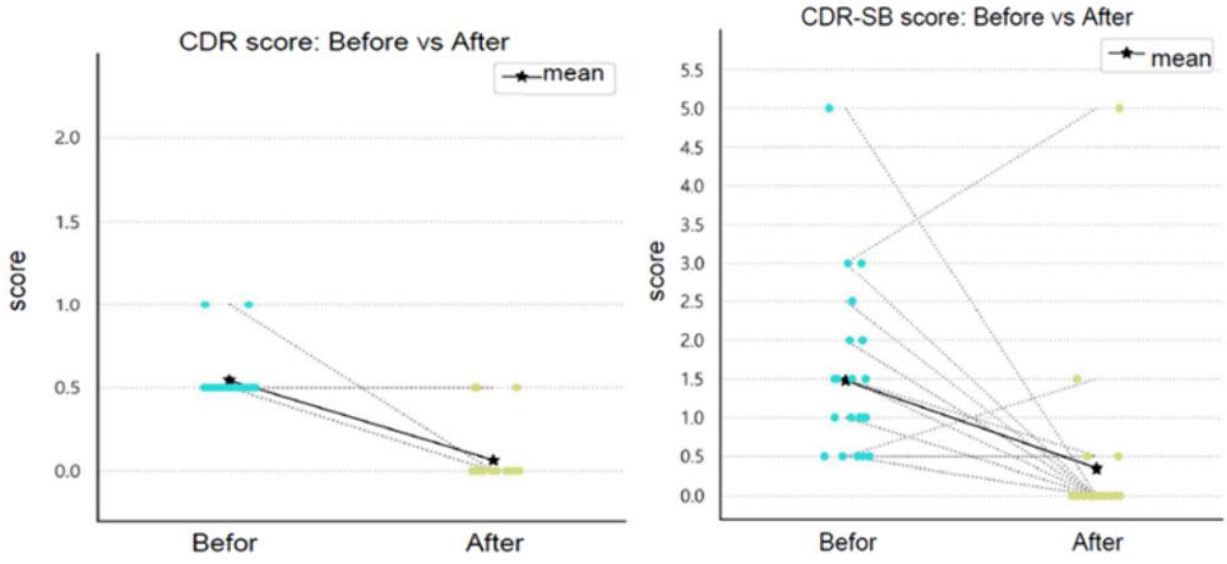
Aims: Recently, transcranial photobiomodulation(tPBM) has gained popularity for treating neurodegenerative diseases[i]. Positive effects including increased blood circulation and ATP production, due to mitochondrial stimulation have been confirmed in various studies[ii]. Human experiments also show that tPBM benefits cognitive function.[iii] We applied tPBM on MCI patients and assessed their cognitive function by CDR, monitored their EEG changes.
Methods: For 8 weeks, 23 subjects with MCI were treated 3 times per week with tPBM(wavelength of 850nm, pulse of 10Hz). CDR and EEG measures were used to assess overall cognitive impairment at baseline and endpoint.
Results: Result The average CDR-SB went from 1.48 to 0.35 and the CDR went from 0.54 to 0.07 after tPBM. Among 23 subjects, 20 improved their CDR-SB, 1 maintained and 2 worsened (Figure 1). Significant reduction in frontotemporal theta/beta-2 ratio(TBR2) confirmed (Figure 2). ***Figure 1***. *Effect of 8-week tPBM on CDR, CDR-SB.*



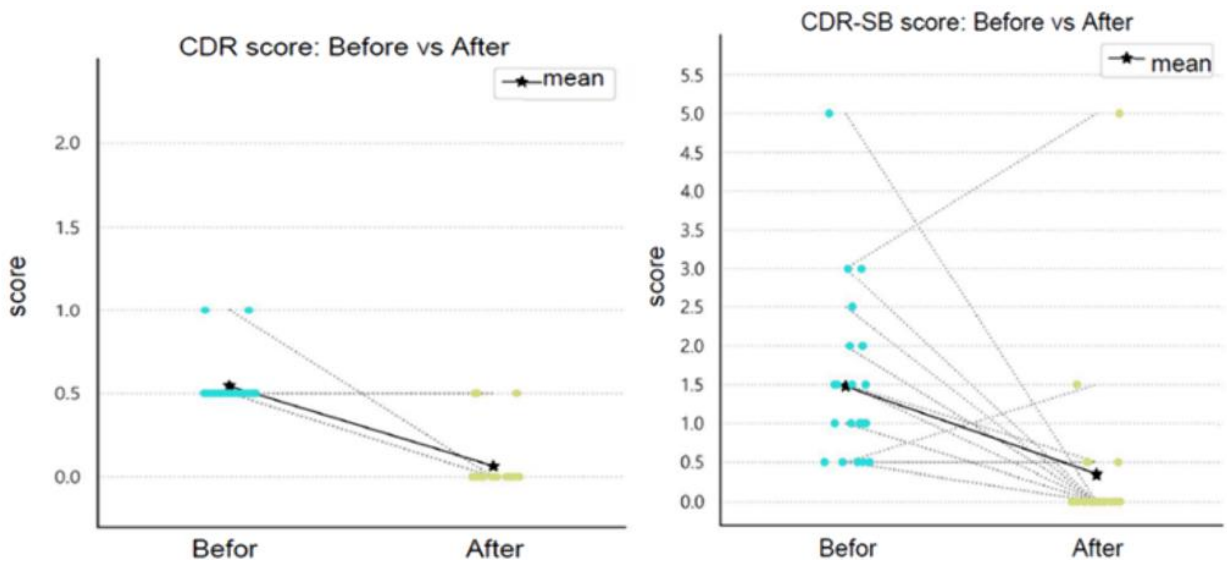
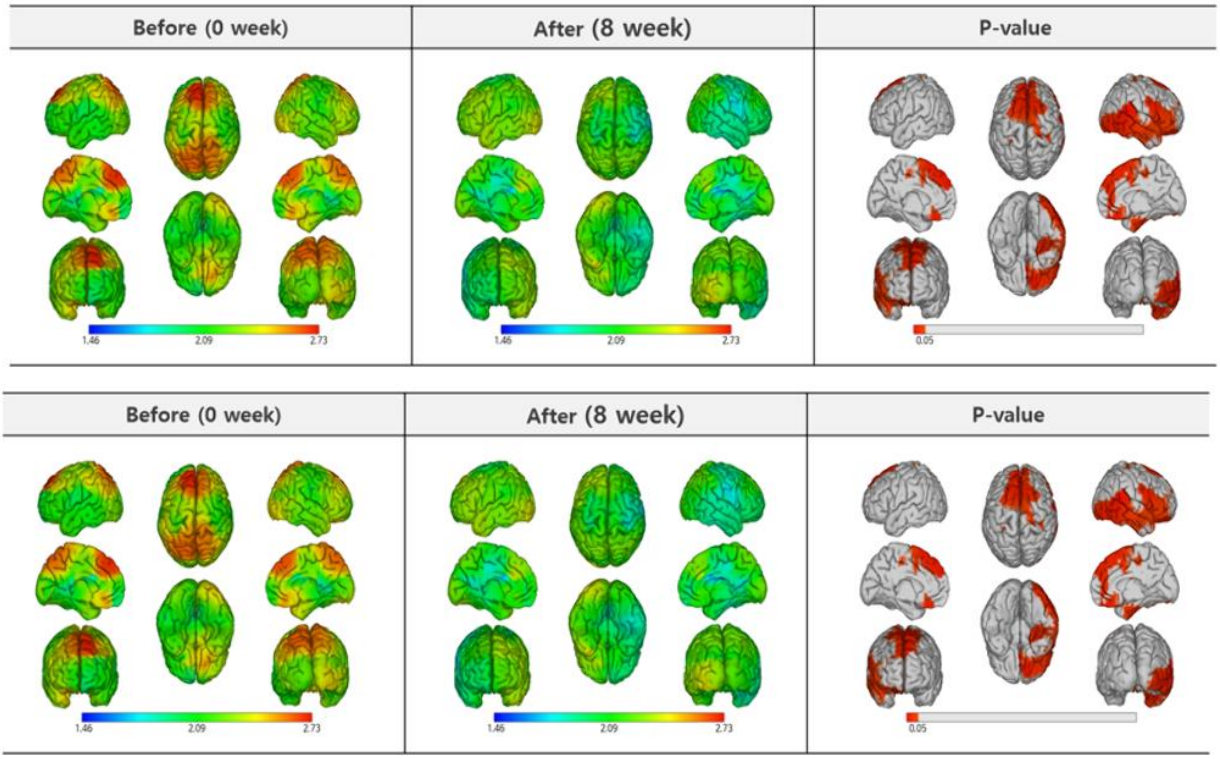


***Figure 2**. Effect of 8-week tPBM on EEG.*



Conclusions: tPBM exerted a procognitive effect in a person with cognitive dysfunction, also changing the slow waves with a favorable decrease[iv]. We found that CDR improved significantly, and source level TBR2, a characteristic of MCI, showed normalization after care. **References** [i] Mitrofanis, J., Henderson, L. A. (2020). How and why does photobiomodulation change brain activity? *Neural Regen. Res*. 15 [ii] Purushothuman, Sivaraman, et al. (2014) Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex–evidence from two transgenic mouse models. *Alzheimers Res Ther*. 6: [iii] Zomorrodi, Reza, et al. (2017) Complementary EEG evidence for a significantly improved

Alzheimer's disease case after photobiomodulation treatment. *26th Annual Scientific Conference, Canadian Academy of Geriatric Psychiatry Toronto*. [iv] Vrankic, M., et al. (2022) EEG-Validated Photobiomodulation Treatment of Dementia—Case Study. *Sensors* 22

Virtual EP - 033

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THERAPEUTIC POTENTIAL OF CHRYSIN IN REGULATION OF INTERLEUKIN-17 SIGNALING IN REPEATED INTRANASAL AMYLOID-BETA-INDUCED ALZHEIMER'S DISEASE MODEL.

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Aims: The aim of the current study was to study the therapeutic potential of chrysin against repeated intranasal Amyloid-beta (Aβ) induced interleukin-17 (IL-17) signaling in the mice model of AD.
Methods: The male BALB/c mice were exposed to daily intranasal $A\beta_{1-42}$ (10µg/10µL) for seven consecutive days. The chrysin was administered at 25, 50 and 100mg/kg of dose orally in 0.5% sodium carboxy methyl cellulose suspension from day 5 of $A\beta_{1-42}$ administration for seven days. Following the treatment, the memory of the animals was appraised by Morris water maze, novel object recognition test and passive avoidance test. Further, the effects of chrysin on $A\beta_{1-42}$ induced IL-17 signaling, redox level was evaluated in the cortex and hippocampus regions of the mice brain by western blot and immunohistochemistry.
Results: The exposure of $A\beta_{1-42}$ through intranasal route induced a significant decline in the spatial, learning and cognitive memory the animals and most interestingly, the exposure of $A\beta_{1-42}$ triggered the IL-17 mediated signaling that resulted in a significant increase in the expression of IL-17RA, Act1 and TRAF6. On the other hand, $A\beta_{1-42}$ also impaired the redox level and inflammatory cytokines in the mice brain. Whereas, the treatment with chrysin at 25, 50 and 100mg/kg orally, alleviated the $A\beta_{1-42}$ mediated memory decline, impaired redox level and inflammation. Specifically, the chrysin downregulated the expression of IL-17 and mediated signaling in the brain regions of the mice.
Conclusions: Chrysin was evidenced to be the potent antioxidant and anti-inflammatory and clearly showed the protective role against the $A\beta_{1-42}$ induced IL-17 mediated inflammation in the mice brain.

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FORMONONETIN MITIGATES MOTOR DYSFUNCTION AND NEUROINFLAMMATION IN PARKINSON'S DISEASE RATS

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Aims: To evaluate the neuroprotective effects of formononetin in a rat model of Parkinson's disease (PD) induced by intracerebroventricular (i.c.v.) administration of 6-hydroxydopamine (6-OHDA)
Methods: Animal Model: Rats were used to develop a PD model through a single i.c.v. injection of 6-OHDA. **Treatment:** Formononetin was administered orally at doses of 25, 50, and 100 mg/kg for 21 days post-6-OHDA injection. **Behavioral Assessments:** Motor coordination, grip strength, and gait were evaluated using the rotarod test, gait analysis, and pole test. **Biochemical Analyses:** Levels of oxidative stress markers (SOD, catalase), proinflammatory cytokines (IL-1β, TNFα, IL-6), and brain monoamines (DA, Ach) were measured. **Immunohistochemistry:** Protein expression of Bcl2 and α-synuclein was assessed to study neuroprotection and aggregation.
Results: Formononetin significantly improved motor coordination, grip strength, and gait performance in rats treated with 6-OHDA. Enhanced antioxidant defenses were observed with increased SOD and catalase activities. Reduced levels of proinflammatory cytokines (IL-1β, TNFα, IL-6) indicated decreased neuroinflammation. Dopaminergic neuronal protection was evidenced by increased dopamine (DA) levels and reduced acetylcholine (Ach) levels. Immunohistochemical analysis showed reduced α-synuclein aggregation and increased Bcl2 expression, highlighting formononetin's anti-apoptotic and neuroprotective effects.
Conclusions: Formononetin exhibits significant neuroprotective properties in the 6-OHDA-induced rat model of PD. The treatment improved motor functions, reduced oxidative stress, and attenuated neuroinflammation. These findings suggest that formononetin could be a promising therapeutic candidate for Parkinson's disease.

Virtual EP - 035

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TARGETING COX-2 AS A POTENTIAL BLOOD BASED BIOMARKER AND A THERAPEUTIC APPROACH IN ALZHEIMER'S DISEASE

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Aims: The study aimed to evaluate the concentration of COX-2 and NFkB p50 in serum of AD, Mild Cognitive Impairment (MCI) and Geriatric Control (GC) and to establish it as a blood based biomarker for early diagnosis and its therapeutic implications.
Methods: The level of proteins and their mRNA in blood of study groups were measured by surface plasmon resonance (SPR) and further validated by western blot and quantitative polymerase chain reaction (qPCR), respectively. The binding of designed peptide with COX-2 was confirmed by SPR. Also, the rescue of neurotoxicity by peptide was checked by MTT assay on SH-SY5Y cells (neuroblastoma cell line).
Results: Proteins and mRNA levels were found to be highly expressed in the blood sample of AD and MCI compared to GC subjects. However, level of COX-2 decreases with disease duration. The peptide showed binding affinity with COX-2 with low dissociation constant in SPR and rescued the neurotoxicity of SH-SY5Y cells by decreasing the level of Aβ, Tau and pTau proteins.
Conclusions: It can be concluded that COX-2 protein can serve as a potential blood-based biomarker for early detection and can be a good platform for therapeutic intervention for AD.

Virtual EP - 036

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AMELIORATING ALZHEIMER'S DISEASE AND RELATED DEMENTIA (ADRD) WITH A NOVEL SMALL MOLECULE AMADORIN IN THREE AD TRANSGENIC MOUSE INTERVENTION MODELS

Raja Khalifah[1], Corinne Jolivalt[2], Saleheh Jahani[2], Lucie Guernsey[2], Seyed Alireza Tayarani Hajian[2], Alexandra Marquez[2]
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Aims: Advanced glycation end-products (AGE*)* formation is an established pathogenic factor in Alzheimer's disease (AD) progression, impacting putative pathogenic mechanisms involving both amyloid beta and tau. Our objectives were to test efficacy of a brain penetrant "Amadorin" drug candidate PTG-630, a potent inhibitor of AGE formation through reducing oxidation catalysis by redox metal ions, in AD mouse models.
Methods: We evaluated the therapeutic potential of PTG-630 in reversing established cognitive dysfunction and neurodegeneration in three established transgenic mouse models of AD, females and males. To mirror the most likely clinical use as an AD/ADRD therapeutic, treatment with PTG-630 (in drinking water) was started only when CNS dysfunctions were established. Studies were performed using: (1) mouse overexpressing human non-mutant tau (htau); (2) mouse with a mutant form of APP (Tg2576); and (3) a triple transgenic (3xTg) mouse overexpressing mutant APP, mutant tau, and mutant presenilin. Barnes maze and object recognition tests were performed before the start of treatment and every 6 weeks thereafter. Brains were collected at termination for Western blot analysis and immunohistology.
Results: Twenty-four weeks of treatment with PTG-630, started after cognitive deficits were apparent, significantly improved learning and memory in the Barnes maze and the object recognition tests in the 3 mouse models. This was accompanied by reduction of phosphorylated tau and soluble amyloid beta in the hippocampus, respective to the model. AGE staining for carboxymethyl lysine (CML) was diminished in the pyramidal cells of the hippocampus of mice treated with PTG-630.
Conclusions: Daily treatment with PTG-630 for 6 months improved cognitive deficits and CNS markers with target engagement in AD mouse models comprising tau, amyloid beta, or both. PTG-630 is a promising disease-modifying drug candidate against ADRD.

Virtual EP - 037

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SYSTEMS GENETICS APPROACH TO DISCOVER AND VALIDATE RESILIENCE-BASED THERAPEUTICS FOR AD PREVENTION

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Aims: Genetic makeup plays a large role in Alzheimer's disease (AD) cognitive trajectory, but has largely been understudied. Importantly, traditional AD mouse models do not recapitulate the range of severity and age at onset of human AD, in part due to lack of genetic diversity. To model AD symptom variability observed in humans and identify causal, translatable genetic variants that confer cognitive resilience to AD, we developed a genetically diverse AD mouse model (AD-BXD).
Methods: We leveraged multi-omic and experimental approaches to find novel, druggable molecular mechanisms underlying cognitive resilience to AD in the frontal cortex. We interrogated conserved resilience-associated gene expression signatures using a cross-species snRNA-seq dataset from human ROSMAP and AD-BXD mice. We then conducted an unbiased search of cell culture responses to FDA-approved drugs to nominate candidate therapeutics to promote resilience gene expression. Given the limitations of transcriptomics, we used a data-independent acquisition (DIA) proteomic approach to comprehensively profile the AD-BXD frontal cortex and nominate genetic variants mediating expression of resilience-associated proteins.
Results: Our transcriptomic analysis revealed resilience gene expression signatures in excitatory and inhibitory neurons and nominated anti-diabetes drugs miglitol and metformin as resilience gene-promoting candidates, and our preliminary in vivo results show that miglitol is brain penetrant. The proteomics study nominated resilience-linked genetic variants that mediate expression of Ces1, a group of proteins involved in lipid metabolism, also expressed in excitatory neurons.
Conclusions: Our work has established preliminary understandings of genetic factors and primary cell types contributing to cognitive resilience to AD. We are currently leveraging derived neurons, astrocytes, and microglia from resilient and susceptible AD-BXD embryonic stem cell lines to characterize cellular mechanisms underlying genetic modifiers of cognitive resilience, and screen candidate resilience-promoting therapeutics.

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AUTOLOGOUS ADIPOSE-DERIVED MESENCHYMAL STEM CELL THERAPY FOR COGNITIVE IMPAIRMENT: A PIONEERING STUDY AT A PUBLIC HOSPITAL IN JAPAN

Masahiro Yasuhara[1], Kazuo Shigematsu[2], Tadaaki Kamitani[2], Satoshi Takatsuka[2], Hisakazu Yamagishi[3]
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Aims: This study aims to evaluate the safety and efficacy of autologous adipose-derived mesenchymal stem cell (ADSC) therapy for cognitive impairment in a public hospital setting. Specific objectives include: 1) Assessing changes in cognitive function using standardized scales following ADSC infusions. 2) Monitoring safety and adverse events associated with ADSC therapy. 3) Exploring potential biomarkers of treatment response, including amyloid-β levels and PET imaging results. 4) Evaluating the feasibility and challenges of implementing advanced regenerative medicine in a public healthcare institution. 5) Gathering preliminary data to inform future larger-scale clinical trials in this field.
Methods: This is a prospective, open-label, single-arm study. Patients aged 40-90 with diagnosed cognitive impairment will receive intravenous infusions of autologous ADSCs. Patients will receive 3-6 infusions of $5.0\times10^{\wedge7}$ to $1.5\times10^{\wedge8}$ cells at monthly intervals, with additional infusions possible based on clinical judgment. Cognitive function will be assessed using standardized scales (MMSE, MoCA-J) before treatment, after each infusion, and two months after the final infusion. Safety will be monitored throughout the study.
Results: We expect to observe: 1) Gradual improvement in MMSE and MoCA-J scores, particularly in patients with mild to moderate impairment. 2) Potential stabilization or slowing of cognitive decline in more severe cases. 3) Possible reduction in amyloid accumulation as measured by PET imaging in a subset of patients. 4) Changes in blood amyloid-β levels, potentially indicating increased clearance. 5) A favorable safety profile with minimal adverse events related to ADSC infusions.
Conclusions: This pioneering study at Yasaka Hospital represents a significant milestone in the field of regenerative medicine for cognitive impairment. By implementing autologous adipose-derived mesenchymal stem cell (ADSC) therapy in a public hospital setting, we are bridging the gap between cutting-edge research and accessible healthcare.

Virtual EP - 039

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NEUROPROTECTIVE ACTION OF CDNF THROUGH REGULATION OF UPR SENSORS.

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Aims: Cerebral dopamine neurotrophic factor (CDNF) promotes dopamine (DA) neuron survival in animal models of Parkinson's disease (PD). Recently, CDNF passed phase I-II clinical trials for PD treatment, yet its molecular mechanism remains unclear. CDNF, part of an evolutionarily conserved family of neurotrophic factors, primarily acts within cells, particularly in the endoplasmic reticulum (ER), where it regulates the unfolded protein response (UPR). Moreover, CDNF has shown promising potential in reducing α-synuclein cell entry, mitigating aggregation, and enhancing locomotor behavior in a mouse model of PD. This study aimed to identify CDNF receptors, characterize their signaling pathways, and understand its molecular mechanisms.
Methods: Using microscale thermophoresis (MST) and bimolecular fluorescence assay (BiFC), we identified interactions between CDNF and UPR sensors (IRE1α, ATF6, PERK) and the ER chaperone BiP (GRP78). The crystal structure of the C-terminal domain of CDNF complexed with nucleotide-binding domain of BiP was solved. Further investigations with pull-down and size-exclusion chromatography (SEC) confirmed interaction of CDNF with BiP, indicating CDNF acts as a cofactor. Mutant CDNF variants with altered binding sites were generated and analyzed for binding to BiP using MST and BiFC assays in cells.
Results: CDNF mutants showed complete or partial loss of BiP binding while maintaining binding to IRE1α and PERK. Some mutants retained their survival-promoting effects on induced pluripotent stem cell-derived (iPSC-derived) human midbrain DA neurons subjected to 6-hydroxydopamine-induced damage. These findings suggest that interaction of CDNF with UPR sensors, rather than BiP, underlies its pro-survival activity in DA neurons.
Conclusions: Our data highlight role of CDNF in the ER stress response and UPR regulation. Understanding these precise molecular interactions will pave the way for developing CDNF-based therapeutics and enhancing the efficacy of existing treatments for PD.

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Virtual EP - 040

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TOWARDS A NEW GENERATION OF ANTI-AMYLOID AGENTS: THE ORALLY ADMINISTRATED ABETA-OLIGOMER INTERACTING PEPTIDE IN THERAPEUTIC PREVENTION

Hedi Zhou[1], Adeola Shobo[2], Mark Hancock[2], Fatima Ansari[2], Sara Touj[3], Medhinee Malvankar[3], Pei Wu[2], Louis-Charles Masson[2], Thierry Choquette[2], M. Mallar Chakravarty[4,5], Rebecca Mckinney[2], Gerhard Multhaup[2]
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Aims: In a multidisciplinary and highly translational approach, we tested the potential of an Aβ-Interacting Peptide (AIP) as a new anti-amyloid preventive strategy targeting Aβ accumulation as the primary event in Alzheimer disease (AD) pathogenesis. Over the past decade, we have evaluated the safety and efficacy of protease resistant D-amino acid AIP (D-AIP). D-AIP selectively binds to soluble oligomers of Aβ42 *in vitro* (Barucker et al. 2015), neutralizes Aβ42 oligomer toxicity in *Drospohila* models (Zhong et al. 2019), crosses the BBB (Shobo et al. 2022), and forms heteromeric complexes with toxic Aβ oligomers in the brains of 3xTg-AD mouse. Here, we investigated effects of D-AIP on Aβpathogenesis in 3xTg-AD mice.
Methods: 3xTg mice were orally treated with D-AIP from 4 to 6-months-old. Liquid chromatography mass spectrometry was used to detect and quantify D-AIP in brain homogenates and plasma. D-AIP and Aβ42 oligomers were localized in 3xTg brains by matrix-assisted laser desorption ionization mass spectrometry imaging. Immunohistochemistry was used to track amyloid pathology, microglia and astrocyte reactivity in brain sections. An ultrasensitive Meso Scale Discovery immunoassay was used to quantify Aβ species and follow the progression of amyloid deposition.
Results: Orally dosed D-AIP possessed favourable biostability, pharmacokinetics, and brain region distribution. Notably, D-AIP treatment attenuated plaque amyloid pathology and neuroinflammation at the lag-phase of amyloid aggregation in male and female 3xTg mice. Additionally, behaviour and structural analysis showed that D-AIP treatment had no adverse effects on memory and cognition.
Conclusions: Our findings demonstrate that D-AIP oral administration effectively targeted Aβ oligomers and prevented AD-associated deposition and neurotoxicity in an AD mouse model at very early stages of amyloid deposition. Since D-AIP had no observable adverse effect, can be orally delivered and is low-priced in manufacture, D-AIP shows great promise as a next-generation therapeutic for AD.

Virtual EP - 041

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EFFECTS OF AUTOLOGOUS SERUM ON TREM2 AND APOE IN A PERSONALIZED ALZHEIMER'S PATIENT-DERIVED ASSAY

Nicoleta Carmen Cosma, Neriman Eren, Berk Üsekes, Susanna Gerike, Oliver Peters, Julian Hellmann-Regen
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Aims: Age-related deterioration of the immune system to a chronic low-grade inflammatory state has been implicated in the pathogenesis of late-onset Alzheimer's diesease (AD). The triggering receptor expressed on myeloid cells 2 (TREM2) and it's ligant Apolipoprotein E (APOE) play a key role in amyloid beta (Aβ) clearance, underscoring their relevance in AD. Whether TREM2 expression can be modulated in the aged macrophage population and the influence of the patient's own milieu on the TREM2 and APOE is not sufficiently understood.
Methods: Using cells from AD-patients and matched controls (CO), we first designed a monocyte-derived macrophages (Mo-MΦs) assay to assess the individualized TREM2 synthesis in vitro. In a second step we assessed the influence of each participant's own milieu, by examining the effect of short- (1 day) and long- (10 days) term differentiation of the cells in the presence of the donor´s autologous serum (AS) into M1-, M2- or M0-macrophages. Sex differences and Aβ-uptake were assessed.
Results: In short-term differentiated M2-macrophages we observed increased TREM2 synthesis in CO- but not AD-derived cells. Long-term M2- and M0- differentiation resulted in an increase of TREM2 in both AD and CO while M1-differentiation increased TREM2 in AD-cells only. AS decreased APOE levels in M2- but increased levels in M1-macrophages. Higher TREM2 and lower APOE levels were detected in female vs. male AD cells. Aβ-uptake was decreased in long-term differentiated CO- and AD-derived cells particularly in APOEε4(+) carriers.
Conclusions: This study presents, for the first time, a personalized Mo-MΦ cell culture assay for functionally studying TREM2 and APOE in the context of a patient's own aged milieu. Our approach offers a promising tool for future diagnostic and therapeutic research in personalized medicine, especially in the context of AD.

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INVESTIGATING MICROGLIAL MECHANORECEPTOR MEDIATED AMYLOID BETA CLEARANCE IN ALZHEIMER'S DISEASE

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Aims: Mechanoreceptors respond to changes in mechanical pressure or distortion within a biological environment. Piezo1, an abundant mechanoreceptor expressed in microglia, plays a crucial role in clearing amyloid beta from the brain. We are investigating the mechanism behind Piezo1-mediated clearance of amyloid beta in an Alzheimer's disease model. Additionally, we are exploring the expression of other potential mechanoreceptors in microglia.
Methods: The experiments are conducted using cell lines and primary microglia isolated from post-natal pup brains. We have shortlisted several mechanoreceptors based on literature and our existing scRNAseq data from microglia. This shortlist is being validated through qPCR and immunocytochemistry. To study phagocytosis, the cells will be stimulated with a mechanoreceptor agonist for 24 hours, followed by exposure to TAMRA-tagged amyloid beta 1-42 fibrils for 4 hours before FACS analysis or fluorescence measurement using a spectrophotometer.
Results: From the initial qPCR data, we found that Piezo1 is abundantly expressed among mechanoreceptors in microglia. Other mechanoreceptors, such as Trpv4, Kcnk4, and Asic3, are also expressed but at much lower levels. Upon activation of Piezo1 with the Yoda1 agonist, the phagocytosis of amyloid beta is enhanced. However, the underlying mechanism remains unclear and is yet to be defined.
Conclusions: Piezo1 is the abundant mechanoreceptor expressed in microglia, and its activation enhances phagocytosis, although the molecular mechanism remains unclear. A report suggests that Piezo1 acts through NF-κB-mediated inflammatory signaling upon LPS activation. We will investigate the immune response triggered by microglial Piezo1 and its impact on cellular health.

Virtual EP - 043

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ASTROCYTE-SPECIFIC KNOCKOUT OF P38ALPHA MAPK REDUCES NEUROINFLAMMATION AND ENHANCES SYNAPTIC STRENGTH IN THE CONTEXT OF NORMAL AGING

Caleb Bailey, Christopher Gant, Meggie Coleman, Verda Davis, Hilaree Frazier, Christopher Norris, Linda Van Eldik, David Braun
University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: Exciting recent developments indicate that preservation of cognition during the development of Alzheimer's disease (AD) depends upon severing the link between initial amyloid accumulation and later tau involvement. Multiple lines of evidence indicate that aberrant astrocyte activation is a critical link in this causal chain, one that is accessible to non-invasive biomarker detection. Work from our lab and others suggests that one regulator of astrocyte activation, the stress kinase p38α MAPK, may be crucial. We are in the process of defining how astrocyte p38alpha is involved in modulating astrocyte phenotypes and corresponding neural function in the context of aging and AD.
Methods: Mice at 3 months of age underwent astrocyte-specific knockout of p38α. The mice were allowed to age to at least 12 months, and up to 22 months, prior to undergoing assessments including: memory and motor performance, synaptic function, neuroinflammatory changes, and metabolic alterations.
Results: In aged mice (18+ months) the loss of astrocyte p38α was associated with reduced hippocampal neuroinflammation and increased synaptic strength, but only in female mice. Additionally, the knockout affected locomotor function but not hippocampal-dependent short-term memory by 12 months of age. Further, these changes were associated with an increase in uncoupled respiration in mitochondria. Interestingly, there was no change in overall GFAP staining.
Conclusions: Loss of astrocyte p38alpha can preserve neuroinflammatory and synaptic changes associated with normal aging in female mice, likely due to their enhanced neuroinflammation and reduced synaptic strength relative to males. Whether this is true in the context of AD-type neuropathological change, regardless of sex, is unknown. This question is the subject of ongoing studies of astrocyte p38α knockout during various stages of amyloid accumulation and associated glial activation.

Virtual EP - 044

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DIFFERENCES IN BODY COMPOSITION AMONG PATIENTS WITH SPORADIC AND IATROGENIC CEREBRAL AMYLOID ANGIOPATHY

Camilla Strazzabosco, Benedetta Storti, Giulia Marinoni, Carolina De Toma, Isabella Canavero, Estaban Zacarias Mateos, Nicola Rifino, Giorgio Boncoraglio, Anna Bersano
Fondazione IRCCS Istituto Neurologico Carlo Besta, Cerebrovascular Unit, Milano, Italy

Aims: Cerebrovascular disease is linked to body composition, as excess visceral body fat raises the risk of stroke by contributing to hypertension, inflammation, and metabolic imbalances. The aim of the study is to evaluate differences in body composition between patients with sporadic cerebral amyloid angiopathy (CAA) and iatrogenic CAA (iCAA).
Methods: Given the differences in body composition based on sex, only male patients affected by CAA or iCAA with an available body circumferences and skinfold measurements were recruited. Clinical characteristics, anthropometric measurements and nutritional assessment were analysed (**Graph1**). A p-value < 0.05, based on a two-tailed test Student's t-test, was considered statistically significant.

		CAA (n = 14)	iCAA (n = 7)	p- Value
Patient feature				
Age at onset of first symptor	**M ± DS (years)**	**71.75 ± 7.44**	**57.66 ± 10.85**	**0.004**
Weight	M ± DS (Kg)	74.08 ± 10.38	69.31 ± 9.23	0.251
Height	M ± DS (cm)	174.00 6.212	171.05 ± 5.94	0.310
BMI	M ± DS (Kg/m²)	24.93 ± 3.06	24.33 ± 3.67	0.684
Risk Factor				
Hypertension	%	28.57	57.14	
Dyslipidemia	%	50	57.14	
Alcohol consumption				
Rare	%	57.14	100	
Moderate	%	7.14	0	
High	%	35.71	0	
Smoking				
Non-smoker	%	57.14	85.71	
Ex-smoker	%	35.71	14.28	
Current smoker	%	7.14	0	
History of cerebrovascular events				
TFNEs	%	14.28	14.28	
Transient ischemic attack	%	0	42.85	
Stroke	%	71.42	85.71	
Risk of malnutrition				
Yes	%	57.14	57.15	
No	%	42.85	42.86	
Adherence to the Mediterranean Diet				
Low	%	21.42	78.57	
Moderate	%	0	85.71	
High	%	14.28	0	
Body circumferences				
Arm	**M ± DS (cm)**	**28.13 ± 2.71**	**29.86 ±1.03**	**0.049**
Waist	M ± DS (cm)	101.58 ± 8.57	93.56 ± 9.79	0.091
Hips	M ± DS (cm)	97.07 ± 21.25	99.08 ± 3.50	0.726
Calf	M ± DS (cm)	34.24 ± 2.76	34.22 ± 2.33	0.987
Skinfolds				
Bicipital	M ± DS (mm)	5.86 ± 2.05	6.15 ± 1.06	0.661
Tricipital	M ± DS (mm)	9.53 ± 3.31	16.02 ± 2.54	0.601
Subscapular	M ± DS (mm)	14.39 ± 3.84	16.02 ± 2.54	0.261
Suprailiac	M ± DS (mm)	16.08 ± 7.28	17.5 ± 4.58	0.593
Body Composition				
Body density	**M ± DS (Kg/L)**	**1.04 ± 0.01**	**1.03 ± 0.007**	**0.005**
% FM	**M ± DS (%)**	**24.26 ± 4.58**	**29.82 ± 3.25**	**0.005**
Kg Fat Mass	M ± DS (Kg)	18.60 ± 5.80	21.04 ± 3.59	0.243
Kg Fat Free Mass	**M ± DS (Kg)**	**56.81 ± 5.20**	**49.22 ± 4.14**	**0.002**

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Kg Fat Mass	M ± DS (Kg)	18.60 ± 5.80	21.04 ± 3.59	0.243
Kg Fat Free Mass	**M ± DS (Kg)**	**56.81 ± 5.20**	**49.22 ± 4.14**	**0.002**

Results: Seven patients with iCAA and 14 with CAA were recruited. CAA patients were older at symptom onset (68.4 ± 8.0 years vs. 51.7 ± 10.0 years; $p < 0.01$). They also had a smaller arm circumference (28.1 ± 2.7 cm vs. 29.9 ± 1.0 cm; $p < 0.05$), higher body density (1.04 ± 0.01 kg/L vs. 1.03 ± 0.007 kg/L; $p < 0.01$), lower fat mass percentage (24.3 ± 4.6% vs. 29.8 ± 3.3%; $p < 0.01$), and greater lean body mass (56.8 ± 5.2 kg vs. 49.2 ± 4.1 kg; $p < 0.01$). No statistically significant difference was found in fat mass in kilograms.

Conclusions: Male patients with CAA and iCAA may differ in body composition, suggesting potential implications for clinical management and therapeutic strategies. Typically, a reduction in lean body mass is expected with age, especially in males. However, an inverse relationship between age and body composition

was observed in this study. Taking into account the influence of sex on body composition, in future studies it will be necessary to examine the same variables in female patient groups.

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A MULTI-TARGET THERAPY TO REDUCE DISEASE PROGRESSION AND RESTORE COGNITIVE FUNCTIONS OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) involves multiple pathological mechanisms, including Aβ aggregation, neuroinflammation and neuronal cell death, leading to cognitive decline. We present STM-003, a novel drug, targeting all these mechanisms to retard disease progression and improve cognitive function in AD.
Methods: STM-003 was administered intravenously to 3xTg AD mice (>12 months old) twice weekly for six weeks, with wild-type and untreated AD mice as controls. Cognitive behaviors were evaluated using the Morris water maze and tail suspension tests. Brain activity and structural changes were assessed using 18F-FDG PET and MRI. Mechanism studies included microglial polarization (flow cytometry), cytokine modulation (qPCR, ELISA), Aβ plaque reduction (Congo red staining, ELISA), and neuron viability assays in hippocampal HT-22 cells.
Results: STM-003 improved cognitive performance shown by water maze escape latency from 56 sec to 20 sec and tail suspension inactivity from 68% to 37%. 18F-FDG PET showed increased cortex and hippocampus activity (normalized uptake values: cortex from 931 to 1745, hippocampus from 838 to 1526). MRI showed 6.4% increase in the brain volume. Mechanism studies demonstrated a shift in microglia polarization from the pro-inflammatory M1 state to the anti-inflammatory M2 state, characterized by decreased CD14, CD86, CD80 and increased CD163, CD206 expression. Decreased TNF-α and increased TGF-β confirm the alleviated neuroinflammation. STM-003 reduced plaque burden from 1.3% to 0.03%, and lowered Aβ42/40 ratio from 8.5 to 7.4 in the brain. Additionally, STM-003 enhanced neuronal cell proliferation by 30%, and reduced oxidative stress, and mitigated Aβ-induced neuronal death.
Conclusions: STM-003 demonstrated in an AD mouse model the multifunctional efficacies in retarding the disease progression and recovering the cognitive behavior. These findings position STM-003 as a promising therapeutic candidate for both early- and late-stage Alzheimer's disease.

Virtual EP - 046

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LECANEMAB LONG-TERM EFFICACY AND SAFETY IN THE ASIA REGION: A SUBGROUP ANALYSIS FROM THE PHASE 3 CLARITY AD TRIAL

Christopher Chen[1], Kentaro Torii[2], Masaki Nakagawa[2], Tomoo Ogawa[2], David Li[3], Amitabh Dash[4], Shobha Dhadda[3], Steven Hersch[3], Michael Irizarry[3], Lynn Kramer[3]
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Aims: To evaluate the long-term efficacy and safety of lecanemab from the Asia region of the open-label extension phase (OLE) of Clarity AD.
Methods: Clarity AD is an 18-month, randomized study (core) in patients with early AD, followed by an OLE phase where all eligible participants received open-label lecanemab. Clinical (CDR-SB, ADAS-Cog14, and ADCS MCI-ADL) and safety outcomes measures were evaluated overall as well as by examining 'delayed start' (core:placebo followed by OLE:lecanemab) and 'early start' (core:lecanemab followed by OLE:lecanemab) cohorts. Time to worsening on CDR-SB over 36 months was assessed through changes in AD severity stages. Analyses were conducted in the Asia region subgroup.
Results: Out of 294 subjects in the Asia region of Clarity AD (Japan:152; Korea:129; Singapore:13), 275 entered the OLE phase. There was a slowing decline of 25% with lecanemab in CDR-SB at 18 months compared to placebo (adjusted mean difference: -0.349; 95% confidence intervals: -0.773, 0.076). Lecanemab-treated participants continued to accrue benefit through 36 months. Participants who started lecanemab early, sustained cognitive benefits through 36 months, while delayed start participants did not catch up to the early start group. Similar results were observed for ADAS-Cog14 and ADCS MCI-ADL scores. Lecanemab also delayed progression to more severe AD stages. Continued lecanemab use was well tolerated with no new safety signals in the Asia region. After first six months, ARIA rates are low and similar to ARIA rates on placebo, with no association to accelerated long-term progression.

Conclusions: The efficacy and safety profile of lecanemab was maintained with continuous treatment beyond 18 months. The delayed start lecanemab group does not catch up to early start lecanemab group, reflecting importance of early treatment initiation, and Asia region was similar to the overall population.

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NATIVE HAWAIIAN AND PACIFIC ISLANDER PARTICIPATION IN ALZHEIMER'S DISEASE CLINICAL TRIALS: EXPLORATION OF ZIP CODE BASED HEAT MAP PATTERNS

Nina Krupa[1,2], Kylie Herndon[1], Kaelyn Pacpaco[1], D-Dré Wright[1,2], Ryan Nakamura[1,2], Anita Cheung[1,2], Anson Lee[1,2], Julia Jahansooz[1,2], Masako Matsunaga[2], Samuel Kim[1], Enrique Carrazana[2], Kore Liow[1,2]
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Aims: Alzheimer's Disease (AD) is the most common neurodegenerative disorder in the United States, and it disproportionately burdens minority populations. Previous research demonstrated that Asian and Native Hawaiian patients were less likely than White patients to participate in AD clinical trials. Native Hawaiians and Pacific Islanders (NHPI) make up 27% of the population in Hawaii and 0.5% of the United States population. The goal of this study was to determine what percentage of AD clinical trial participants were NHPI, as well as patterns in their demographics.
Methods: A retrospective chart review of AD patients (ICD G31.84) who participated in AD clinical trials at two outpatient neurological clinics between the year 2020 and 2024 was conducted. One-way ANOVA or Kruskal-Wallis rank sum test for continuous variables and Fisher's Exact Test or Pearson's Chi-squared test for categorical variables were used to examine differences across racial groups. ZIP code heat maps were used to depict participation of various ethnocultural racial groups.
Results: Total of 244 patients participated in AD clinical trials. Overall, White patients had the highest percentage of participation (31%), followed by Asians (24%), and NHPI (10%) patients. Based on ZIP code heat maps the three ethnocultural racial groups had different patterns of referral to AD clinical trials. NHPI patients represented, on average, the youngest group diagnosed with AD at 71 years old (p=0.01).
Conclusions: In a majority minority state like Hawaii, the NHPI population makes up 20% of the population in this memory clinic, however, they are under-represented in participation in AD clinical trials (10%). ZIP code-based heat maps can provide insights into the pattern of referrals and clinical trial participation for NHPI as well as to their counterparts.

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THE ROLE OF COGNITIVE WORKSHOPS AS AN ENRICHED ENVIRONMENT IN REDUCING COGNITIVE DEFICITS IN ELDERLY WITH DEMENTIA

Kamelija Horvatović[1,2,3], Gracia Grabarić[1], Jana Majdak[1], Lucija Malčić[4], Maja Miloš[5], Izidora Mustak[6], Angelika Pejić[1], Nela Perić[1], Tea Petrović[1], Korina Pervan[1], Mirna Rešetar[2]
[1]School of Medicine, University of Zagreb, Zagreb, Croatia, [2]Faculty of Science, University of Zagreb, Zagreb, Croatia, [3]Croatian Institute for Brain Research, Neuropsychopharmacology, Zagreb, Croatia, [4]Faculty of Humanities and Social Sciences, University of Zagreb, Zagreb, Croatia, [5]Faculty of Croatian Studies, University of Zagreb, Zagreb, Croatia, [6]Faculty of Education and Rehabilitation Sciences, University of Zagreb, Zagreb, Croatia

Aims: Recent evidence suggests that creative stimulation and enriched environment (EE) enhance cognitive functions in dementia patients. The "Remember Me" volunteering project explores and validates these findings in real-world settings. Throughout the academic year, a series of cognition-stimulating workshops were conducted in nursing homes for residents with dementia.
Methods: Our study involved 28 participants, including 17 individuals with dementia (DEM) and 11 controls (CTRL), divided into groups based on whether or not they attended weekly creative workshops, serving as a form of EE. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) at baseline and after 3 months of EE. The data analysis was performed by the Kruskal-Wallis test for correlation between groups, followed by the Uncorrected Dunn's post-hoc test for intergroup comparisons with a significance level of $p<0.05$. The Wilcoxon matched-pairs signed rank t-test was conducted for within-group comparison (pre- and post-intervention).
Results: A significant increase in the total MoCA scores was detected within the DEM+EE group (+18%,p=0.02) and the CTRL group (+12%,p=0.03) after 3 months, in contrast to decrement in the DEMw/oEE (-12%,p=0.13). Visuocontructional functions were most positively affected by EE, whereas the DEM+EE group showed a significant increment (+138%,p=0.03) compared to DEMw/oEE. EE also contributed to a slight improvement in delayed recall in the DEM+EE group (+22%,p=0.31), while in the DEMw/oEE, all participants' scores dropped to 0. EE further proved beneficial for orientation and attention among our participants.
Conclusions: The findings from this study highlight the potential of EE as a valuable non-pharmacological intervention for mitigating cognitive decline in dementia. These results underscore the importance of incorporating creative and enriching activities into the care protocols for individuals with dementia to enhance their cognitive health and quality of life.

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Virtual EP - 049

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ASSOCIATION OF CHOROID PLEXUS VOLUME AND PREECLAMPSIA : A PROSPECTIVE COHORT STUDY

Boyao Chen[1], Linfeng Yang[2], Tao Chen[2], Meng Li[3], Lingfei Guo[1], Na Wang[1,4], Xinyue Zhang[1], Zhenyu Cheng[4], Yiwen Chen[1], Pengcheng Liang[1], Xinxin Huo[1], Fushuai Zhang[4]
[1]Shandong Provincial Hospital Affiliated to Shandong First Medical University, Department Of Radiology, Jinan, China, [2]Jinan Maternity and Child Care Hospital Affiliated to Shandong First Medical University, Jinan, China, [3]Jena University Hospital, Department Of Psychiatry And Psychotherapy, Jena, Germany, [4]School of Medical Imaging, Binzhou Medical University, Jinan, China

Aims: This study aims to investigate alterations in choroid plexus volume (CPV) and susceptibility values of the choroid plexus obtained from quantitative susceptibility mapping (QSM) in patients with preeclampsia, focusing on the contributing factors of these alterations.
Methods: This study enrolled 270 participants, comprising 107 nonpregnant healthy controls (NPHC), 59 pregnant healthy controls (PHC), and 103 patients with preeclampsia. All participants were scanned on a 1.5-T MR scanner. The results of clinical characteristics were collected from all the participants. One-way ANOVA tests were used to analyze the differences in choroid plexus volume and susceptibility values of the choroid plexus among the three groups. Partial Pearson correlation analysis was used to detect the relationships between variables and these differences. In addition, receiver operating characteristic (ROC) analysis was employed to evaluate the diagnostic performance of the two imaging measures, by incorporating other clinical variables, various models were constructed.
Results: Patients with preeclampsia exhibited smaller CPV and higher susceptibility values of Chp compared to the other groups. Significant negative correlations were observed between body mass index (BMI), mean atrial pressure and CPV. Additionally, BMI, mean atrial pressure, hemoglobin, hematocrit were significantly related to susceptibility values of Chp. Compared with other models, the combination of CPV, susceptibility values of Chp, BMI and gestational week more effectively distinguished preeclampsia from healthy pregnancy group (AUC = 0.798, $P < 0.001$).

Table 1. Clinical characteristics of the participants.

Variables	NPHC n 107	PHC n 59	Preeclampsia n 103	F/t/ χ^2 value	P* value	P value (post hoc)		
						NPHC vs.Preeclampsia	PHC vs. Preeclampsia	NPHC vs. PHC
Age (years)	30.81±4.34	29.68±3.67	30.32±4.89	1.26	0.285[a]	-	-	-
Gestational week (week)	-	30.82±5.99	33.81±3.34	30.84	<0.001 [t]	-	-	-
Body Mass Index (kg/m²)	22.30±2.97	22.77±3.42	25.41±4.35	20.86	<0.001[a]	<0.001	<0.001	0.424
Systolic pressure (mmHg)	111.28±9.33	112.28±10.63	156.10±14.03	461.54	<0.001[a]	<0.001	<0.001	0.600
Diastolic pressure (mmHg)	69.36±8.09	71.74±7.52	100.45±9.02	414.91	<0.001[a]	<0.001	<0.001	0.084
Mean atrial pressure (mmHg)	83.34±7.45	82.36±17.26	117.84±14.95	221.31	<0.001[a]	<0.001	<0.001	0.649
Hemoglobin (g/L)	128.21±10.35	115.70±13.08	124.78±11.90	21.90	<0.001[a]	0.034	<0.001	<0.001
Hematocrit (%)	39.55±2.83	35.29±3.55	37.74±3.37	33.105	<0.001[a]	<0.001	<0.001	<0.001
Platelet (10^9/L)	39.55±2.83	35.29±3.55	37.74±3.37	15.95	<0.001[a]	<0.001	0.279	0.001
Glucose (mmol/L)	4.66±0.50	4.50±0.38	4.76±0.96	2.62	0.075[a]	0.023	0.237	0.194
Creatinine (μmol /I.)	49.80±10.69	44.33±14.11	55.76±16.29	13.13	<0.001[a]	0.002	<0.001	0.016
ALT (U/L)	14.04±7.62	12.30±5.63	22.12±31.70	5.84	0.003	0.005	0.004	0.604
AST (U/L)	17.43±6.38	15.79±5.43	24.82±19.84	11.76	<0.001[a]	<0.001	<0.001	0.449
CPV(cm^3)	0.99±0.34	0.99±0.24	0.89±0.24	3.94	0.021	0.012	0.031	0.979
TIV(cm^3)	1383.91±141.73	139.50±129.18	138.35±121.57	0.17	0.845	-	-	-
CPV/eTIV($\times 10^{-3}$)	0.71±0.22	0.71±0.17	0.64±0.17	3.83	0.023	0.013	0.034	0.999
Susceptibility values of Chp [ppb($\times 10^{-9}$)]	3.80±11.98	5.12±9.84	11.67±11.78	13.33	<0.001[a]	<0.001	0.001	0.482

The data are presented as the means + standard deviations. [a]: ANOVA test; [t]: two-sample t test; NPHC: nonpregnant healthy control; PHC: pregnant healthy control; kg: kilograms; CPV: choroid plexus volume; eTIV: estimated total intracranial volume; Chp: choroid plexus. *FDR correction, P < 0.05.

Table 2. Determinants of susceptibility values: results of multiple stepwise linear regression analysis.

	Factors	β	Standardized β	T	P	R of Model	P of Model
CPV/eTIV	BMI	-9.464E-6	-0.19	-3.12	0.002	0.035	0.002
Susceptibility values of Chp	Group	4.29	0.32	5.47	<0.001		
	Hemoglobin	0.21	0.22	3.82	<0.001	0.13	<0.001
	Hematocrit	0.39	0.12	3.44	0.001		

Significant p values < 0.05.

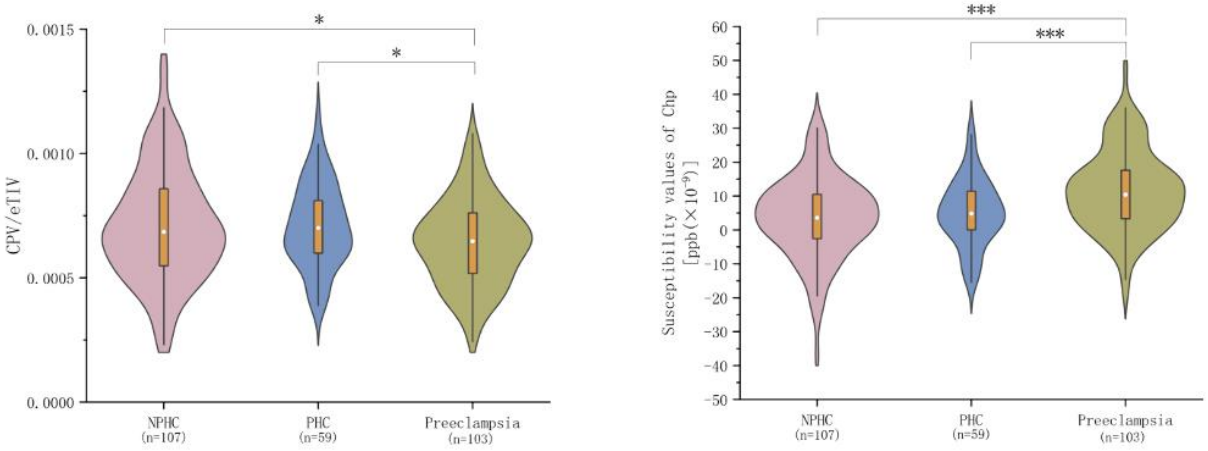

Figure1. Significant differences in CPV/eTIV and susceptibility values of Chp between the preeclampsia, NPHC and PHC groups. NPHC: nonpregnant healthy control; PHC: pregnant healthy control; PE: preeclampsia. *p<=0.05, **p<=0.01, ***p<=0.001.

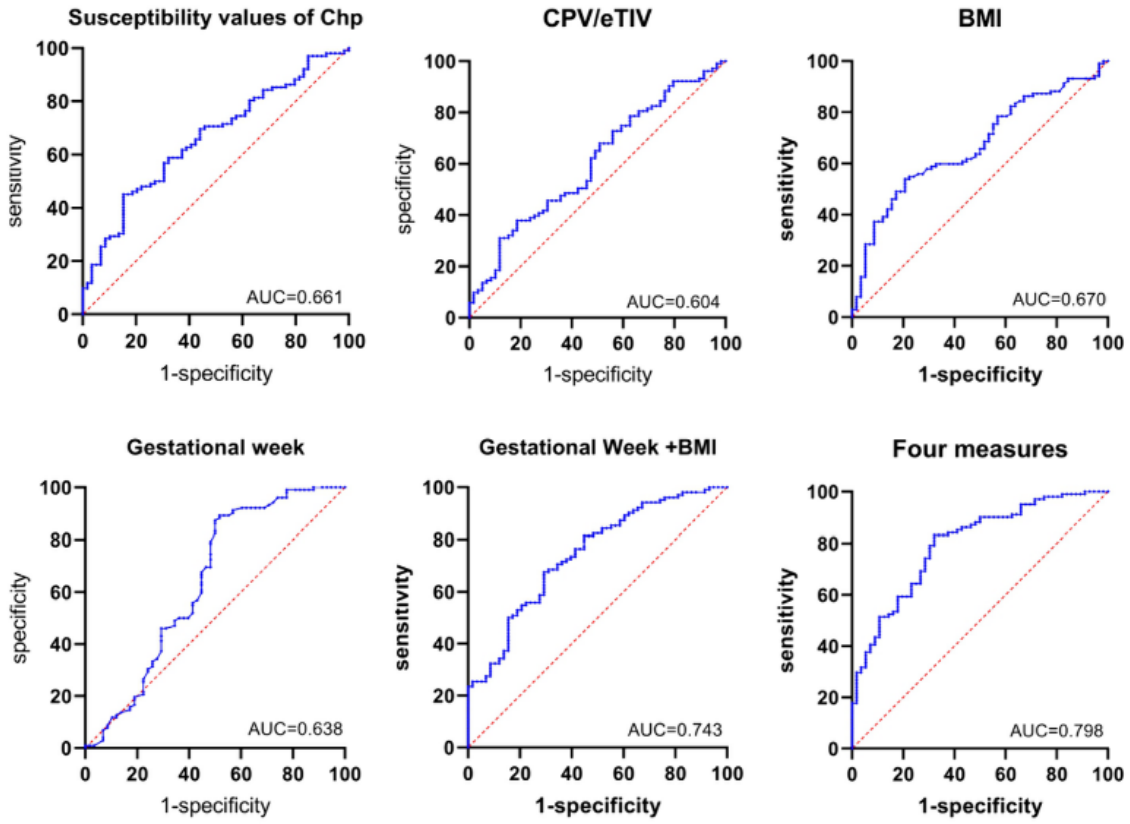

Figure3. Receiver operating characteristic (ROC) curves of the four measures for discriminating the preeclampsia from pregancy. The area under the curve (AUC) for the combination of four measures using logistic regression (CPV/eTIV, susceptibility values of Chp, BMI, gestational week) is greater than that of the combination of BMI and gestational week(AUC 0.798 vs.0.745, Z = -2.059, p = 0.039).

Table4. Diagnostic accuracy of susceptibility value of nucleus accumbens, gestational week and hematocrit to detect preeclampsia from pregancy

Test result variable(s)	AUC(95% CI)	p value	Cutoff value (%)	Sensitivity	Specificity
CPV/eTIV	0.600 (0.508 - 0.691)	0.039	1118.928	0.921	0.821
Susceptibility values of Chp	0.664 (0.578 - 0.749)	0.001	-3.868	0.858	0.850
Gestational week	0.628 (0.527 - 0.728)	0.008	22.575	1.000	0.875
BMI	0.712 (0.631 - 0.793)	<0.001	17.501	0.990	0.964
Gestational week+BMI	0.745 (0.666 - 0.824)	<0.001	0.234	0.990	0.929
Four measures*	0.798 (0.727 - 0.869)	<0.001	0.194	0.990	0.911

AUC, area under the curve; CI, confidence interval; BMI: Body Mass Index; Chp: choroid plexus. *logistic regression of CPV/eTIV, susceptibility values of Chp, BMI, gestational week.

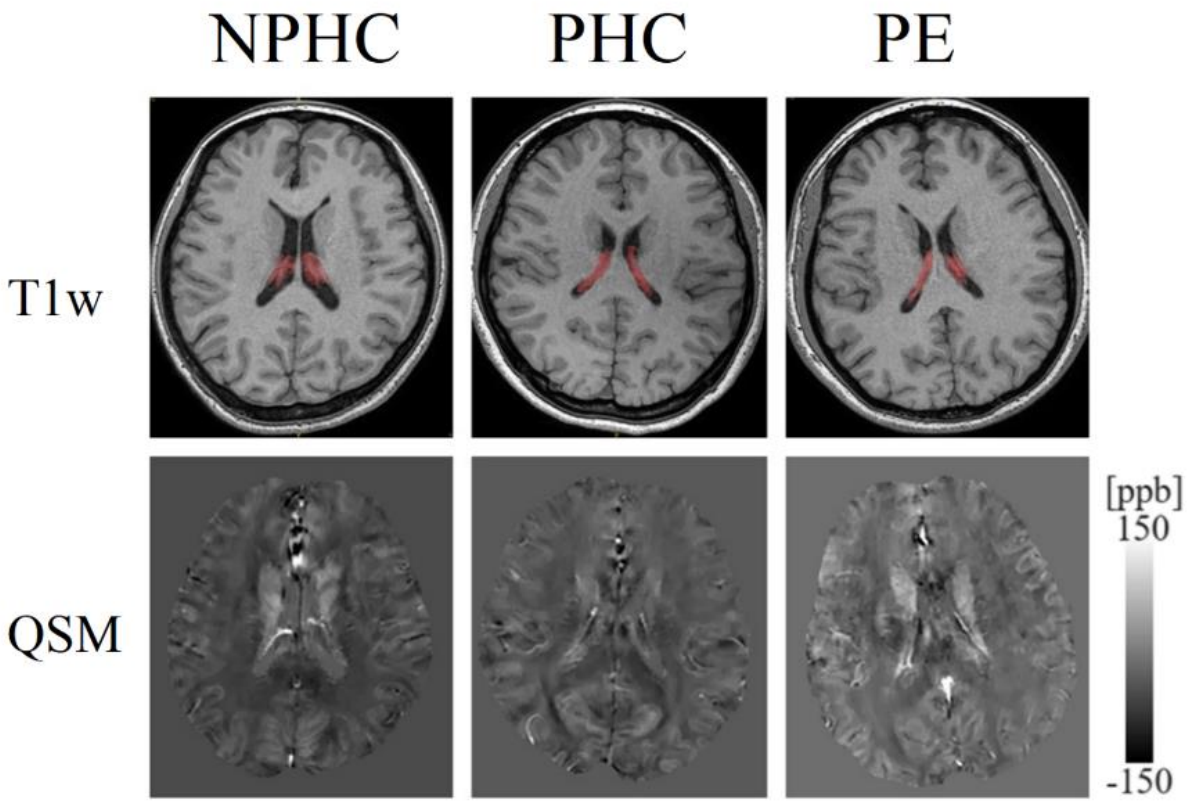

Figure4. Differences in CPV and susceptibility values of Chp among the three groups. The images are from example participants from the three groups (NPHC, PHC and Preeclampsia). The CPV of the preeclampsia patient is larger, and the susceptibility values of the Chp is greater in patients with preeclampsia.

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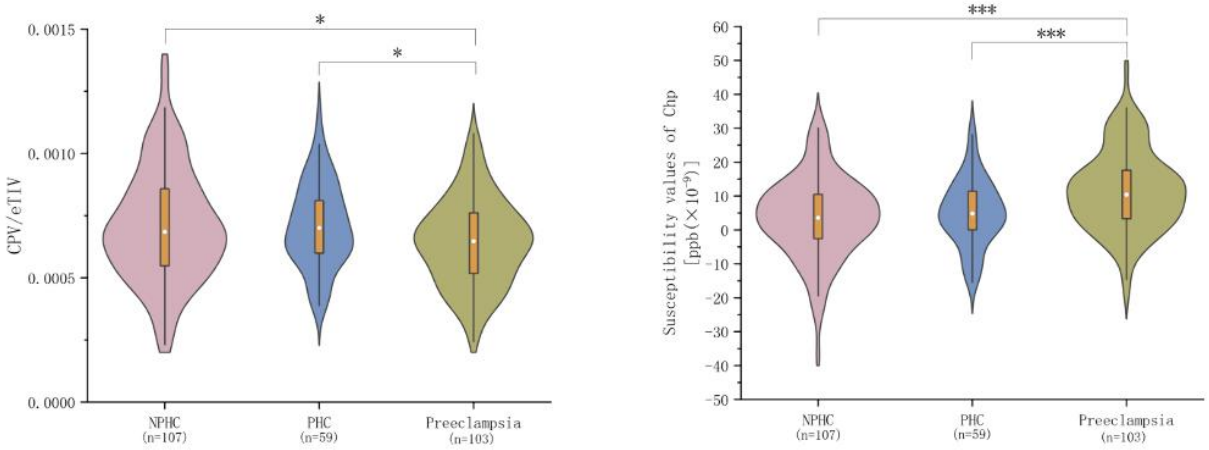

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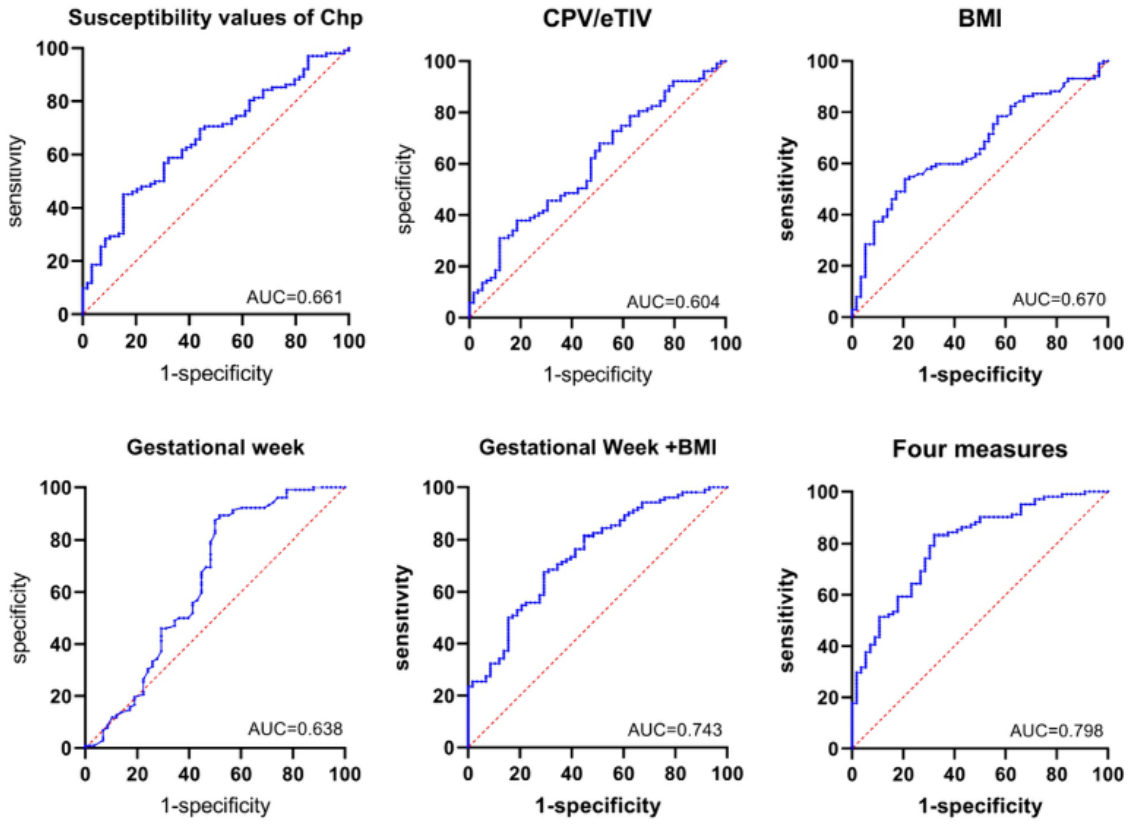

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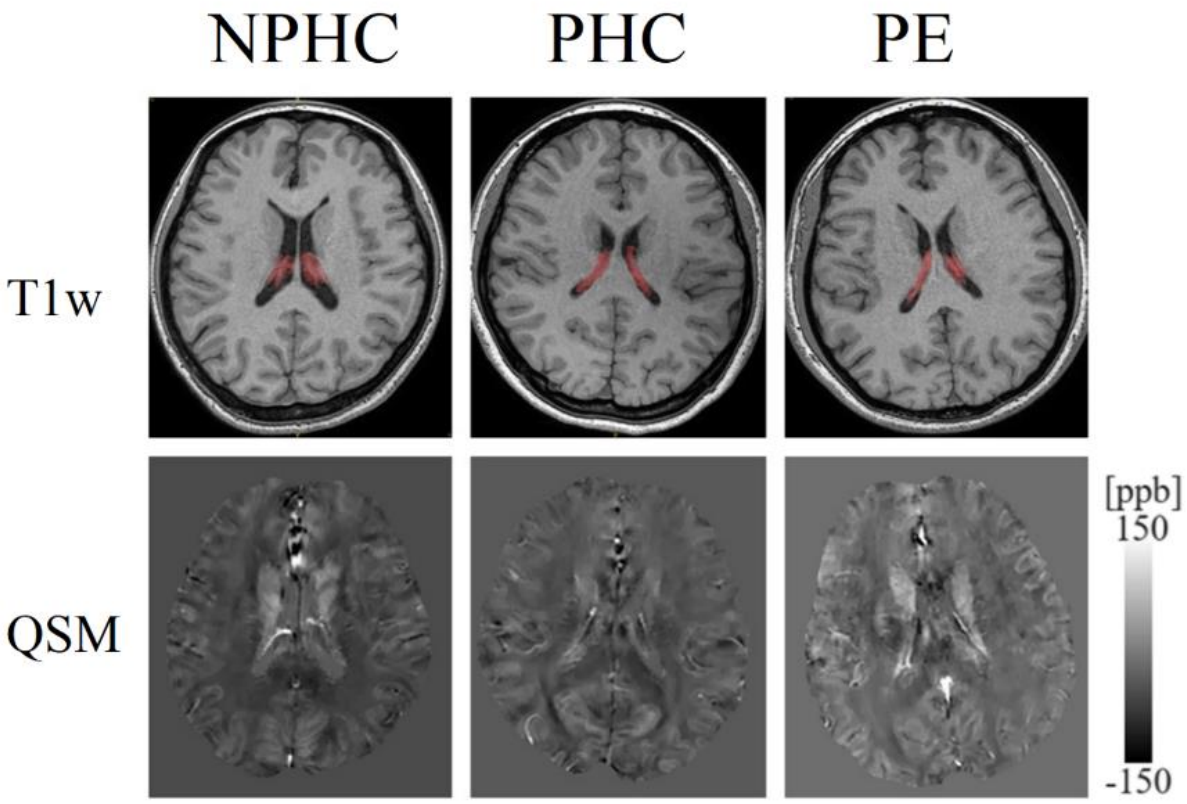

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Conclusions: In this study, we found that the glymphatic system impaired in patients with preeclampsia and that BMI, hemoglobin and hematocrit could be the influencing factors. Furthermore, by combining these two imaging measures with various clinical indicators, we developed a classification model for preeclampsia that not only facilitates early diagnosis but also provides a theoretical foundation for subsequent treatment.

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Virtual EP - 050

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COMPARISON OF SEMI-QUANTITATIVE AMYLOID PET VISUAL ASSESSMENT AND THE CENTILOID SCALE IN CLINICAL PRACTICE AND BORDERLINE CASES ANALYSIS

Jiří Cerman[1], Adéla Škorvagová[2], Štěpán Kozák[3], Aleš Kavka[3], Kamila Dvořák[4], Jakub Hort[2]
[1]Charles University, 2nd Faculty of Medicine, Department Of Neurology, Praha, Czech Republic, [2]Second Faculty of Medicine, Charles University, Motol University Hospital, Memory Clinic, Department Of Neurology, Prague, Czech Republic, [3]Department of Nuclear Medicine –, Praha, Czech Republic, [4]Czech Technical University in Prague, Faculty Of Biomedical Engineering, Kladno, Czech Republic

Aims: With the advent of new therapies for Alzheimer's disease (AD) that target the amyloid beta (Aβ) protein, early and accurate diagnosis is essential, as reflected in new diagnostic criteria that define the disease biologically using biomarkers. Amyloid PET is a non-invasive method to visualise cortical Aβ. PET images are usually scored either negative or positive, but there are also semi-quantitative assessment methods based on the presence of subcortical Aβ (stage 0 = negative, stage 1 = positive cortex, negative striatum, stage 2 = positive cortex and striatum). Among the quantitative assessment methods, the most widely used is the centiloid scale (CL), which can help to differentiate AD from other dementias. The aim of this study was to compare semi-quantitative visual assessment with automated quantitative assessment of amyloid PET using CL in clinical practice and to analyse borderline cases (stage 1).
Methods: We retrospectively analysed a cohort of 177 patients from the Czech Brain Aging Study, who underwent flutemetamol amyloid PET. Images were evaluated visually and semiquantitatively by two nuclear medicine physicians. Quantification was performed using Neurona PET software according to the published CL methodology.
Results: The CL scale and visual reading were in excellent agreement (AUC 0.998, 95%CI=0.995-1.001, $p<0.001$). Images were visaully rated as positive at CL score 20.5 with 100% sensitivity and 96% specificity and at CL 30.7 with 94% sensitivity and 100% specificity. Stage 1 patients (n=9, median CL=31.7) compared to stage 2 patients (n=84, median CL=82.6) had significantly lower CL values ($F=25.4$, $p<0.001$).
Conclusions: The analysis demonstrated the utility and high reliability of the CL in clinical practice. Patients with visually negative subcortical structures had lower or borderline centiloid scores and therefore require special attention, especially when considering disease-modifying therapy.

Virtual EP - 051

Virtual E-Posters and Oral On-Demand
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AN ACCURATE AND ROBUST MACHINE LEARNING-BASED AMYLOID B ESTIMATION SYSTEM WITH LOW-COST PLASMA BIOMARKERS AND CLINICAL INFORMATION

Jiayuan Xu, Fumie Costen
The University of Manchester, Electrical And Electronic Engineering, Manchester, United Kingdom

Aims: Alzheimer's disease (AD) largely affects the daily functioning and life quality of the elderly population. The amyloid β (Aβ) accumulation in the brain has been identified as the hallmark of AD pathophysiology. Aβ PET positivity can be considered an important criterion of AD risk assessment. However, the current detection method, Positron Emission Tomography (PET) imaging is expensive. Low-cost plasma biomarkers can be used to estimate the Aβ PET positivity. If a patient is estimated to be positive based on plasma biomarkers, they can pay for a PET scan to confirm Aβ PET positivity, which would allow them to receive disease-modifiable therapies. Therefore, developing a low-cost brain Aβ estimation system for AD prognosis is crucial.
Methods: We proposed a highly accurate and robust machine learning system to estimate the brain Aβ with plasma biomarkers (Aβ 42, Aβ 40, Phosphorylated tau (pTau) 181, Neurofilament light chain (NFL)), Apolipoprotein E (APOE) genotype and clinical information (Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), age, education year and gender). We introduced a sample generation method to address the limited patient sample issue, and a feature matching technique to improve the model generalisation ability.
Results: Our system achieved excellent performance in Area Under the Curve (AUC) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Our designed architecture was also tested on the external dataset, the Centre for Neurodegeneration and Translational Neuroscience (CNTN). The results will be presented at the conference.
Conclusions: Our research provides a cost-efficient method for brain Aβ estimation with plasma biomarkers and clinical information. The results showed an improved performance by comparing with the state-of-the-art methods, and a good generalisation ability on the external dataset.

Virtual EP - 052

Virtual E-Posters and Oral On-Demand
VIRTUAL E-POSTERS IN ONLINE GALLERY AND MOBILE APP ONLY

LEWY BODY DEMENTIA WITH POSITIVE AMYLOID PET FINDINGS: A CASE REPORT

Moon Ho Park
Korea University, Neurology, Ansan, Korea, Republic of

Aims: Dementia with Lewy bodies (DLB) is a multifaceted neurodegenerative condition marked by cognitive impairment, motor dysfunction, and visual hallucinations. Although DLB is typically linked to the presence of Lewy bodies in the brain, some patients may exhibit atypical characteristics, including positive amyloid PET and Fp-CIT PET scan results—findings more frequently associated with Alzheimer's and Parkinson's diseases, respectively.
Methods: We report a case involving a patient whose clinical presentation aligns with DLB, yet also shows positive amyloid PET and Fp-CIT PET results, emphasizing the diagnostic complexities and consequences of such presentations.
Results: A 72-year-old man presented with a gradual decline in cognitive abilities, marked by fluctuations in attention and alertness, recurrent visual hallucinations, and parkinsonian features such as bradykinesia and resting tremor. A thorough neuropsychological assessment indicated impairments in executive functioning, visuospatial skills, and memory. Neurological examination revealed asymmetric rigidity and bradykinesia, more severe on the right side. Initial imaging studies included an amyloid PET scan, which unexpectedly showed significant amyloid accumulation in the cortical regions, aligning with Alzheimer's disease pathology. Furthermore, an Fp-CIT PET scan demonstrated decreased dopamine transporter binding, suggesting dopaminergic dysfunction typically observed in Parkinson's disease.
Conclusions: Despite these findings, which point to overlapping Alzheimer's and Parkinsonian pathology, the patient's clinical features were more consistent with the diagnostic criteria for DLB. To better understand the interplay between the pathological mechanisms underlying both Alzheimer's and Parkinsonian conditions, it is essential to conduct well-structured longitudinal clinico-pathological studies. Such research should aim to enhance early diagnostic accuracy and support the development of future disease-modifying treatments.

Virtual EP - 053

Virtual E-Posters and Oral On-Demand
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DEVELOPMENT OF HIGH-THROUGHPUT AGGREGATE-BASED ASSAYS FOR EARLY BLOOD-BASED DIAGNOSIS OF NEURODEGENERATIVE DISEASES

Chieh Sang[1,2], Asher Dworkin[1,2], Peter Swann[3,4], Timothy Rittman[3,4], John O'Brien[3,4], David Klenerman[1,2]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]UK Dementia Research Institute at Cambridge, Cambridge, United Kingdom, [3]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom, [4]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Aims: A major hallmark of neurodegeneration is the accumulation of soluble and insoluble aggregated proteins in the brain. Recent longitudinal studies support it and show a timeline where biomarkers of amyloidosis precede tauopathy, neurodegeneration, and cognitive decline. Less invasive blood biomarkers have demonstrated diagnostic potentials. However, few studies specifically target the aggregated forms of these biomarker proteins, which are directly relevant to clinical pathology. Additionally, our recent findings suggest that biomarker proteins are variably affected by conventional -80 degree storage conditions. In the present study, we have developed sensitive automated assays that specifically target aggregated proteins. By recruiting fresh, unfrozen plasma samples, we investigated whether relevant aggregate species accumulate in blood and assessed the diagnostic potential in relation to Alzheimer's disease (AD) and AD-relevant clinical phenotypes.
Methods: We developed an automated single-molecule pulldown (SiMPull) platform that supports high-throughput, sensitive assays in multi-well microplates. The use of identical capture/detection antibody pairs enables selective detection of aggregated forms of proteins in a sandwich assay format. Samples were imaged using total internal reflection fluorescence microscopy (TIRFM).
Results: We have successfully developed and validated aggregate-based SiMPull assays for t-tau, p-tau 202/205, abeta 40/42, and alpha-synuclein. Blood plasma from retrospective cohorts of patients with AD, AD-relevant symptoms, and healthy controls were freshly recruited and imaged within 24r of collection.
Conclusions: Quantitative analysis of the protein quantities and morphologies in plasma indicates that combining biomarker features with a matrix of aggregate biomarker assays provide valuable insights into the clinical relevance of blood-based biomarkers of AD. This ongoing work lays the foundation for further development of blood-based diagnostic tools for neurodegenerative disorders.

Virtual EP - 054

Virtual E-Posters and Oral On-Demand
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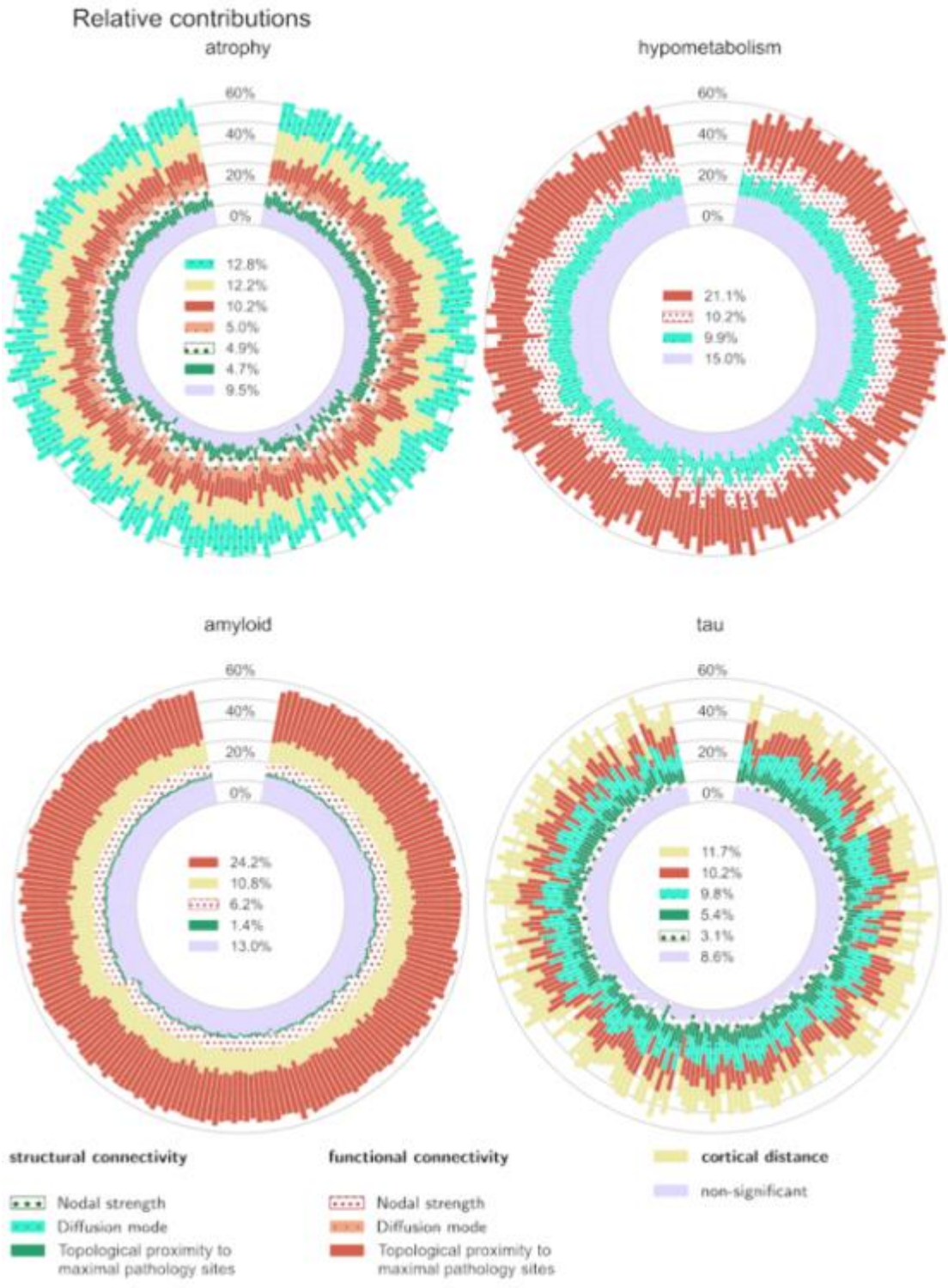
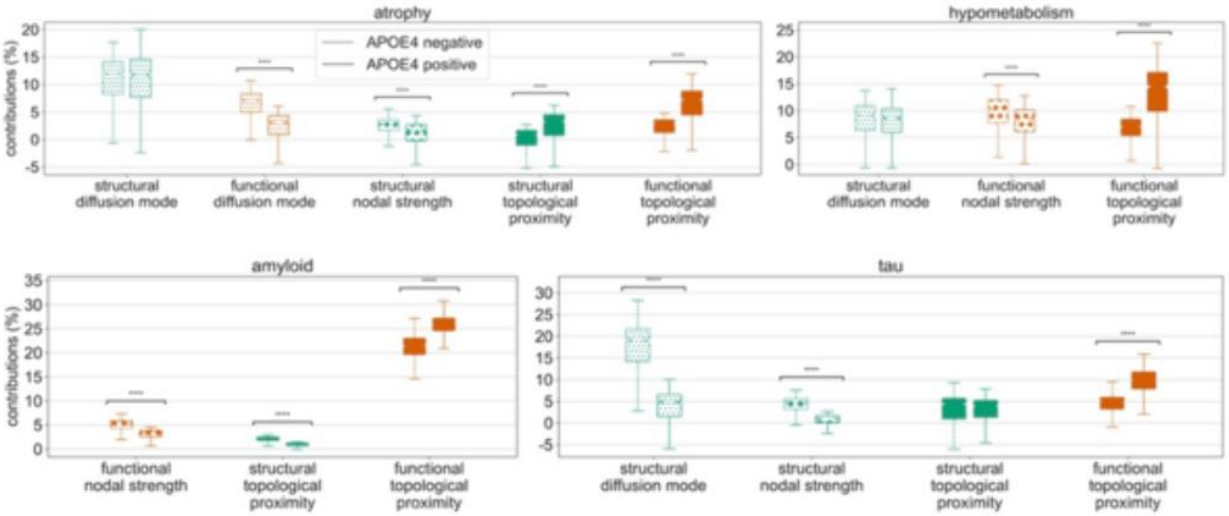
CONTRIBUTIONS OF CONNECTIONAL PATHWAYS TO SHAPING ALZHEIMER'S DISEASE PATHOLOGIES

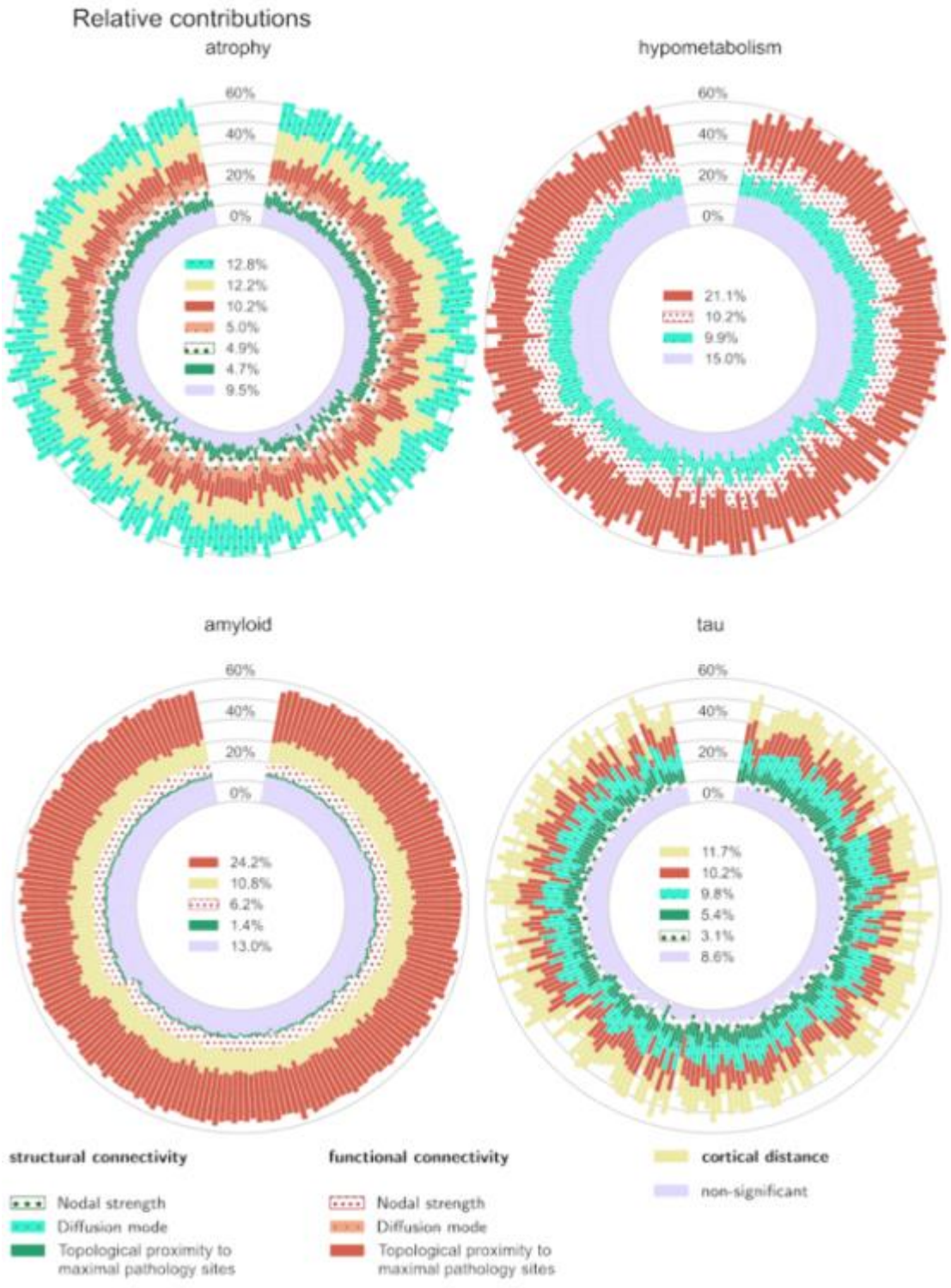
Salma Bougacha[1], Daniel Roquet[1], Brigitte Landeau[1], Elise Saul[1], Mikaël Naveau[1], Siya Sherif[1], Alexandre Bejanin[1], Marc Dhenain[2], Ashish Raj[3], Denis Vivien[1], Gaël Chetelat[4]
[1]Normandy University Unicaen, Inserm, U1237, Phind "physiopathology And Imaging Of Neurological Disorders", Neuropresage Team, Caen, France, [2]Université Paris-Saclay, Cea, Cnrs, Laboratoire Des Maladies Neurodégénératives : Mécanismes, Thérapies, Imagerie, F-92265, Fontenay-aux-roses, France, [3]University of California San Francisco, San Francisco, United States of America, [4]Cyceron, Caen, France

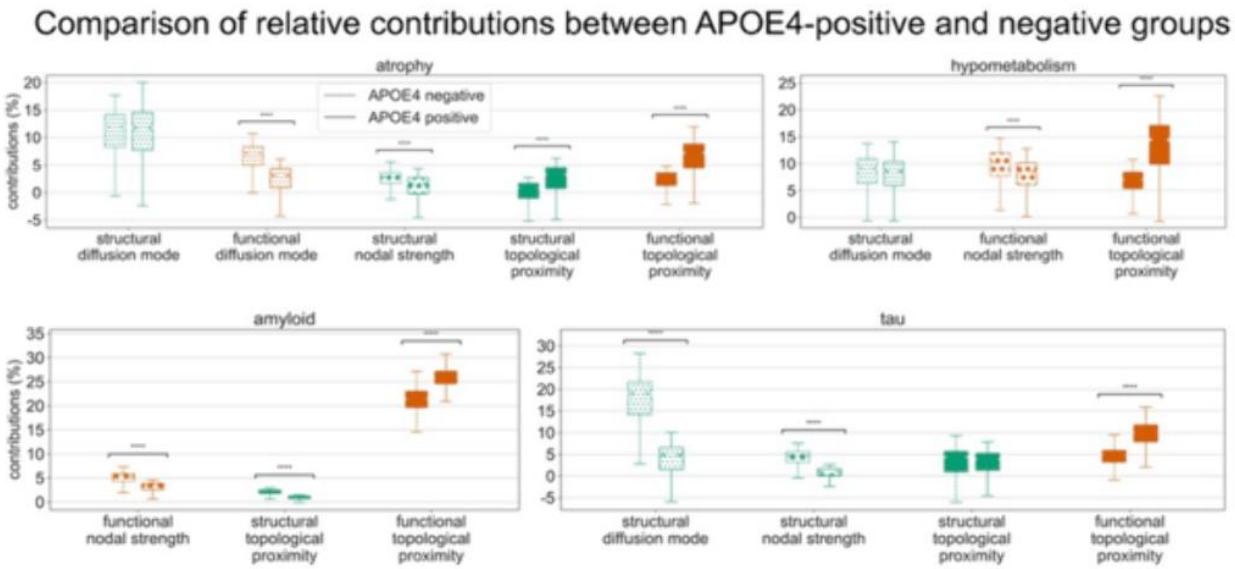
Aims: The four primary biomarkers of Alzheimer's disease—gray matter atrophy, glucose hypometabolism, amyloid-β deposition, and tau deposition—are distributed across the brain in spatial patterns influenced by the brain's network of structural and functional connections.
Methods: In this case-control study, we used several predictors representing different potential mechanisms of disease propagation through both structural and functional pathways. These were used to predict the spatial distribution of the four biomarkers in amyloid-positive patients, while controlling for spatial distance along the cortex. For each biomarker, we assessed how much each predictor contributed to the total variance explained by our model. Additionally, we compared the contributions between carriers and non-carriers of the APOE-ε4 allele, a genetic risk factor for Alzheimer's disease.
Results: Functional connectome-based proximity to regions with the highest levels of pathology explained a significant portion of the variance in all biomarkers. Functional pathways were especially important for glucose hypometabolism and amyloid deposition, explaining over 30% of the variance for both. In contrast, structural pathways were more predictive for gray matter atrophy and tau deposition, with inter-regional diffusion playing a key role. The presence of the APOE-ε4 allele modulated the contributions to all biomarkers, reflecting impaired brain connectivity in ε4 carriers.


Relative contributions
atrophy
60%
40%
20%
0%
12.8%
12.2%
10.2%
5.0%
4.9%
4.7%
9.5%
hypometabolism
60%
40%
20%
0%
21.1%
10.2%
9.9%
15.0%
amyloid
60%
40%
20%
0%
24.2%
10.8%
6.2%
1.4%
13.0%
tau
60%
40%
20%
0%
11.7%
10.2%
9.8%
5.4%
3.1%
8.6%
structural connectivity
Nodal strength
Diffusion mode
Topological proximity to maximal pathology sites
functional connectivity
Nodal strength
Diffusion mode
Topological proximity to maximal pathology sites
cortical distance
non-significant

Comparison of relative contributions between APOE4-positive and negative groups




Relative contributions
atrophy
60%
40%
20%
0%
12.8%
12.2%
10.2%
5.0%
4.9%
4.7%
9.5%
hypometabolism
60%
40%
20%
0%
21.1%
10.2%
9.9%
15.0%
amyloid
60%
40%
20%
0%
24.2%
10.8%
6.2%
1.4%
13.0%
tau
60%
40%
20%
0%
11.7%
10.2%
9.8%
5.4%
3.1%
8.6%
structural connectivity
Nodal strength
Diffusion mode
Topological proximity to maximal pathology sites
functional connectivity
Nodal strength
Diffusion mode
Topological proximity to maximal pathology sites
cortical distance
non-significant



Conclusions: Our methodology provides a framework for analyzing the contributions of multiple concurrent mechanisms to the spread of Alzheimer's disease biomarkers. It also highlights how genetic factors like the APOE-ε4 allele can modify these contributions. This approach could be applied to other neurodegenerative diseases to understand the impact of different spreading mechanisms and genetic factors on disease progression.

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Virtual EP - 055

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ASSOCIATION OF ALZHEIMER'S DISEASE BIOMARKERS WITH LOW PREMORBID INTELLECTUAL FUNCTIONING IN A MULTI-ETHNIC COMMUNITY-DWELLING COHORT: A CROSS-SECTIONAL STUDY OF HABS-HD

Lubnaa Abdullah[1], Zhengyang Zhou[2], Melissa Petersen[3], James Hall[3], Fan Zhang[3], Sid O'Bryant[3]
[1]University of North TExas Health Science Center, Family Medicine, Fort worth, United States of America, [2]university of north texas health science center, Public Health, fort worth, United States of America, [3]UNTHSC, Fort worth, United States of America

Aims: As the life expectancy of those living with low premorbid functioning reaches estimates consistent with the general population, it becomes more important to understand how low intellectual ability impacts brain aging. Despite more systematic inclusion of individuals with Down's Syndrome (DS) in Alzheimer's Disease (AD) research, few studies have examined cognitive aging among diverse individuals with intellectual disability (ID) excluding DS. This study aims to preliminarily investigate the relationship between low premorbid intellectual functioning (pIQ), ethno-racial diversity, and AD plasma biomarkers in a diverse community-dwelling cohort.
Methods: Participants were drawn from the Health & Aging Brain Study – Health Disparities (HABS-HD), categorized by low ($z \leq -2.00$) or average ($z = 0.00 \pm 1.00$) pIQ based on word reading scores. Plasma biomarkers including Aβ40, Aβ42, Aβ42/40, phosphorylated tau 181 (p-Tau181), neurofilament light chain (NfL), and total tau (t-tau) assessed using Simoa technology. Statistical analyses were conducted to evaluate whether the biomarker profiles differed between low and averages pIQ groups.
Results: Individuals with low pIQ exhibited significantly higher levels of p-Tau181 ($p < 0.05$), NfL ($p < 0.05$), and t-tau ($p < 0.05$) compared to those with average pIQ. Stratified analysis by ethnicity revealed differential associations, with Hispanic and NHW participants showing distinct biomarker profiles relative to NHB individuals
Conclusions: The findings demonstrate low pIQ is a reliable factor associated with AD biomarker outcomes, with lower pIQ tended to be associated with increased AD and neurodegenerative biomarkers. Ethnicity appears to modulate these associations, suggesting complex interactions between low premorbid functioning and AD susceptibility across diverse populations. This study highlights the importance of considering pIQ and ethnicity in neurodegenerative processes, particularly in vulnerable populations such as those with intellectual developmental disability.

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Virtual EP - 056

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VOXEL-WISE FREE-WATER DIFFUSION AS A MARKER OF NEUROINFLAMAMTION AND CSF DISRUPTION IN ALZHEIMER'S DISEASE

Brandon Hall[1], Etienne Aumont[1], Seyyed Ali Hosseini[1], Joseph Therriault[1], Nesrine Rahmouni[1], Arthur Macedo[1], Stijn Servaes[1], Jaime Fernandez-Arias[1], Yi-Ting Wang[1], Lydia Trudel[1], Kely Quispialaya-Socualaya[1], Yansheng Zheng[1], Chris Hsiao[2], Robert Hopewell[2], Tharick Pascoal[3], Pedro Rosa-Neto[2]
[1]McGill University, Montreal, Canada, [2]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada, [3]University of Pittsburgh, Pittsburgh, United States of America

Aims: The glymphatic hypothesis identifies cerebrospinal fluid (CSF) dysregulation and fluid stagnation via inflammation as important features in Alzheimer's disease (AD) pathology. To investigate these factors in connection to AD proteinopathy, we modeled voxel-wise freewater volume fraction (FVF)—a neuroinflammation marker—in association with cortical amyloid-β oligomers and phosphorylated tau in older adults.
Methods: We used data from 253 participants over 65 years old (**Table 1**) from the TRIAD cohort in voxel-wise association models between CVF, amyloid-β PET and tau PET. Model covariates: age, sex, APOE4 status, with amyloid-β in the tau model. FVF derived from diffusion MRI via the NODDI-Watson algorithm; higher values indicate greater percentage fluid with isotropic diffusion. Amyloid-β and tau was measured with ([^{18}F]AZD4694) and ([^{18}F]MK2640) PET SUVR scans, respectively. Random field theory multiple comparison corrections performed with cluster thresholds of p-value < 0.001.

Table 1: participant demographics	
	total
N	253
% female	60.6%
age ***mean (sd)***	71.9 (4.9)
% APOE positive	34.4%

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	total
N	253
% female	60.6%
age ***mean (sd)***	71.9 (4.9)
% APOE positive	34.4%

Results: CVF and tau: Positively associated in clusters resembling Braak stage regions I-IV. Negatively assocated in lateral ventricles and sub-arachnoid space. (**Figure 1**) CVF and amyloid-β: Negatively associated in lateral, third, and fourth ventricles; cerebral aqueduct and central canal; hippocampal sulci; and sub-arachnoid space. (**Figure 2**) In both models, ventricular radioactivity decreases. The expanding ventricles have high FVF due to CSF content, but low PET signal.

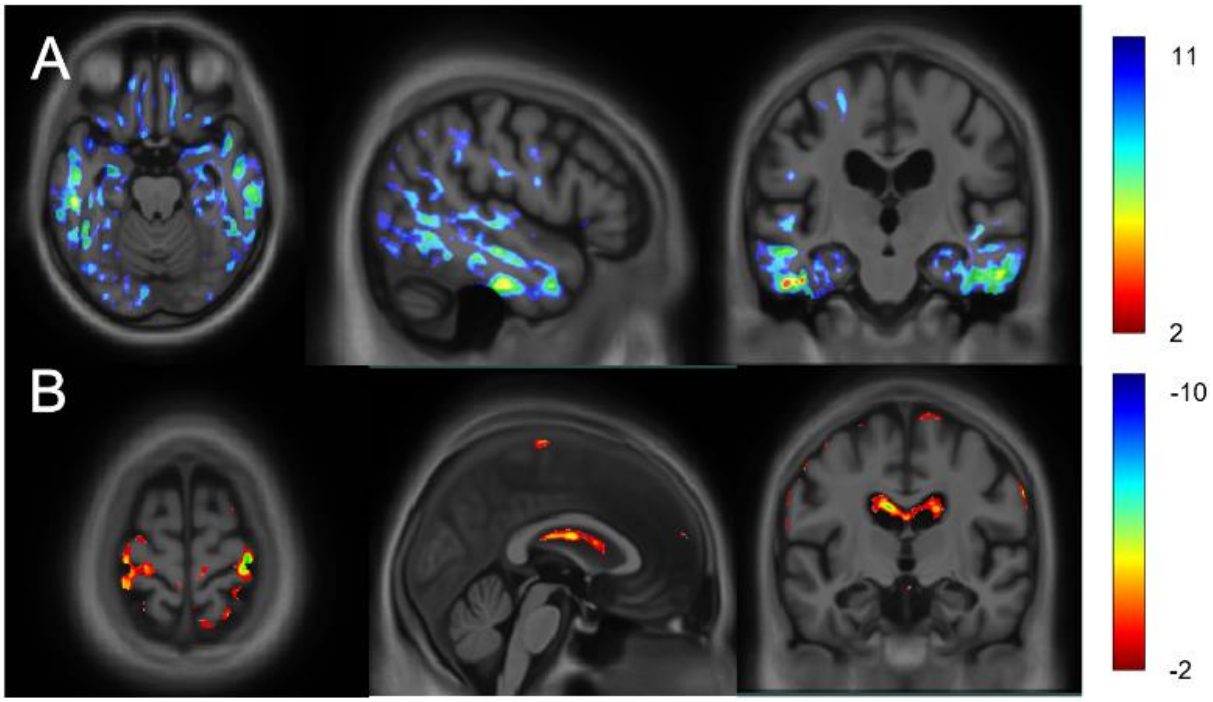


Figure 1: a map of model t-values of tau PET associations with FVF projected onto T1 template. A) Positive clusters of association in grey matter are prominent in the medial and lateral temporal regions, with smaller clusters in the occipital and inferior frontal: analogous to Braak stage regions I-IV. This may reflect inflammation in those areas, as voxels with more extracellular isotropically diffusing water have higher FVF. B) Negative clusters in the lateral ventricles may reflect reduced tau tracer circulation due to decreased CSF influx; the cluster extent is reduced by amyloid-β correction. The superior lateral clusters may be due to reduced FVF in those areas as tauopathy progresses; again, the cluster extent is reduced by amyloid-β correction.

CVF ~ amyloid-β + age + gender + APOE4

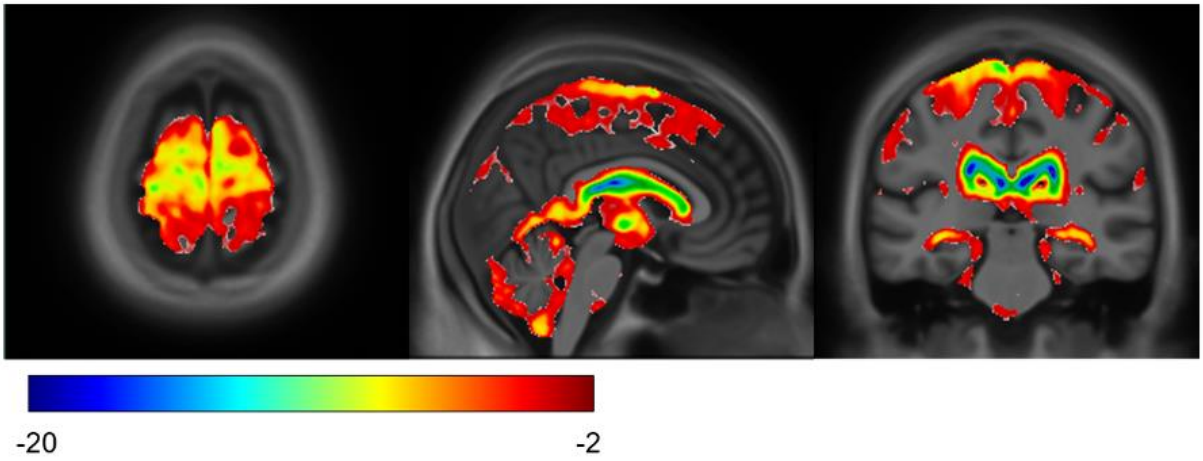
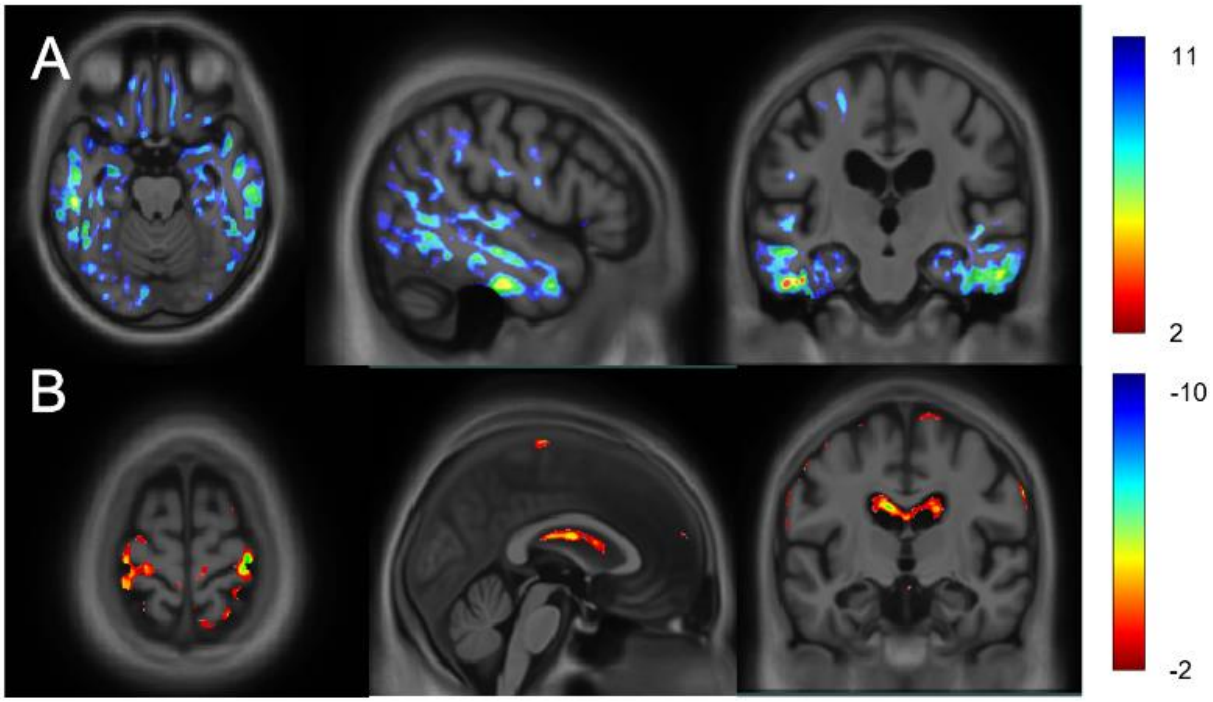


Figure 2: a map of model t-values of amyloid-β PET associations with CVF projected onto T1 template. Cluster regions with high t-values in the periventricular white matter are due to conversion of voxels with data from predominantly white matter regions (low FVF) to data from expanded ventricular regions (high FVF). A similar effect is demonstrated in the expanding hippocampal sulcus. However, the lack of positive associations in grey matter regions vulnerable to AD-induced neuroinflammation indicates that these positive associations are not a proxy for neuroinflammation. The superior medial associations indicates reduced FVF with greater amyloid-β pathology.



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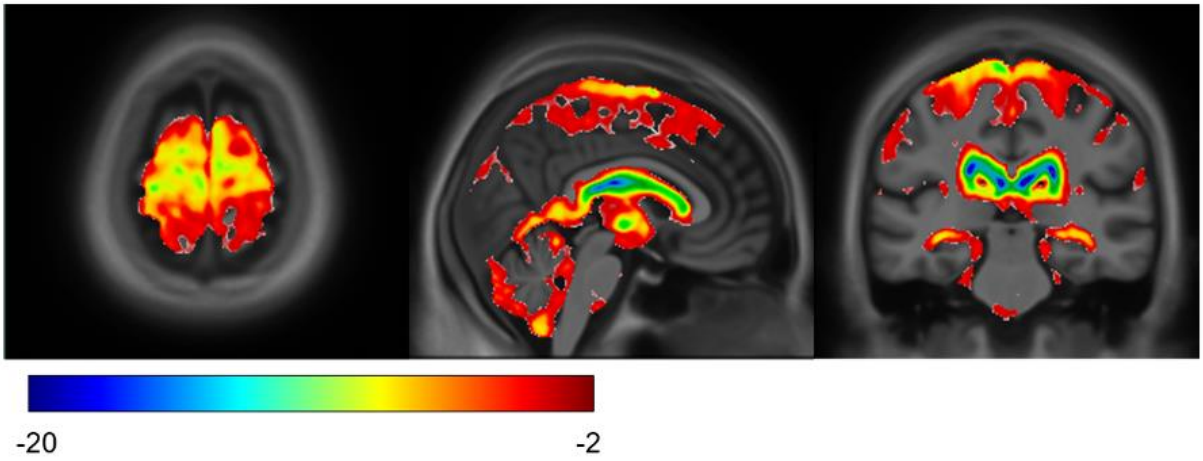
CVF ~ amyloid-β + age + gender + APOE4



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Conclusions: Increased FVF Braak-like regions suggests that neuroinflammation in grey matter occurs secondary to tauopathy, not amyloidopathy. This non-invasive biomarker may help quantify AD neuroinflammation and what it responds to. Additionally, decreased FVF with increased amyloid-β in the subarachnoid suggests CSF efflux failure, as CSF efflux into the superior sagittal sinus occurs via arachnoid granulations. This association occurs in the tau model, but is removed by amyloid-β correction. Decreased radioactivity in expanding ventricles and sulci suggests reduced CSF production, thus tracer circulation.

Virtual EP - 057

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DETERMINING THE RELATIONSHIP BETWEEN SERUM OXYLIPIN LEVELS AND RETINAL THICKNESS IN ALZHEIMER'S DISEASE: AN EXPLORATORY ANALYSIS

Saffire Krance[1], Wendy Hatch[2], Lisa Xiong[3], Di Yu[3], Walter Swardfager[3], Wendy Lou[4], Alex Kiss[5], William Lin[3], Ameer Taha[6], Chris Husdon[7], Peter Kertes[2], Sandra Black[8]
[1]Dalhousie University, Internal Medicine, Halifax, Canada, [2]University of Toronto, Ophthalmology And Vision Sciences, Toronto, Canada, [3]University of Toronto, Pharmacology, Toronto, Canada, [4]University of Toronto, Dalla Lana School Of Public Health, Toronto, Canada, [5]Sunnybrook Hospital, Toronto, Canada, [6]University of California, Davis, Davis, United States of America, [7]University of Waterloo, Waterloo, Canada, [8]University of Toronto, Neurology, Toronto, Canada

Aims: To determine in an exploratory analysis whether serum oxylipin levels predict retinal thickness on spectral domain-optical coherence tomography (SD-OCT) in subjects with Alzheimer's disease or mild cognitive impairment (ADMCI).
Methods: ADMCI subjects were recruited in the Ontario Neurodegenerative Research Initiative. Subjects with serum oxylipin levels and bilateral baseline SD-OCT scans were included. pRNFL and macular scans were obtained. Global pRNFL, mean macular total retinal thickness (RT), and mean macular ganglion cell layer thickness (GCL) were each summed across eyes for analysis. Missing oxylipin data were imputed if ≤25% were missing, if >25% were converted into categorical variables, and if >85% missing were excluded. Correlation matrices explored relationships between oxylipins and retinal layers. Oxylipins achieving significant correlations with retinal layers were tested in linear regression models as predictors of retinal thickness controlling for age and sex.
Results: Fourty-four, 45, and 47 subjects met inclusion criteria for GCL, RT, and pRNFL studies, respectively. Mean ages were 70-71.2 (SD=8.6-8.8). Subjects were 49-53% male across groups. Summed GCL thickness across eyes was 76.3µm (SD=6.8), RT was 617.6µm (SD=29.0), and pRNFL was 186.7µm (SD=18.4). Of 71 oxylipins, 3, 5, and 5 had significant correlations with pRNFL, RT, and GCL, respectively. In regression models, (1) higher PGD2 and lower LTE4 levels predicted a thinner pRNFL (B=-0.348, p=0.010; B=0.375, p=0.008); (2) higher 13-oxo-ODE, lower 12,13-DiHOME/EpOME ratio, and lower 14,15-EpETRE predicted a thinner RT (B=-0.252, p=0.048; B=0.412, p=0.009; B=0.378, p=0.005).
Conclusions: Specific profiles of circulating oxylipins may reflect pathological changes occurring in the retina during ADMCI neurodegeneration. Future work can determine whether circulating oxylipin levels have a direct effect on the retina given their inflammatory and neovascularization functions, or if they are reflecting the severity of direct eye-brain pathological processes.

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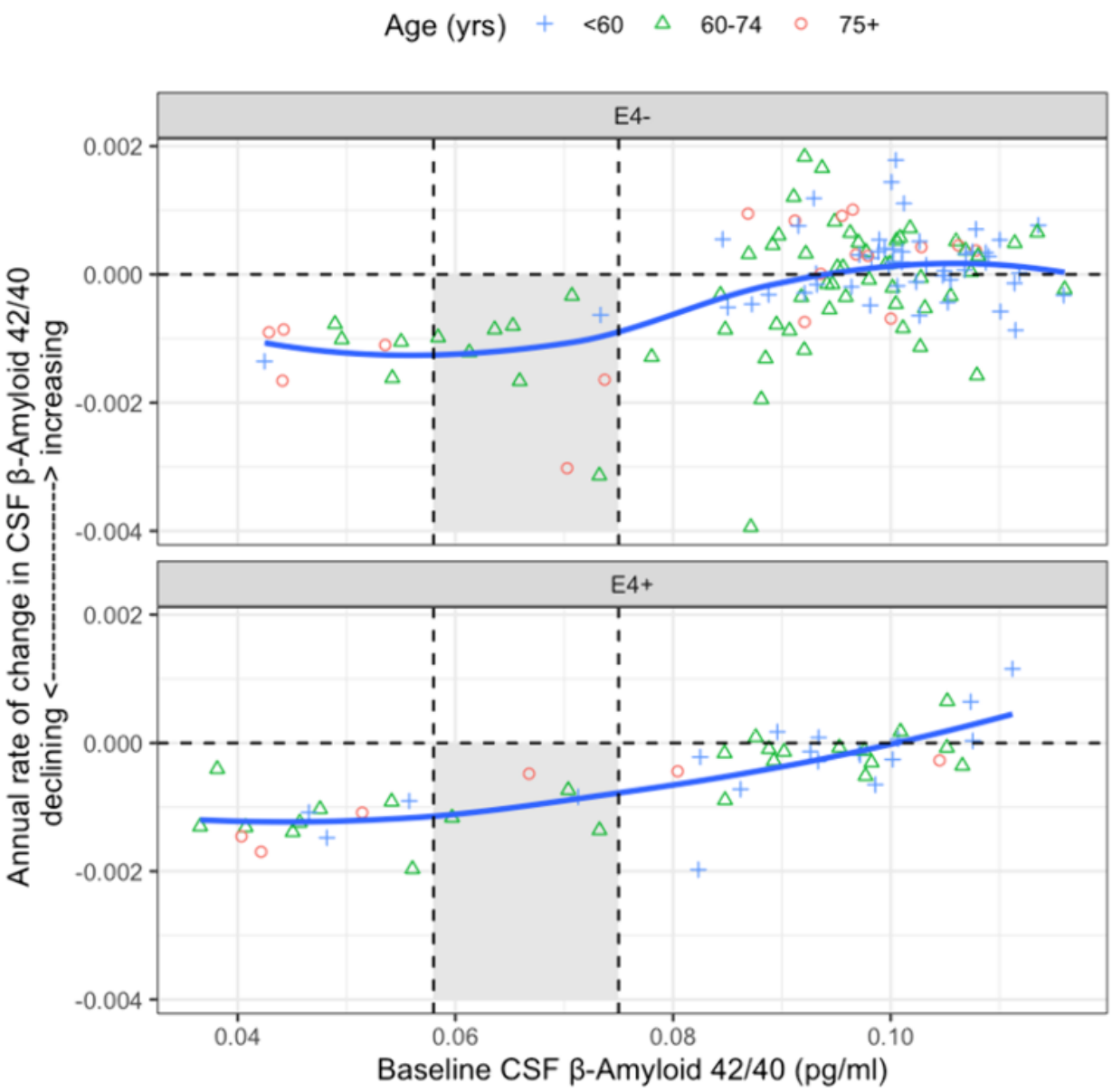
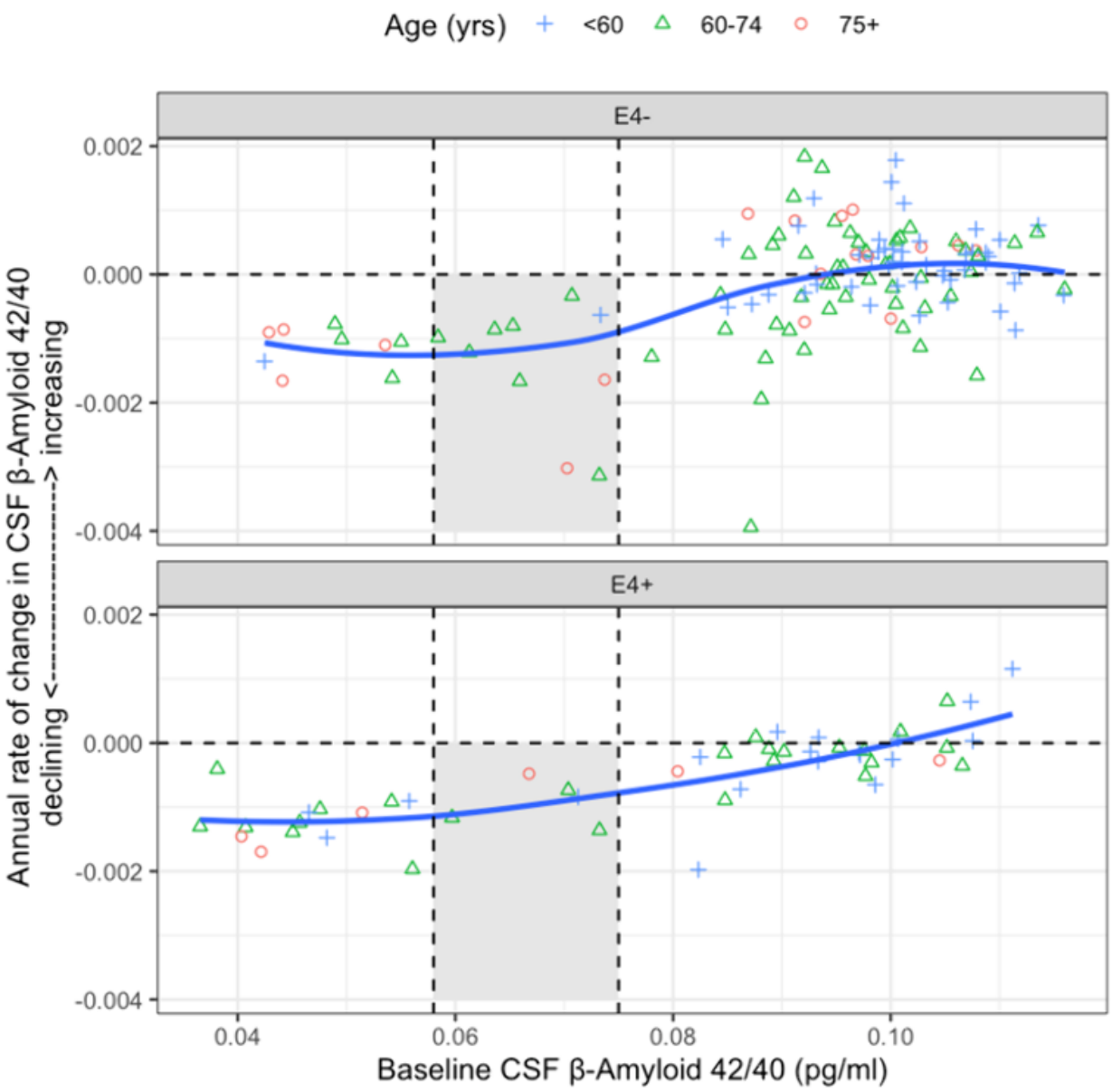
ASSESSMENT OF PRECLINICAL AD IN COGNITIVELY NORMAL ADULTS WITH CSF B-AMYLOID 42/40 RATIO

Ge Li[1,2,3], Deidre Jansson[2], Jane Shofer[2,3], Elizabeth Colasurdo[2], Carl Sikkema[2], Rachel Radwan[4], John Lawson[4], Chris Dague[4], Francesca De Simone[4], Murray Raskind[2,3], Jeffery Iliff[2,3], Elaine Peskind[2,3]
[1]VA Puget Sound Health Care System, Geriatric Research Education And Clinical Center, Seattle, United States of America, [2]VA Puget Sound Health Care System, Northwest Mental Illness Research, Education, And Clinical Center, SEATTLE, United States of America, [3]University of Washington, Psychiatry And Behavioral Sciences, SEATTLE, United States of America, [4]Fujirebio Diagnostics Inc., Malvern, United States of America

Aims: To assess the frequency of brain amyloid positivity (A+) and progression of A+ using the CSF Lumipulse® G β-Amyloid Ratio (1-42 /1-40, 42/40 ratio) in cognitively normal adults.
Methods: Cognitively normal adults (n=176, mean age 63 [range 27-88] years; 37% male and 9% non-white) with at least one follow-up measurement of CSF β-Amyloid 42/40 ratio were selected from the biorepository at VA Puget Sound Health Care system. The mean duration of follow-up was 2 years (range 0.1-12). CSF β-Amyloid 1-42 and β-Amyloid 1-40 were measured with the Fujirebio Lumipulse® G assays. Two different thresholds were used to determine A+, 0.058 recommended by FDA, and 0.075 used to determine A+ by Keshavan et al. Linear mixed effects regression of CSF β-Amyloid 42/40 on study follow-up year was used, with random intercepts and slopes to estimate intercept (baseline ratio) and slope (longitudinal change) terms for each participant.
Results: A+ started to emerge at ages 50-59 years, more commonly in APOE *ε4* carriers (4/15, 27%) than non-carriers (2/35, 6%) using the 0.075 threshold. Once the β-Amyloid 42/40 ratio dropped below the threshold, the ratio continued to decline, including those participants with ratios between two different thresholds (gray area in Figure 1). The lower initial ratios, the faster the rate of decline. The association between CSF β-Amyloid 42/40 longitudinal change and baseline ratio were similar across APOE ε4 group.
Figure 1. Individual participant CSF β-Amyloid 42/40 ratio change by the baseline ratio


Age (yrs) <60 60-74 75+
E4-
E4+
0.002
0.000
-0.002
-0.004
0.04
0.06
0.08
0.10
Annual rate of change in CSF β-Amyloid 42/40
declining <---------> increasing
Baseline CSF β-Amyloid 42/40 (pg/ml)



Conclusions: Preclinical AD started to be seen in the 6th decade, especially in APOE *ε4* carriers. Once a participant's CSF β-Amyloid 42/40 ratio dropped below the most liberal threshold for A+, it continued to decline, suggesting progression of amyloid pathology in brain.

Virtual EP - 059

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COMPARE DIAGNOSTIC ACCURACY OF ALZHEIMER'S CEREBROSPINAL FLUID CORE BIOMARKERS BY LUMIPULSE, INNOTEST AND ELECSYS IN CHINESE POPULATION: A PUMCH DEMENTIA COHORT STUDY

Chenhui Mao, Yutong Zou, Tianyi Wang, Longze Sha, Meiqi Wu, Shanshan Chu, Wei Jin, Li Shang, Bo Li, Yixuan Huang, Yuyue Qiu, Jialu Bao, Wenjun Wang, Yuhan Jiang, Yunfan You, Yuanheng Li, Liling Dong, Feng Feng, Li Huo, Ling Qiu, Jing Gao
Peking Union Medical College Hospital, Beijing, China

Aims: This study aimed at evaluating diagnostic efficacy of Alzheimer's Disease (AD) core biomarkers by different methods in Chinese population.
Methods: Participants were recruited from PUMCH dementia cohort. Cerebrospinal fluid (CSF) samples were collected based on the Alzheimer's Association international guidelines. One manual immunoassay (INNOTEST, performed in two independent laboratories) and two fully automated immunoassays (Lumipulse G and Roche Elecsys) were selected and used for the measurement of CSF core biomarkers including $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, t-tau, and p-tau_{181}, as well as calculating three ratios ($A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$, t-tau/$A\beta_{1\text{-}42}$ and p-$tau_{181}/A\beta_{1\text{-}42}$). The cutoffs and accuracy of biomarkers and ratios were defined in differentiating clinically diagnosed AD and non-AD, PET biomarker diagnosed AD and non-AD, as well as AD and cognitive normal controls.
Results: 309 participants were selected, including 176 clinically diagnosed AD, 114 non-AD and 19 cognitive normal controls (CN). While differentiating clinically diagnosed AD and non-AD, the highest accuracy was reached by Elecsys in testing $A\beta_{1\text{-}42}$ and by Lumipulse G in testing t-tau, p-tau_{181} and the three ratios. While differentiating amyloid PET+ and amyloid PET-, the highest accuracy was reached by INNOTEST in testing $A\beta_{1\text{-}42}$ and t-tau and by Lumipulse G in testing p-tau_{181} and the three ratios. While differentiating PET+ and CN, the highest accuracy was reached by INNOTEST in testing $A\beta_{1\text{-}42}$ and t-tau, by Lumipulse G in testing p-tau_{181} and the two ratios ($A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ and t-tau/$A\beta_{1\text{-}42}$) and by Elecsys in testing p-$tau_{181}/A\beta_{1\text{-}42}$.
Conclusions: All the three immunoassays were eligible for clinical test. The performance of automated assays was better than manual assays. Standard operation procedure and experienced operator were important for accuracy of INNOTEST. Ratios had better accuracy than absolute value. The cutoffs were incomparable among different methods and different clinical circumstances.

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VALIDATION OF PERIPHERAL MICRORNA PROFILES FOR EARLY DIAGNOSIS OF SPORADIC ALZHEIMER'S DISEASE IN A FINNISH COHORT: FINDINGS FROM PROAD PROJECT

Maria Tsamou[1], Keano Samaritakis[1], Fabienne Kremers[1], Susanna Skalicky[2], Matthias Hackl[2], Roosa Kallionpaa[3], Erwin Roggen[1]
[1]ToxGenSolutions, Maastricht, Netherlands, [2]TamiRNA, Vienna, Austria, [3]Auria Biobank, Turku, Finland

Aims: Up to now, although many efforts have been made for identification of reliable molecular biomarkers for the diagnosis of late-onset or sporadic Alzheimer's disease (sAD), there is still lack in timely detection of the disease before the appearance of the first clinical symptoms. Previously, changes in peripheral microRNA (miR) expression were found to be responsive to mild cognitive impairment (MCI), a reversible condition. In this study, the confirmation of the identified changes in peripheral miR expression related to memory loss in an independent study population was evaluated.
Methods: A set of candidates circulating miRs, previously shown to be associated with MCI when compared to controls, was measured in plasma samples of 104 MCI patients, 220 AD patients, 130 non-AD dementia patients and 450 healthy controls, age- and gender-matched, 19 miRs were measured in plasma by RT-qPCR. Plasma samples were retrieved from Auria Biobank, using the current diagnostic criteria for each condition. Logistic regression models were used to explore the associations of interest between the relative miR expression in plasma and the clinical condition of the participants.
Results: Findings revealed an inverse association between the relative expression of miR-146a-5p and the odds of having MCI, AD and non-AD dementia (vs. control). Each doubling in the relative expression of miR-125b-5p and miR-128-3p in plasma would decrease the odds of having MCI (vs. control) and either non-AD dementia or AD (vs. control), respectively.
Conclusions: These candidate human circulating miRs may be of great importance in overlapping processes in neurological disorders. There is an urgent need for confirming these proposed early predictive biomarkers for sAD, which can further contribute not only to societal but also to economic benefits.

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Virtual E-Posters and Oral On-Demand
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CLINICAL VALIDATION OF PLASMA BIOMARKERS FOR ALZHEIMER'S DISEASE DETECTION

Lourdes Álvarez-Sánchez[1], Laura Ferré-González[1], Carmen Peña Bautista[2], Ángel Balaguer[1], Julian Luis Amengual[1], Miquel Baquero[3], Laura Cubas[2], Bonaventura Casanova[1], Consuelo Cháfer Pericas[1]
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Aims: This work aims to validate a combination of plasma biomarkers and demographic variables for establishing cut-offs, which could be clinically implemented for AD diagnosis.
Methods: Plasma biomarkers (Aβ42/Aβ40, p-Tau181, t-Tau, NfL, GFAP) were measured by single molecule assay (SIMOA®) technology. Also, ApoE genotype and demographic variables were obtained from a cohort of patients (n= 478; AD (n=254) and non-AD (n=224)). They were classified according to the cerebrospinal fluid (CSF) Aβ42/Aβ40 levels. A Ridge Logistic regression model was used to predict the occurrence of AD in this cohort of patients. Then, cut-offs for the model and for specific AD predictors were evaluated. A three-range strategy consisting of two different cut-off values was employed.
Results: The predictive model including plasma Aβ42/Aβ40, p-Tau181, GFAP, ApoE genotype, and age was optimal for predicting CSF Aβ42/Aβ40 positivity (AUC 0.93, sensitivity 0.86, specificity 0.82). The model including only plasma biomarkers (Aβ42/Aβ40, p-Tau181, GFAP) provided reliable predictive results (AUC 0.88, sensitivity 0.83, specificity 0.78). As single biomarker, GFAP showed the best performance in discriminating between AD (CSF Aβ42/Aβ40 positive) and non-AD groups (AUC 0.859). The established cut-offs in a three-range strategy performed satisfactorily for the validated predictive model (probability) and individual plasma GFAP (concentration).
Conclusions: Plasma GFAP and the validated predictive model based on plasma biomarkers, represent a relevant step toward the development of a potential clinical approach for specific AD diagnosis, which should be assessed in further research.

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PROMISING CLINICAL TOOLS FOR SPECIFIC ALZHEIMER'S DISEASE SCREENING FROM PLASMA PTAU217 AND AUTOMATIC TECHNOLOGY

Lourdes Álvarez-Sánchez[1], Carmen Peña Bautista[2], Laura Ferré-González[1], Ángel Balaguer[1], Julian Luis Amengual[1], Miquel Baquero[3], Consuelo Cháfer Pericas[4]
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Aims: The aim of the present work is to evaluate the capacity of plasma p-tau217 as screening biomarker for distinguish patients with Alzheimer's disease (AD) from other pathologies and controls.
Methods: Plasma p-Tau217 was determined in a cohort of patients (n= 259), diagnosed as AD (n= 127), and non-AD (n= 132), using the CSF amyloid β (Aβ) Aβ42/Aβ40 ratio. A logistic regression model was developed to predict AD in this cohort. A two-cut-off strategy was proposed to stratify the patients into Aβ-negative, Aβ-positive, and uncertain.
Results: Intermediate p-Tau217 levels would require confirmatory testing. A nomogram and a two-cut-off strategy for specific AD screening were developed as a promising clinical tool.
Conclusions: This study provided a satisfactory two-cut-off strategy for Aβ positivity screening at a cognitive disorder unit.

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PLASMA P-TAU217 STABILITY IN NON-FASTING CONDITIONS: ADDITIONAL RESULTS FROM A PILOT STUDY IN HEALTHY ADULTS

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Aims: Blood tests for neurodegenerative diseases including Alzheimer's disease have recently developed from promising research endeavours to valued clinical tools. However, several external factors, including the non-fasting state, have been reported to confound biomarker quantification. We investigated the effect of food intake on plasma phosphorylated tau (p-tau) 217 and brain-derived tau (BD-tau); two biomarkers with high specificity to AD-type neurodegeneration.
Methods: 111 cognitively healthy participants (60±7 y, 64 females) underwent a standardized meal test (postprandial group, PG). Plasma p-tau217, and BD-tau concentrations were measured via Simoa assays fasting and 15, 30, 45, 60, 120, and 180 min after test meal ingestion. In addition, we followed a fasting subgroup (n=26; fasting group, FG), who did not ingest any food or liquids. Statistical analysis was performed using linear mixed models for group x time interaction.
Results: In the PG group, both biomarkers changed significantly after test meal ingestion with a decrease in the early postprandial phase and a subsequent increase. Baseline levels were not reached within the 3 hours observation period. Fluctuations in BD-tau, but not p-tau217, were significantly greater after food intake than in the fasting state (Δ 10% FG vs. PG, $p<0.05$). As reported previously, significant food-dependent alterations have also been observed for other p-tau epitopes, such as p-tau181 (Δ 20% FG vs. PG, $p<0.05$) and p-tau231 (Δ 10% FG vs. PG, $p<0.05$).
Conclusions: Our data suggest that p-tau217 was robust against food-induced dynamics. This may be a contributing factor to the superior diagnostic performance of plasma p-tau217 compared to other blood biomarkers. The observed dynamics in BD-tau suggest an involvement of mechanisms regulating CNS tau expression in the postprandial state. Confounding factors as the non-fasting state should be apparent to researchers and clinicians.

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AGE AND SEX EFFECTS ON LEVELS AND EFFECTIVENESS OF BLOOD BIOMARKERS OF ALZHEIMER'S DISEASE

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Aims: Given that levels of AD biomarkers have been shown to vary by age, and studies have produced mixed results on the variance of AD biomarker levels by sex, we sought to investigate these factors when considering these biomarkers' potential uses in clinical settings.
Methods: Biomarker data was from the cohort of patients enrolled in UPenn's Alzheimer's Disease Research Center (ADRC) cohort.
In addition, there were also AD pathology cases from the ADRC from which levels of pTau-181 (N = 27), GFAP (N = 36), and NfL (N = 26) were measured.
All statistical analyses were conducted in R, using ROC analyses.
Results: While pTau-217 and pTau-181 levels differed between the sexes (p=0.000604), this effect diminished when covarying for diagnosis group. For Aβ42/40 and NfL, there was no significant difference in levels between the sexes, with or without diagnosis group as a covariate. However, while GFAP levels were not significantly different between sexes, when covarying for diagnosis group, there was a significant difference in level by sex (p=9.35x10-7), indicating a groupwise effect of sex. There were significant differences found in the performance of pTau-217 in discriminating NC (regardless of PET status) from AD Probable, NC/PET- from MCI/PET+, and NC/PET- from NC/PET+, wherein pTau-217 had a higher AUC when regarding males than females in these analyses.
Conclusions: A major takeaway was that in all BBMs analyzed, the performance of discrimination of NC/PET- from AD Probable did not significantly differ between sexes or age groups, indicating that they may be useful in clinical settings for both males and females. However, the sex differences in levels and performance among the BBMs in other groups may be an interesting topic for further study.

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ASSOCIATIONS OF PLASMA AND CSF OSTEOCALCIN LEVELS WITH COGNITIVE FUNCTION AND CSF ATN BIOMARKERS

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Aims: The bone-derived osteocalcin (OCN) has been proven to play crucial roles in brain development and cognitive function in animal experiments. However, whether OCN is associated with Alzheimer's disease (AD)-type pathologies in humans remains largely unknown. We investigated the alterations of OCN in plasma and cerebrospinal fluid (CSF) in AD, and the relationship of OCN with cognitive function and CSF AD biomarkers.
Methods: 238 cognitively unimpaired participants, 37 PiB-PET-positive AD dementia patients, and 15 patients with non-AD neurodegenerative diseases were enrolled in this study. OCN in plasma and cerebrospinal fluid (CSF) were measured by ELISA kits.
Results: In the clinical diagnosis-based subgroup, plasma and CSF levels of OCN were significantly higher in AD dementia compared to cognitively unimpaired participants. In the ATN framework-based subgroup, plasma and CSF OCN levels were significantly higher in Aβ+ participants, and OCN levels were also increased in preclinical AD. In plasma, the OCN level in the AD dementia group was higher than that in the non-AD neurodegenerative group. CSF OCN levels were negatively correlated with CSF Aβ42 and positively correlated with CSF p-tau/ Aβ42 and t-tau/Aβ42. Additionally, plasma OCN levels were negatively correlated with MMSE scores. High CSF OCN levels significantly enhanced the effect of CSF Aβ42 on CSF t-tau or p-tau. Both plasma and CSF OCN could discriminate AD dementia patients from CU and discriminate Aβ+ participants from Aβ- participants. Moreover, the diagnostic values were elevated when partial core AD biomarkers were combined with CSF or plasma OCN levels.
Conclusions: This study provides clinical evidence for the relationship between OCN and AD, suggesting OCN may be associated with brain Aβ deposition, tau hyperphosphorylation, and neurodegeneration.

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AXONAL DAMAGE AND COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE: LINKING NFL LEVELS TO CLOCK-DRAWING TEST PERFORMANCE

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Aims: Neurofilament light chain (NfL) is a biomarker of neuronal damage, with elevated levels in cerebrospinal fluid and blood of patients with Alzheimer disease (AD), indicating axonal neurodegeneration. The clock-drawing test assesses cognitive and visuospatial functions, often impaired in Alzheimer's disease. In this study, we investigated the relationship between NFL levels and cognitive functions.
Methods: We enrolled AD patients according to the NIA-AA 2024 guidelines. All patients underwent a complete neuropsychological battery and lumbar puncture. We assessed NfL levels in CSF samples using commercially available immunoassay kits for NfL, run on the ultrasensitive SR-X Biomarker Detection System (Quanterix). Serum NfL values were normalized by logarithmic transformation, and statistical analysis with age-adjusted non-parametric correlation was performed.
Results: 42 patients were enrolled in this study with a median age (25-75th percentile) of 76 years (73-79) and a mean education of 9,8 years; 23 were females. From CSF analysis, the median value of NfL (25th-75th percentile) was 77.8 (50.2-114.3). Statistical analysis revealed a negative correlation between Clock-Drawing Test scores (median 5; 25th-75th percentile 2.5-7) and high Log10NfL values ($p = 0.03$; Rho = -0.33).
Conclusions: Our study highlights a direct implication of axonal damage on the clinical picture, demonstrating a clear correlation between NfL levels and scores on the clock-drawing test.

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IMMUNOASSAY-BASED P-TAU205 MEASUREMENTS CAN BE USED IN COMBINATION WITH AB AND P-TAU217 TO STAGE ALZHEIMER´S DISEASE

Juan Lantero Rodriguez[1], Oskar Hansson[2], Shorena Janelidze[3], Sebastian Palmqvist[4], Niklas Mattsson-Carlgren[5], Erik Stomrud[5], Henrik Zetterberg[6,7], Kaj Blennow[7], Gemma Salvadó[8], Laia Montoliu-Gaya[1]
[1]Institute of Neuroscience and Physiology, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [2]Lund University, Clinical Sciences Malmo, Lund, Sweden, [3]Clinical Memory Research Unit, Department Of Clinical Sciences, Malmö, Sweden, [4]Lund University, Clinical Sciences In Malmö, Lund, Sweden, [5]Lund University, Lund, Sweden, [6]7Clinical Neurochemistry Laboratory, Mölndal, Sweden, [7]Clinical Neurochemistry Laboratory, Mölndal, Sweden, [8]Lund University, Clinical Memory Research Unit, Lund, Sweden

Aims: Phosphorylated tau at position 205 (p-tau205) shows a stronger association with tau pathology and emerges later in the Alzheimer's disease (AD) continuum compared to other tau phosphorylations, such as p-tau217. This study aimed to evaluate the role of p-tau205 in staging AD using immunoassay-based measurements.
Methods: We analysed the levels of CSF p-205 using an in-house immunoassay in two large, independent cohorts (BioFINDER-2 [n=1,364] and BioFINDER-1 [n=705]). Four CSF stages were defined based on fluid biomarker abnormality (Stage-0: all negative; Stage-1: Aβ40/42 positive (Aβ+); Stage-2: Aβ+ p-tau217+; Stage-3: Aβ+ p-tau217+p-tau205+). We investigated how these stages were associated with Aβ-PET, tau-PET, neurodegeneration, and cognition, both cross-sectionally and longitudinally.
Results: In both cohorts, changes in AD hallmarks across CSF immunoassay-based stages showed that Aβ-PET became abnormal between stages 0 and 1, Tau-PET and cognitive measures (mPACC and MMSE) by stage-2, and neurodegeneration markers, such as cortical thickness and CSF NfL, at stage-3 (Fig.1). CSF stages closely reflected tau-PET changes, with 0% and 5% of participants being tau-PET negative in stages 0 and 1, compared to 49% and 78% positive in stages 2 and 3. Notably, 64% of participants in stage-3 showed late neocortical tau-PET deposition (Fig.2). CSF stages also revealed significant differences in longitudinal Aβ and tau-PET accumulation, cortical thinning, and cognitive decline. Individuals at later CSF stages had higher hazard ratios for progression to dementia, even after adjusting for initial cognitive status (Stage-3: 6.4 [4.3, 9.6]; Stage-2: 3.2 [1.7, 5.9]; Stage-1: 1.9 [0.9, 3.9] vs. Stage-0)

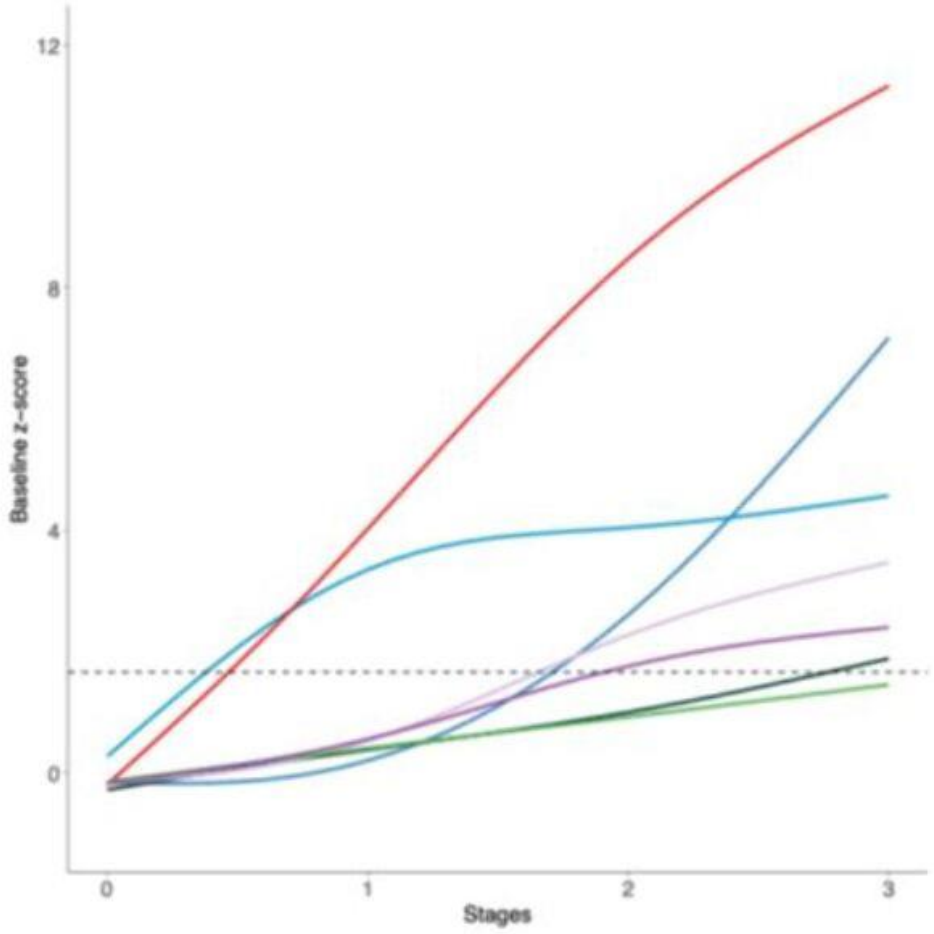


Fig1. LOESS analysis of AD biomarkers in relation to CSF-Stages in BioFinder-2: Amyloid-PET (red), Aβ ratio (light blue), Tau-PET (dark blue), mPACC (dark purple), MMSE (light purple), CSF NfL (dark green), cortical thickness (light green).

(Fig.3).

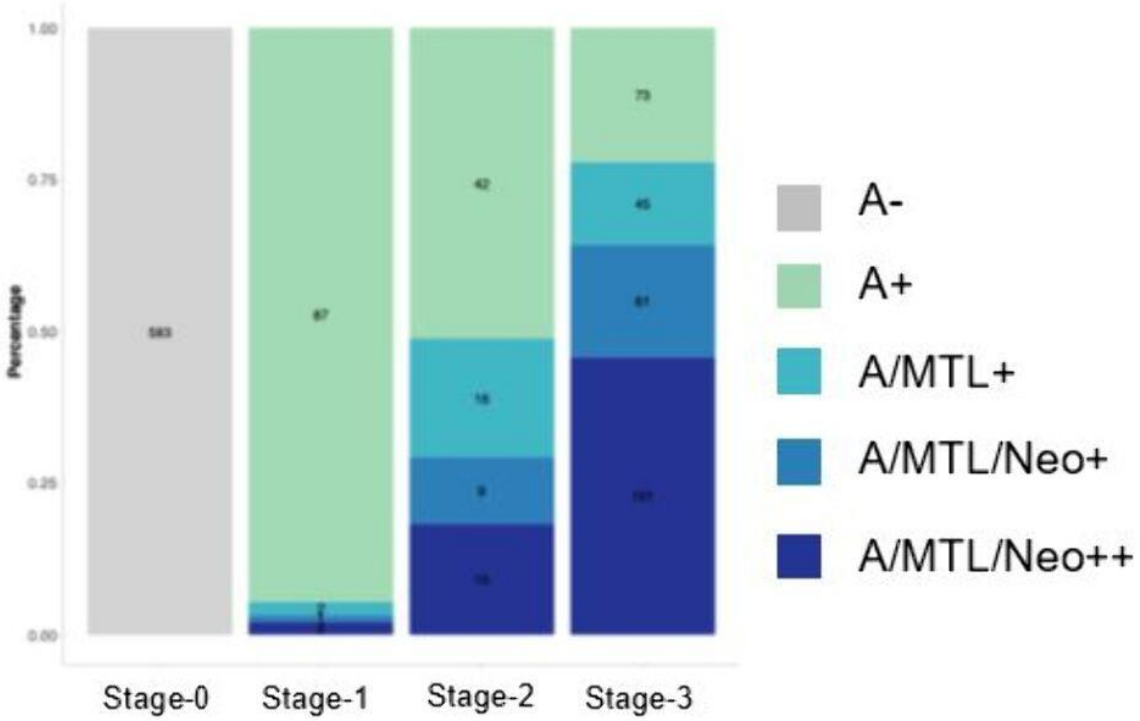


Fig. 2. Association of CSF-stages with Amyloid and Tau PET imaging stages.

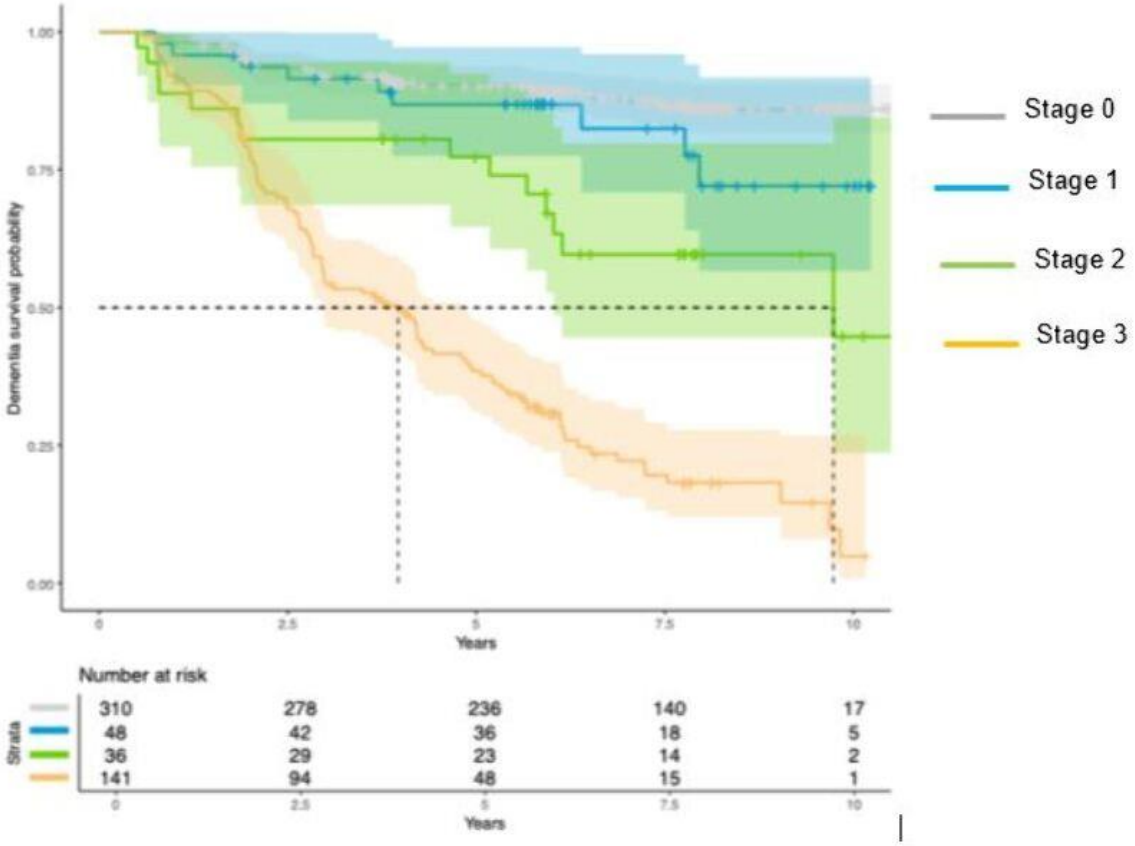
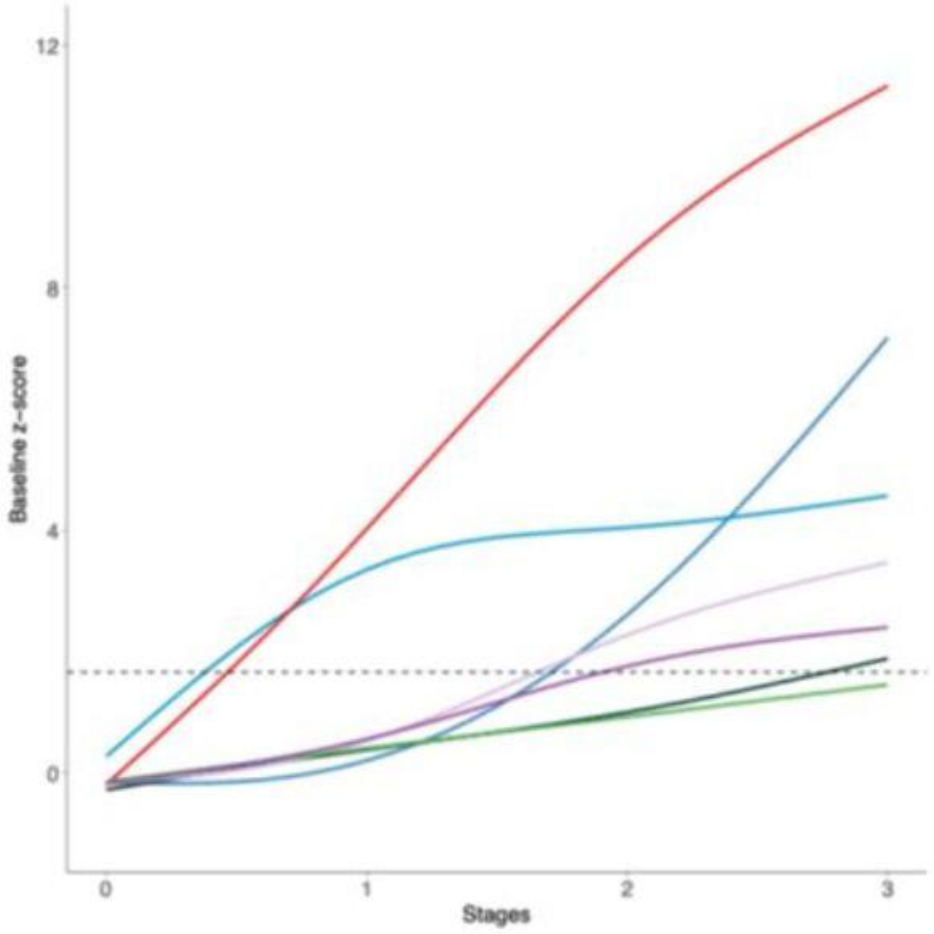


Fig3. Survival analysis of cognitive decline over the course of 10 years in participants classified in CSF-stages at baseline. Stage-0 (grey), Stage-1 (blue), Stage-2 (green), Stage-3 (orange).



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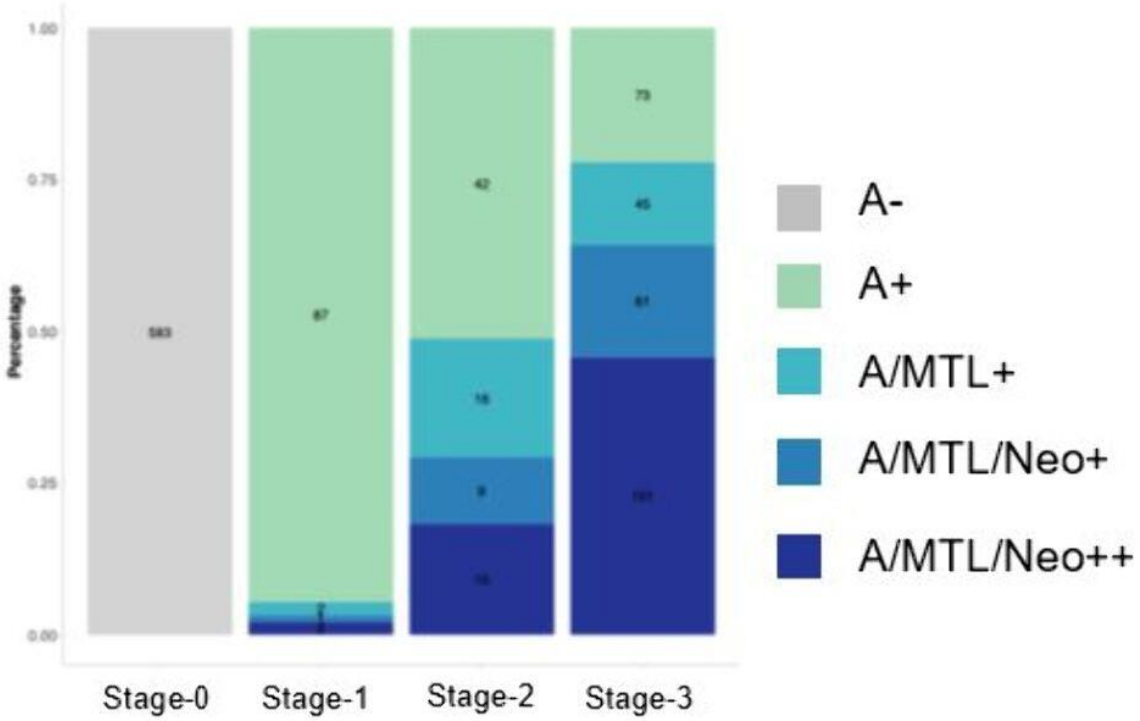

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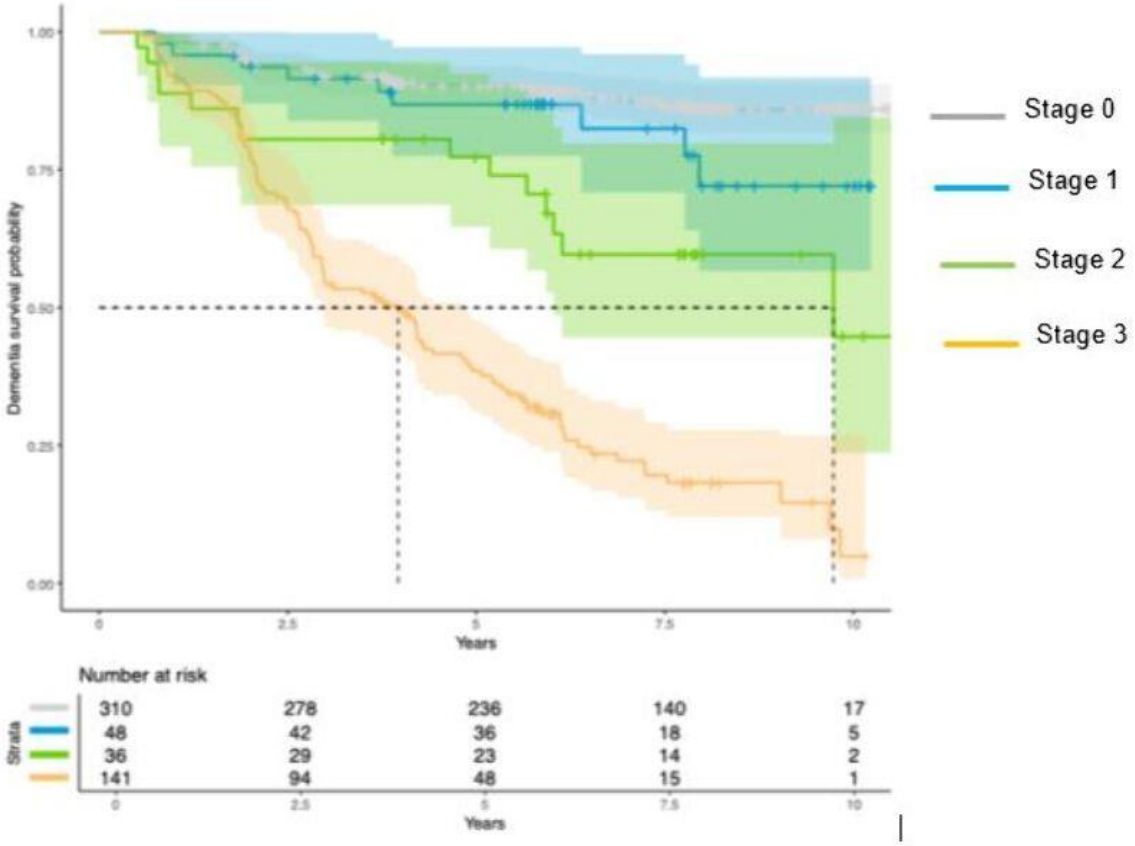

Fig3. Survival analysis of cognitive decline over the course of 10 years in participants classified in CSF-stages at baseline. Stage-0 (grey), Stage-1 (blue), Stage-2 (green), Stage-3 (orange).

Conclusions: CSF p-tau205, combined with Aβ and p-tau217 immunoassay-based measurements, can help stage patients across the AD continuum and predict longitudinal decline, which may improve prognosis and selection of participants for clinical trials.

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INTERLABORATORY VARIATION OF PLASMA AMYLOID-BETA (AB1-42) AND PHOSPHORYLATED TAU217 ON LUMIPULSE PLATFORM

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Aims: There is an urgent need for cost effective, easily accessible and noninvasive methods that can aid with the assessment of Alzheimer's disease (AD) pathology. Proteins in plasma including Aβ1-42, and forms of phosphorylated Tau, total Tau, pTau181, pTau217, and pTau231 have been proposed as plasma biomarkers to potentially aid in the diagnosis and monitoring of AD. Although some biomarkers have been FDA-cleared in CSF, none have been cleared in plasma.
Methods: To assess the precision and accuracy of Fujirebio Lumipulse Aβ1-42 and pTau217 in plasma as an RUO in an early AD trial two levels of quality controls (QC) were run, and 68 clinical trial plasma samples compared between two independent labs.
Results: Fujirebio low and high QC for Aβ1-42 and pTau217 were run for 12 days and analyzed. Mean and %CVs of 22.12 pg/mL (6.4%) for the low QC and 210.47 pg/mL (6.2%) for the high QC. For pTau217 0.48 pg/mL (17.3%) low control and 3.88 pg/mL (3.1%) for the high control. The pTau217 low control, recovered values were slightly greater than the stated manufacturer's range. Upon repeat of the two controls for those two days, and reanalysis, the low control mean and %CV was 0.45 pg/mL (6.4%). Next, 69 plasma samples previously analyzed by another laboratory for Aβ1-42 and 68 samples for pTau217. Aβ1-42 slope of 1.058 and a y-intercept of 2.1 pg/mL for Aβ1-42. pTau217 slope was 0.985 and the y-intercept was -0.019 pg/mL.
Conclusions: Precision performance of the RUO plasma assays is generally acceptable but we caution to accept the values that are only within the stated manufacturer's ranges. Plasma assays for Aβ1-42 and pTau217 can lead to results which are consistent across labs.

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A TRANSLATIONAL APPROACH TO ESTABLISH SEVEN SIRTUINS AS A BLOOD BASED BIOMARKER FOR ALZHEIMER'S DISEASE

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Aims: To establish seven Sirtuins as a potential biomarker for the early detection of the Alzheimer Disease.
Methods: This study evaluated the level of serum Sirtuins (SIRT1–SIRT7) in three study groups: AD, mild cognitive impairment (MCI) and geriatric control (GC) by the label free surface plasmon resonance (SPR) technology and was further validated by the Western blot experiment. ROC analysis was performed to differentiate the study group based on the concentration of serum SIRT proteins.
Results: Out of seven Sirtuins, serum level of SIRT1, SIRT3 and SIRT6 (mean ± SD) were significantly decreased in AD (1.65 ± 0.56, 3.15 ± 0.28, 3.36 ± 0.32 ng/µl), compared to MCI (2.17 ± 0.39, 3.60 ± 0.51, 3.73 ± 0.48 ng/µl) and GC (2.84 ± 0.47, 4.55 ± 0.48, 4.65 ± 0.55 ng/µl). ROC analysis showed the cut-off value with high sensitivity and specificity for cognitive impairment (AD and MCI). The concentration declined significantly with the disease progression. No specific difference was observed in the case of other SIRTs between the study groups.
Conclusions: This study for the first time reports the concentration of all seven Sirtuins in serum of AD and MCI patients and reveals an inverse relationship between serum level of SIRT1, SIRT3 and SIRT6 and AD. The cut-off values with sensitivity and specificity shows the clinical relevance of SIRT3 and SIRT6 as serum protein markers for AD.

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ASSOCIATION OF PLASMA TRAIL LEVELS WITH AB42 AND P-TAU181 IN PATIENTS WITH ALZHEIMER'S DISEASE

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[1]Chongqing General Hospital, Chongqing University, Chongqing, China, [2]Chongqing Medical University, Chongqing, China

Aims: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is involved in the pathogenesis of Alzheimer's disease (AD). This study aimed to investigate the association between plasma TRAIL levels and plasma amyloid-β (Aβ) 42 and phosphorylated tau protein 181 (p-tau181) levels in patients with AD, patients with amnestic mild cognitive impairment (aMCI) and cognitively normal (CN) subjects.
Methods: A total of 396 participants, including 78 AD patients, 70 aMCI patients, and 70 age- and sex-matched CN controls as well as a cohort of 178 CN subjects of different ages, were enrolled in this study. Plasma TRAIL levels were determined using enzyme-linked immunosorbent assays. The correlations among plasma TRAIL levels, plasma Aβ42 and p-tau181 levels, and apolipoprotein E (APOE) genotypes were analyzed. The optimal diagnostic sensitivity and specificity were determined using receiver operating characteristic curve analysis.
Results: The plasma TRAIL levels increased with age and were positively correlated with age. The plasma TRAIL levels did not differ between females and males(Fig. 1e). Plasma TRAIL levels were higher in the AD than in the aMCI and in the CN group. There was no significant difference between the aMCI group and the CN group (Fig 2a). There was a positive correlation between plasma TRAIL levels and p-tau181 levels (Figure 3d and Figure 4). However, plasma Aβ42 levels were not correlated with plasma TRAIL levels. The AUC for the combination of plasma TRAIL, p-tau181 and Aβ42 levels to distinguish AD patients and aMCI patients from CN individuals was 0.717 (Fig. 5).
Conclusions: Plasma TRAIL levels increase with age and are significantly elevated in AD patients. The association between plasma TRAIL levels and ptau181 levels suggests that TRAIL has a possible role in the pathogenesis of AD through mechanisms related to tau pathology.

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REVIEW ON LOW LIMITS OF DETECTION FOR ASSAYING PLASMA BIOMARKERS ASSOCIATED WITH NEURODEGENERATIVE DISEASE

Charles S.Y. Yang
MAgQu Co., Ltd., New Taipei City, Taiwan

Aims: Due to the ultra-low concentrations, ultra-sensitive technologies are needed to precisely assay the plasma biomarkers associated with Alzheimer disease, Parkinson's disease, frontotemporal dementia and other neurodegenerative diseases. In this work, the reported analytical sensitivities, i.e., low limits of detection (LLoD), in published papers or on websites with versatile assay technologies are summarized.
Methods: The ultra-sensitive assay technologies included in this work are chemiluminescent enzyme immunoassay, electrochemiluminescence, multimer detection system, high sensitivity chemiluminescence enzyme immunoassay, immunomagnetic reduction, nucleic acid linked immuno-sandwich assay, single molecule array, single molecule counting, successive proximity extension amplification reaction, surface plasmon resonance, multi-analyte profiling, liquid chromatography mass spectrometry, and immunoprecipitation mass spectrometry. The biomarkers of interest include $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, secondary structure of Aβ, oligomers of Aβ, sAPPα, sAPPβ, T-Tau, pTau181, pTau231, pTau217, α-synuclein, p-α-synuclein129, NfL, BDNF, GFAP, TDP-43, UCH-L1 and SNAP-25.
Results: The detected signals of included assay technologies are either of optical, magnetic or spectrum-based. Most of the low limits of detection (LLoD) with versatile assay technologies are between 0.1 to 100 pg/ml. Few technologies such as immunomagnetic reduction are able to assy biomarkers at levels lower than 1 fg/ml. The assay with 0.1-100-pg/ml LLoD is sensitive enough to quantitatively detect amyloid β, T-Tau, pTau, NfL, BDNF, GFAP, etc., which shows levels of several pg/ml or several tens of pg/ml in human blood. However, plasma α-synuclein, p-α-synuclein and TDP-43 are at levels of severla tens or hundreds fg/ml, which could be prscisely assyed using technolgoies having LLoD of 1 fg/ml or lower.
Conclusions: With such ultra-sensitive technologies, the era of assaying plasma biomarkers for assessing neurodegenerative diseases is coming. Remarkably, new assay technologies or kits are being developed day to day. It would be better to update frequently.

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SOCIAL COGNITION PROFILE IN TAIWANESE PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND EARLY ALZHEIMER'S DISEASE

Bo-Xuan Huang, Ta-Fu Chen, Yu-Wen Cheng
National Taiwan University Hospital, Neurology, Taipei, Taiwan

Aims: We hypothesized that Taiwanese early Alzheimer's disease (AD) patients showed social cognition changes. This study examined the social cognition profiles of subjects living with subjective cognitive decline (SCD), mild cognitive impairment (MCI), and AD using social cognition assessments.
Methods: This study enrolled 57 SCD, 54 MCI, and 98 AD participants from the memory clinic at National Taiwan University Hospital. All participants underwent social cognition battery consist of Revised Self-Monitoring Scale (RSMS), the Basic Moral Reasoning (BMR), the Interpersonal Reactivity Index (IRI), the Social Norms Questionnaire (SNQ-22), the Social Behavior Observer Checklist (SBOCL), the Mild Behavioral Impairment Checklist (MBI-C), the Social Display Rule (SDR), and the Social Interaction Vocabulary Task (SIVT). The social cognition profile was compared between the three diagnostic groups using analysis of covariance adjusting for age, sex, and education.
Results: The AD patients scored significantly lower compared to either MCI and SCD groups on the "self-presentation" scale of RSMS ($p=0.007$ and $p=0.004$, respectively), the "perspective taking" scale of IRI ($p<0.001$ for both), and the SIVT ($p=0.006$ and <0.001). Conversely, they scored higher on MBI-C subscales including "decreased motivation" ($p=0.002$ and <0.001) and "impulse dyscontrol" (p 0.016 and <0.001), and the SBOCL (both $p<0.001$). On the "social expression" scale of RSMS ($p=0.004$), the "fantasy" scale of IRI ($p=0.027$), and the "social inappropriateness" of MBI-C ($p=0.043$), AD scored lower than SCD but not MCI groups. Notably, none of the assessed social cognitive scale showed significant difference between the SCD and MCI groups.
Conclusions: Specific social cognition scales demonstrated significant differences between SCD, MCI, and AD. While further validation is needed, these findings suggest social cognition changes in AD population which could impact their life quality and increase the burden of caregivers.

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NEUROPSYCHOLOGICAL VALIDATION OF A BRIEF PROTOCOL FOR DIGITAL ASSESSMENT OF COGNITION

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[1]Linus Health, Boston, United States of America, [2]Linus Health, BOSTON, United States of America

Aims: To establish the validity of a 7-minute digital assessment of cognition (DAC) protocol against comprehensive neuropsychological evaluation.
Methods: DAC protocol consisted of two 6-word Philadelphia (repeatable) Verbal Learning Tests [P(r)VLT] – immediate free recall test trials, the semantic/"animal" fluency test (60 s), three 5-digit trials of the Backwards Digit Span Test (BDST), and the P(r)VLT-delay free recall and delay recognition tests. Throughout the test administration, participants spoke their responses out loud, and the iPad recorded all of their speech for later processing and analysis. The protocol was administered using an 11-inch Apple iPad Pro. A trained examiner proctored the test; however, all test instructions were delivered verbally by the iPad. A 3-hour paper and pencil neuropsychological protocol was used for the clinical evaluation of 118 patients resulting in a diagnosis of 33 healthy controls (HC), 59 patients with mild cognitive impairment (MCI), and 24 patients with dementia, and assessed executive control/working memory, information processing speed, general intellectual abilities, language/lexical access, visuospatial/visuoconstructional abilities, and episodic memory. These neuropsychological tests were expressed as z-scores derived from available normative data or demographically corrected scores in the literature. A partial list of these tests and their relevant subtests included the BNT, CVLT Long Delay Free Recall and Recognition Discriminability, KBNA Sequence Subtest, WAIS-IV Digits Forward and Backward, WAIS-III Similarities Subtest, and WMS-IV Symbol Span Subtest.
Results: The DAC protocol achieved 90% accuracy for classifying MCI, 83% accuracy for dementia, and 88% accuracy for CU, compared to the cognitive classification based on the paper and pencil neuropsychological tests.

Conclusions: A brief (7-min) protocol for digital assessment of cognition shows excellent concordance in cognitive classification with a 3-hour comprehensive neuropsychological evaluation.

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MODELING ALZHEIMER'S DISEASE PROGRESSION USING A LATENT COGNITIVE VARIABLE BASED ON CONFIRMATORY FACTOR ANALYSIS OF LONGITUDINAL COGNITIVE DATA

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Montreal Neurological Institute-Hospital, Mcconnell Brain Imaging Centre, Montréal, Canada

Aims: Studying the progression of Alzheimer's disease (AD) presents significant challenges due to the difficulty in identifying the exact onset of clinically probable AD. We hypothesize that a unified latent cognitive score, combining multiple cognitive assessments, can facilitate analysis and modeling progression of AD, enabling refined tracking of disease onset and cognitive decline. By integrating multiple cognitive assessments, this method minimizes potential multicollinearity while leveraging the combined information from these scores and accounting for measurement error in each test.
Methods: Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were used to construct a latent cognitive score derived from the Montreal Cognitive Assessment (MoCA), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13), and Clinical Dementia Rating Sum of Boxes (CDR-SB) using multilevel confirmatory factor analysis (CFA) implemented with lavaan on R v4.2.2. Through a nonlinear mixed-effects modeling, we then modeled a continuous trajectory representing the progression of AD based on the longitudinal values of this latent score.
Results: The progression model optimized by the latent score demonstrated a robust fit to the data (figure 1). Comparing the model's Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) revealed that this approach provides a better fit than using any single cognitive scores mentioned above, alone or in a simple combination.

AIC and BIC of different fits

score	Latent score	ADAS	MOCA	CDRSB	ADAS+MOCA+CDRSB
AIC	3,683	18,911	17,038	10,421	40,818
BIC	3,725	18953	17,081	10,462	40,974

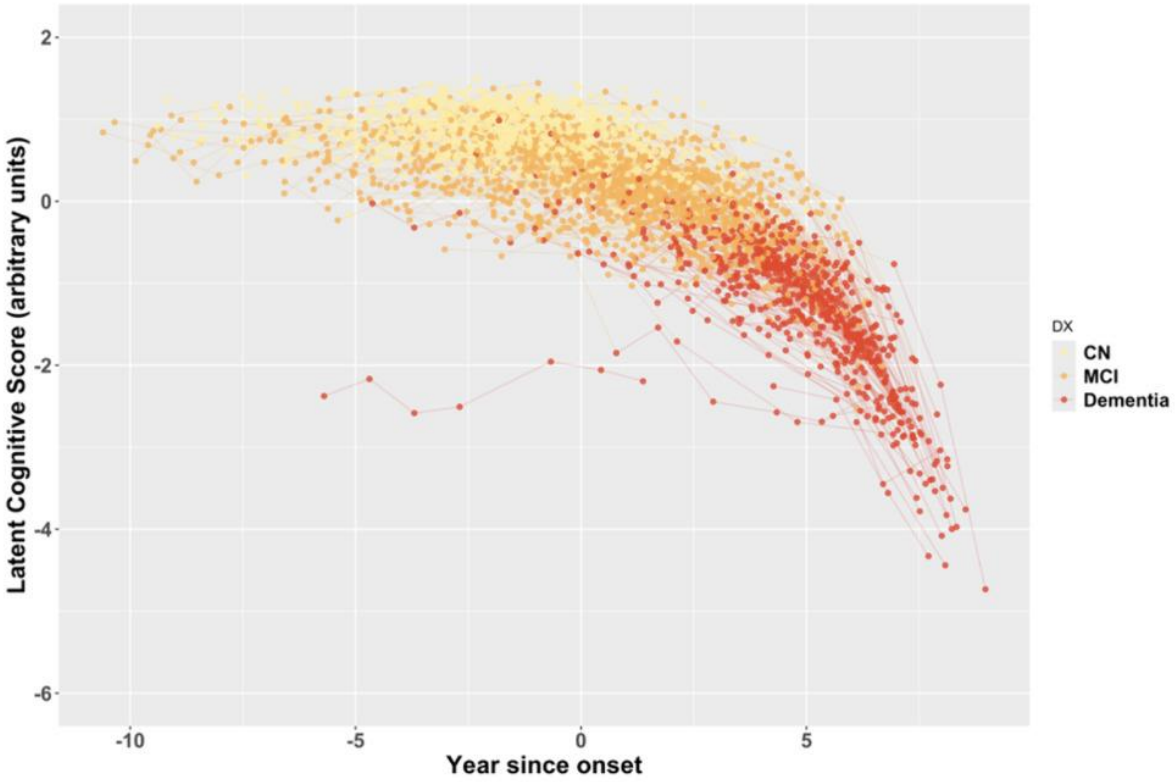

Figure 1: Estimated timeline of AD progression based on the Latent score

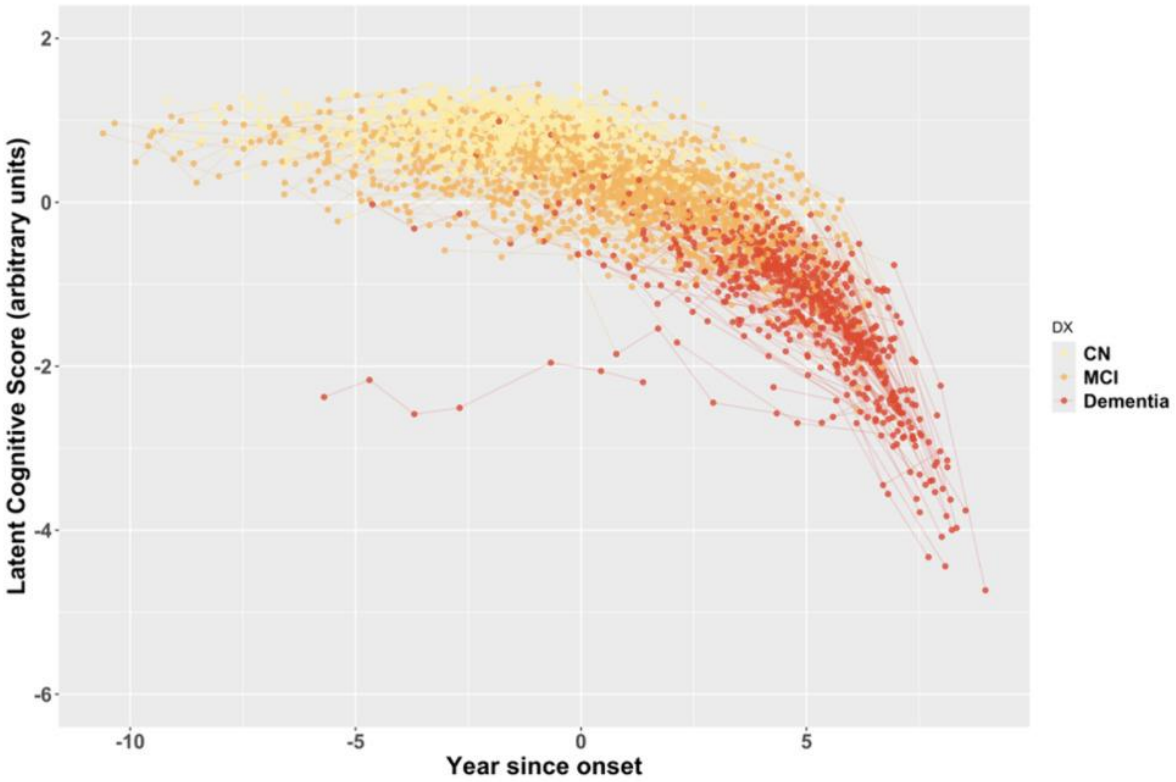

Figure 1: Estimated timeline of AD progression based on the Latent score

Conclusions: A CFA-based latent cognitive score provides a statistically robust alternative to using individual cognitive scores, offering a stronger model fit for tracking disease progression. Such a model holds significant potential for more effective monitoring and intervention planning in clinical and research settings.

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NEUROPSYCHIATRIC INVENTORY AND INSTRUMENTAL ACTIVITY OF DAILY LIVING PREDICT CSF-BASED DIAGNOSIS ACROSS AMYLOID-TAU PATHOLOGIES IN ALZHEIMER'S DISEASE

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Aims: This study investigated whether neuropsychiatric symptoms and daily functional activities could predict cerebrospinal fluid (CSF) biomarker outcomes associated with the amyloid-tau pathologies in Alzheimer's disease (AD). We model relationships between neuropsychiatric inventory (NPI) scores, instrumental activities of daily living (I-ADL), and CSF biomarkers using Athena Diagnostics criteria.
Methods: A cohort of 452 participants was classified based on CSF biomarker criteria: Consistent AD (196: P-Tau >68 pg/mL, ATI (A-beta 42 to T-tau Index) <0.8), Borderline (B) (125: P-Tau 54–68 pg/mL or ATI 0.8–1.2), Non-consistent AD (Non-AD) (82: P-Tau <54 pg/mL, ATI >1.2), and Indeterminate (IND) (49). Key demographics included age (range 45–93), gender (49.1% female, 50.9% male), and race (72.6% Caucasian, 12.8% African American, 11.9% Other). CSF biomarkers are ATI 0.7 (0.4–1.2), Aβ 42 530.8 (397.6–697.7), T-Tau 405.5 (252.2–647.4), and P-Tau 67.4 (46.9–94.0). Multiple measurements of NPI and I-ADL are summarized as mean, min, max, range, std, and count.
Results: The XGBoost model best distinguished Non-AD vs. B cases, with AUC 0.720 ± 0.028 on the hold-out test set. Classification between B vs. AD groups was more challenging, with AUC 0.551 ± 0.065, likely due to overlapping characteristics in NPI and I-ADL as Non-AD vs B and AD 0.694 ± 0.042. Non-AD vs. IND is AUC 0.629 ± 0.089. In classification across all categories, performance AUC was 0.599 ± 0.036, while Non-AD vs Others AUC: 0.656 ± 0.058.
Conclusions: The strong performance in distinguishing Non-AD from borderline amyloid-tau pathologies highlights the potential of NPI and I-ADL for differentiating AD-related pathologies. However, classification between Borderline vs. AD pathology and multi-group classification remains challenging due to overlapping characteristics in NPI and I-ADL scores. Further enhancing accuracy areas may require incorporating additional biomarkers and refining diagnostic methodologies.

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DIFFERENCES IN THE PREFRONTAL HEMODYNAMIC RESPONSE IN NORMAL AGING AND ACTIVE AGING: A FNIRS STUDY

Clara Iñesta[1], Joaquín Ibáñez-Ballesteros[2], Sergio Molina-Rodríguez[1], Javier Oltra-Cucarella[1], Beatriz Bonete-López[1], Esther Sitges-Maciá[1]
[1]Universidad Miguel Hernández de Elche, Departamento De Psicología De La Salud, Elche, Spain, [2]Universidad Miguel Hernández de Elche, Departamento De Fisiología, Elche, Spain

Aims: The progressive aging of the population and the absence of effective treatments for Dementia highlights the need for early identification of cognitive impairment and biomarkers of brain dysfunction. Considering the evidence on the protective effect of active aging on the brain and cognitive performance, the aim of this work is to analyze the differences on the prefrontal hemodynamic response in a group of cognitively active older adults (GA) and a group of older adults from the community (GC), using the near infrared spectroscopy technique (fNIRS).
Methods: The GA (n=16) and the CG (n=16) were assessed with a battery of neuropsychological tests and a scale of cognitively stimulating activities, and their brain activity was recorded with a NIRS device. A cyclic mental task is used to induce cyclic oscillations of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) in the form of spectral peaks at the task frequency (0.033Hz) compared to the Base Line and analyze changes in cerebral and extracerebral hemodynamic activity.
Results: No differences in cognitive performance between the groups were found. Significant differences were found in the frequency of cognitively stimulating activities ($U = 60.50$, $z = -2.36$, $p = .018$) and in the Spectral Power of the brain signal ($p= .007$) and the surface signal ($p=.008$), with greater amplitude in the CG. This difference suggests a possible compensatory overactivation response in the CG subjects.
Conclusions: The study confirms the protective effect of active aging on the brain and cerebrovascular health, as well as the efficacy of the fNIRS technique to develop early biomarkers of abnormalities in the hemodynamic response of older adults with the aim of preventing pathologies such as dementia.

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METHYL SUBSTITUTION ON FLUORESCENT PROBES EXHIBITS INCREASING FLUORESCENCE DISCRIMINATION OF TAU AND AMYLOID BETA WITH INCREASING LENGTH OF THE FLUOROPHORE

Erin Jessup, Rachel Ehrlich, Kristine Teppang, Jerry Yang
University of California San Diego, Chemistry And Biochemistry, La Jolla, United States of America

Aims: Diagnosing neurodegenerative diseases is often a time-consuming and costly process, with current technologies such as PET scans providing valuable but expensive insights into disease-related proteinopathies. Amyloid-targeting fluorescent probes offer a promising alternative for detecting amyloid aggregates in a more accessible and patient-friendly manner. In this study, we demonstrate that fluorescent probes can exhibit distinct emission profiles when bound to tau and amyloid-β aggregates, allowing for the discrimination of the two proteinopathies.
Methods: We synthesized a family of Aryl Cyano Amides with varying π network lengths, including methylated variants for each compound (see Figure 1). To assess fluorescence emission, we stained human brain tissue containing amyloid-β aggregates and mouse brain tissue with tau deposits using our library of probes. Fluorescence emission intensity was measured by capturing lambda scans with a confocal microscope.

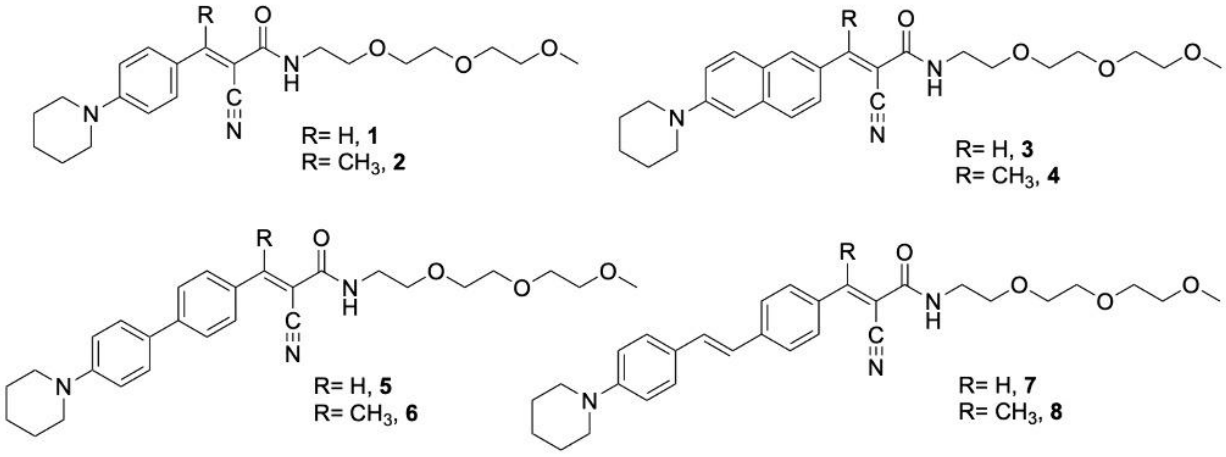

Figure 1 Library of Aryl Cyano Amides probes with increasing pi network length

Results: We observed that increasing π network length in methylated probes resulted in a greater distinction in emission wavelengths between amyloid-β and tau. Notably, Probe 8, the methylated probe with the longest π network, exhibited the largest wavelength shift between amyloid-β and tau (Figure 2b). Additionally, Probes 1, 2, and 4 showed no binding to amyloid-β, highlighting their potential for tau-specific detection.

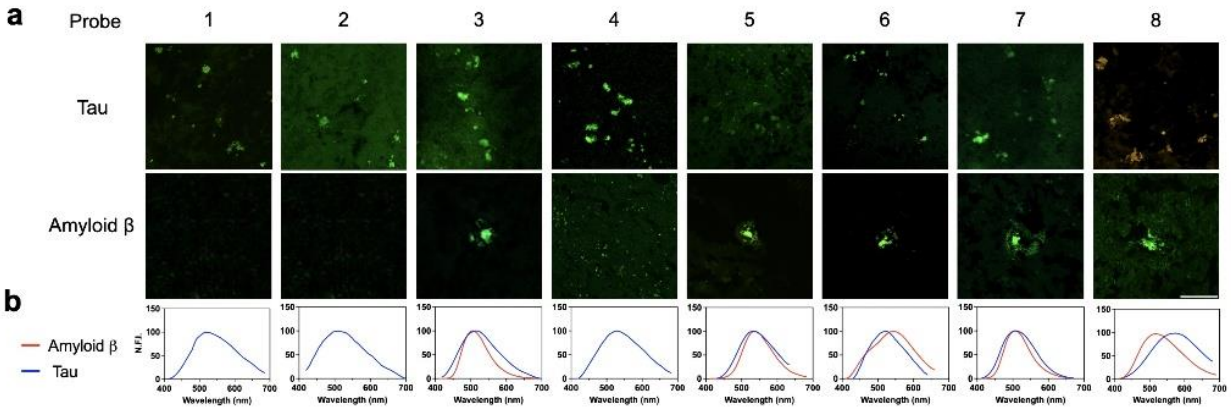

Figure 2 Brain tissue staining with **Probes 1-8 (a)** Images of probes 1-8 bound to tau in tau-positive mouse and amyloid β in Alzheimer's tissue from human. **(b)** Emission wavelengths of probes 1-8 bound to amyloid β and tau. Scale bar= 50um

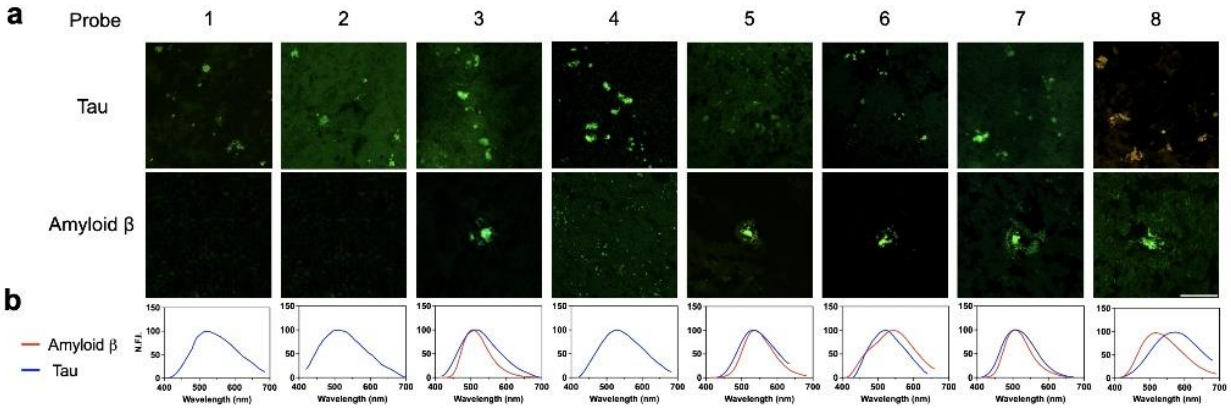

Figure 2 Brain tissue staining with **Probes 1-8 (a)** Images of probes 1-8 bound to tau in tau-positive mouse and amyloid β in Alzheimer's tissue from human. **(b)** Emission wavelengths of probes 1-8 bound to amyloid β and tau. Scale bar= 50um

Conclusions: Our findings demonstrate that adding a methyl substitution and increasing the π network length in amyloid-targeting fluorescent probes enhances the differentiation of emission wavelengths when bound to distinct amyloid species. Using small fluorescent molecules to discriminate between proteinopathies offers a promising alternative to radioactive ligands for aiding in the diagnosis of neurodegenerative diseases in patients.

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UNDERSTANDING THE FACTORS CONTRIBUTING TO ALZHEIMER'S DISEASE MISDIAGNOSIS

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[1]University of Eastern Finland, Institute Of Clinical Medicine, Neurology, Kuopio, Finland, [2]University of Oulu, Research Unit Of Clinical Medicine, Oulu, Finland, [3]Lund University, Division Of Clinical Sciences Helsingborg, Department Of Clinical Sciences Of Lund, Lund, Sweden, [4]Oulu University Hospital, Medical Research Center, Oulu, Finland, [5]Oulu University Hospital, Neurocenter, Oulu, Finland, [6]Kuopio University Hospital, Neuro Center – Neurology, Kuopio, Finland

Aims: Especially the early Alzheimer's disease (AD) diagnosis is particularly challenging to make since earliest diagnostic findings may not have enough specificity. Potential cofounding factors may also increase the risk for misdiagnosis of AD. The aim of this study is to assess the factors contributing to the misdiagnosis of AD.
Methods: This retrospective multicenter study included AD misdiagnosed cases from Ängelholm/Lund, Sweden, and Kuopio and Oulu, Finland. Cases were originally diagnosed with AD, and after follow-up data or neuropathological analysis, were confirmed to have some other diagnosis than AD. Patient records were manually reviewed to identify variables that contributed to the misdiagnosis.
Results: Approximately 80 misdiagnosis cases were identified. Our collaboration will produce aggregated data on individuals misdiagnosed with AD, including a comprehensive clinical profile that covers e.g., age at onset, sociodemographic information, CDR, neuropsychological test results, imaging, CSF biomarkers and co-morbidities.
Conclusions: This study will indicate the factors that increase the risk for misdiagnosis of AD. Factors reviewed include e.g. sociodemographic data, co-morbidities and the limitations in the use and interpretation of the current diagnostic assessments. The results of this study emphasize the urgent need for more disease-specific, cost-effective, and accessible diagnostic tests to enhance the accuracy of AD diagnosis.

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THE CLINICAL HETEROGENEITY OF EARLY-ONSET ALZHEIMER'S DISEASE: PRESENTATION OF THE CLINICAL CASE

Sabina Munasipova[1], Zuleykha Zalyalova[1], Milyausha Yusupova[2], Alsu Akhunova[3]
[1]Kazan State Medical University, Neurology, Kazan, Russian Federation, [2]Hospital of the Federal Medical Biophysical Center named after A.I.Burnazyan, Neurology, Moscow, Russian Federation, [3]Republican Clinical Hospital, Neurology, Kazan, Russian Federation

Aims: description of own clinical observation of laboratory-confirmed Early-onset Alzheimer's disease (EOAD)
Methods: clinical and anamnestic assessment of the patient laboratory tests of CSF and blood serum; MRI of the brain
Results: According to the patient who is Male 54 years old, he had been ill for six months, when he began to notice a decrease in memory for current events, forgetting his things. According to the patient's son, he had been ill for a year and a half, when the family began to notice emotional and personal changes: he became calm, apathetic, showed no interest in surrounding events and people. Actually, he did not notice any memorization of current events. He continued to drive his car, but used only previously known routes.There is no family history of cognitive decline.*Neuropsychological testing.* Elements of limb-kinetic apraxia in the hands. MoCA–25 points with in the visual executive disturbances, delayed reproduction; ACE: 89/100 points: attention 15/18, memory 20/26, speed of verbal associations-14/14, speech-26/26, visual-spatial functions 14/16; FAB-13/18; SDMT 3 mistakes from total 18 comparisons; HADS-anxiety-10, depression-7. MRI of the brain: Structural fronto-temporal atrophy; the volume of the hippocampi is without visible changes. There were not detected other signs of oncological or autoimmune or metabolic disorders. Molecular genetic testing revealed the E3/E3 genotype; C9orf72 gene was negative; Tau p181 in CSF–57–increased; Ab(1-42) in CSF–240–decreased.
Conclusions: Given the absence of a hereditary nature and early atypical onset of the disease, atrophy of the frontotemporal regions of the cerebral cortex with preserved hippocampus, laboratory biomarkers of the E3/E3 genotype, Ab and tau p181 levels in the CSF, the patient was diagnosed with non-Mendelian EOAD with atypical onset and he is possible candidate for therapy with human IgG1 monoclonal antibody (lecanemab).

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WHOLE GENOME SEQUENCING OF ALZHEIMER'S DISEASE IN AFRICAN POPULATIONS: INSIGHTS FROM THE DAWN STUDY

Biniyam Ayele[1], Farid Rajabli[2], Larry Adams[2], Patrice Whitehead[2], Jacob Mccauley[2], Motunrayo Coker[3], Kazeem Akinwande[4], Samuel Diala[4], Mayowa Ogunronbi[4], Scott Kyle[2], Reginald Obiako[3], Kara Hamilton-Nelson[2], Katalina Mcinerney[2], Andrew Zaman[2], Izri Martinez[2], Kolawole Wahab[5], Pedro Mena[2], Albert Akpalu[6], Brian Kunkle[2], Fred Sarfo[7], Jeffery Vance[2], Njideka Okubadejo[8], Olusegun Baiyewu[9], Michael Cuccaro[2], Susan Blanton[2], William Bush[10], Raj Kalaria[11], Goldie Byrd[12], Adesola Ogunniyi[4], Mayowa Owolabi[9], Anthony Griswold[2], Margaret Pericak-Vance[2], Rufus Akinyemi[4]
[1]John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, United States of America, Miami, United States of America, [2]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [3]Ahmadu Bello University, Zaria, Nigeria, [4]Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria, [5]University of Ilorin Teaching Hospital, Ilorin, Nigeria, [6]University of Ghana, Accra, Ghana, [7]Komfo Anokye Teaching Hospital, Kumasi, Ghana, [8]University of Lagos, Lagos, Nigeria, [9]University College Hospital, Ibadan, Nigeria, [10]Department of Population and Quantitative Health Sciences, Institute for Computational Biology, Case Western Reserve University, Cleveland, United States of America, [11]Newcastle University, Newcastle, United Kingdom, [12]Wake Forest School of Medicine, Maya Angelou Center For Health Equity, Winston-Salem, United States of America

Aims: To identify rare, pathogenic AD variants through a whole genome sequencing (WGS) analysis of cohort of individuals from Nigeria, Ghana, Kenya, Ethiopia, and Mozambique.
Methods: We performed whole genome sequencing of 441 individuals from AfDC sites in Nigeria, Ghana, Kenya, Ethiopia, and Mozambique. DNA was extracted at the University of Ibadan, Nigeria and an aliquot shipped to the University of Miami for processing. The sequencing was done using standard PCR-free Illumina whole genome sequencing protocols on the NovaSeqX Plus instrument. We applied an Alzheimer's Disease Sequencing Project (ADSP) developed bioinformatics pipeline and quality control procedures. Variants were filtered for those in 22 established AD genes and risk loci based on the ADSP Gene Verification Committee recommendations including genes with variants causing familial AD (e.g. *PSEN1, PSEN2, APP*) and those with rare susceptibility variants (e.g. *SORL1, TREM2, APOE*). The prioritized rare variants were confirmed using Sanger sequencing.
Results: Of the 441 participants, the mean age at examination was 74.7 years and females accounted for 51.9%. These were divided into AD cases (46.1%), cognitively unimpaired controls (49.2%), and mild cognitive impairment (4.7%). After filtering for AD genes and further filtered for population frequency, we identified a novel mutation in PSEN1 (PSEN1 A431T) in a 63-year-old male AD patient from Nigeria with family history of AD. This variant has never been identified before. Similarly, we identified a previously

reported SORL1 variant introducing a premature stop codon at amino acid 985 (SORL1 R985X) variant in 58-year-old female patients from Nigerian with diagnosis of AD.

Conclusions: We identified a novel PSEN1 variant and a rare SORL1 in this unique African population. This finding supports the importance of the study of diverse ancestries to identify new and recurrent AD causative/risk variants.

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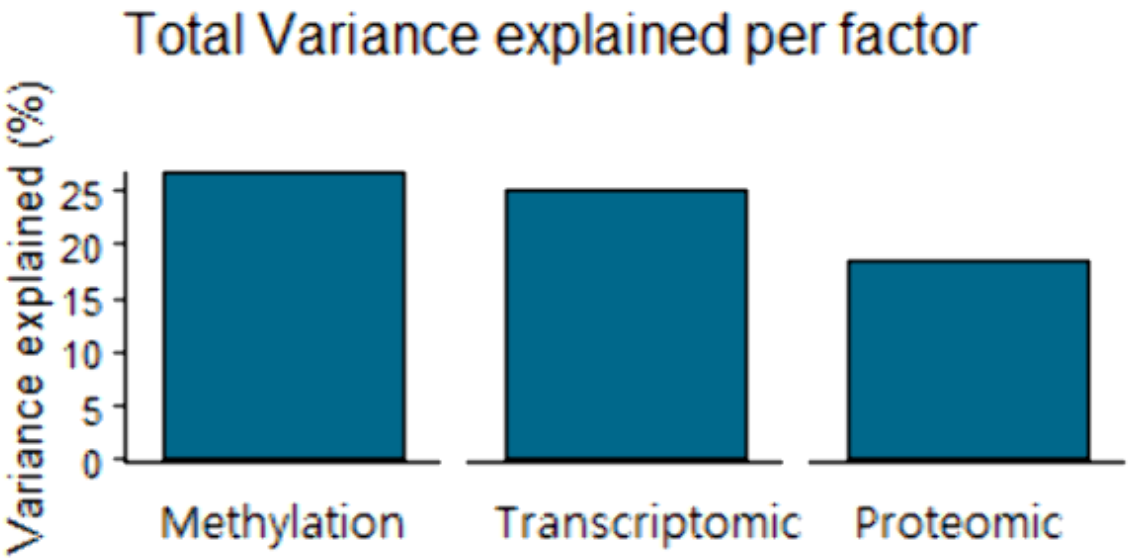
UNRAVELING ALZHEIMER'S DISEASE PATHOGENESIS THROUGH MULTI-OMICS INTEGRATION

Jenny Lee[1,2], Annie Lee[3,4,5]
[1]Ewha Womans University, Department Of Data Science, Seoul, Korea, Republic of, [2]Harvard T.H. Chan School of Public Health, Department Of Biostatistics, Boston, United States of America, [3]Columbia University, Department Of Neurology, New York, United States of America, [4]G.H. Sergievsky Center, Columbia University, New York, United States of America, [5]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, United States of America

Aims: Alzheimer's Disease (AD) has a complex pattern of driver mutations, and much of its clinical and molecular diversity remains unexplained. This study aims to investigate the molecular mechanisms underlying AD using a comprehensive multi-omics integrative approach.
Methods: We applied a multi-omics factor analysis to prefrontal cortex of 445 participants with DNA methylation, transcriptomic, and proteomic data from the Religious Orders Study/Memory and Aging Project (ROS/MAP). Our integrated analysis identified ten latent factors. We investigated the association between these factors and clinico-pathological traits and cardio-cerebral vascular risk factors. Differential gene expression and gene ontology enrichment analyses were performed to uncover molecular pathways associated with the factors.
Results: Participants had a mean age of death of 89 years, with 39% women. The 10 identified factors explained 74% of the total variance across all three omics layers: 30% for DNA methylation, 25% for gene expression, and 19% for proteomics (Figure 1). Two factors (Factors 4 and 7) were significantly associated with steeper cognitive decline, increased risk of AD dementia and pathological AD, and AD pathological hallmarks, including tau, amyloid, TDP-43, and a higher prevalence of APOE ε4 (FDR < 0.05) (Figure 2). These factors were predominantly driven by transcriptomic and proteomic data. Additionally, Factor 7 showed an interaction with sex on AD dementia risk ($p = 0.013$) and was significantly enriched in molecular pathways related to neuronal structure, synaptic transmission, and protein regulation.


Total Variance explained per factor
Variance explained (%)
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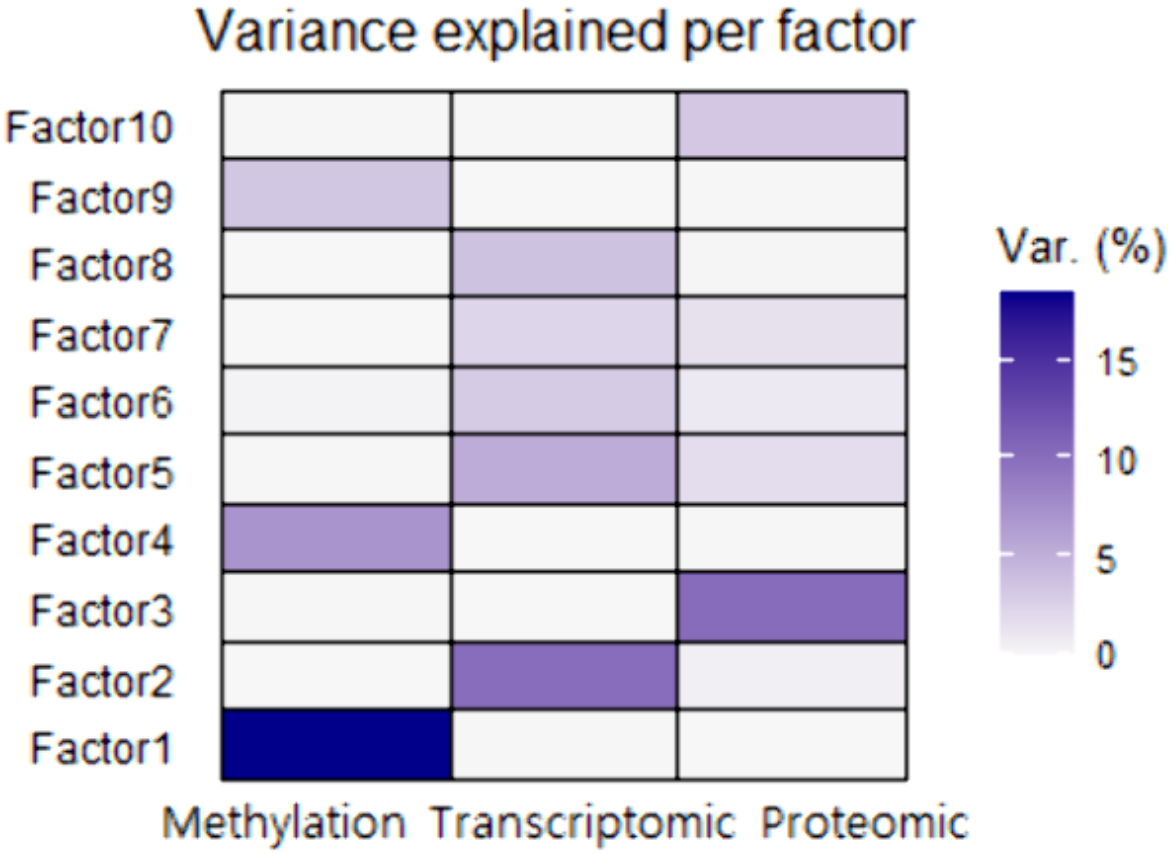
5
10
15
20
25
Methylation
Transcriptomic
Proteomic


Variance explained per factor
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Factor9
Factor8
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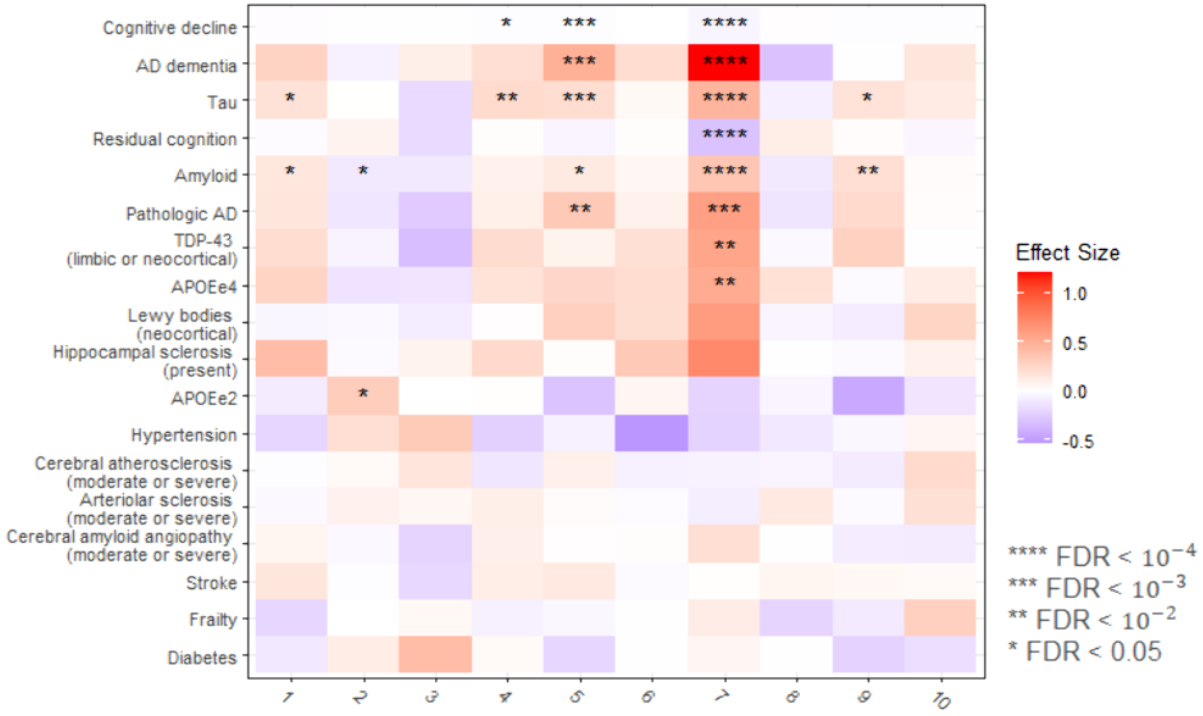
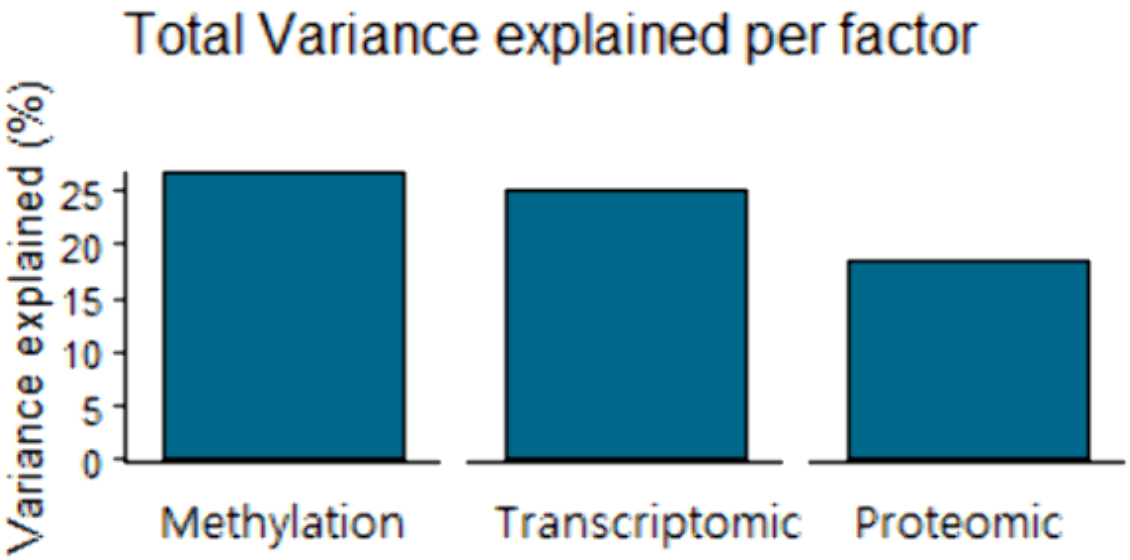
Factor4
Factor3
Factor2
Factor1
Methylation
Transcriptomic
Proteomic
Var. (%)
0
5
10
15

Figure 2. Association between traits (y-axis) and factors (x-axis).




Total Variance explained per factor
Variance explained (%)
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5
10
15
20
25
Methylation
Transcriptomic
Proteomic

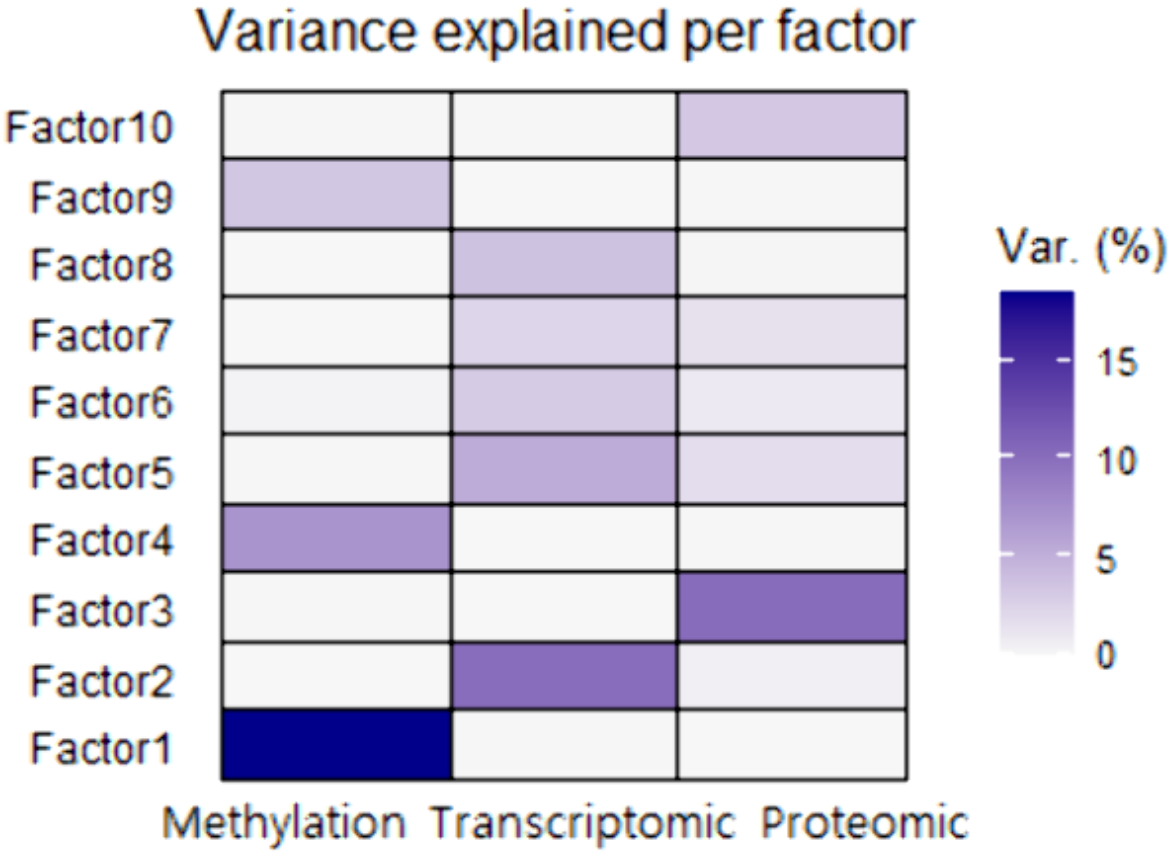
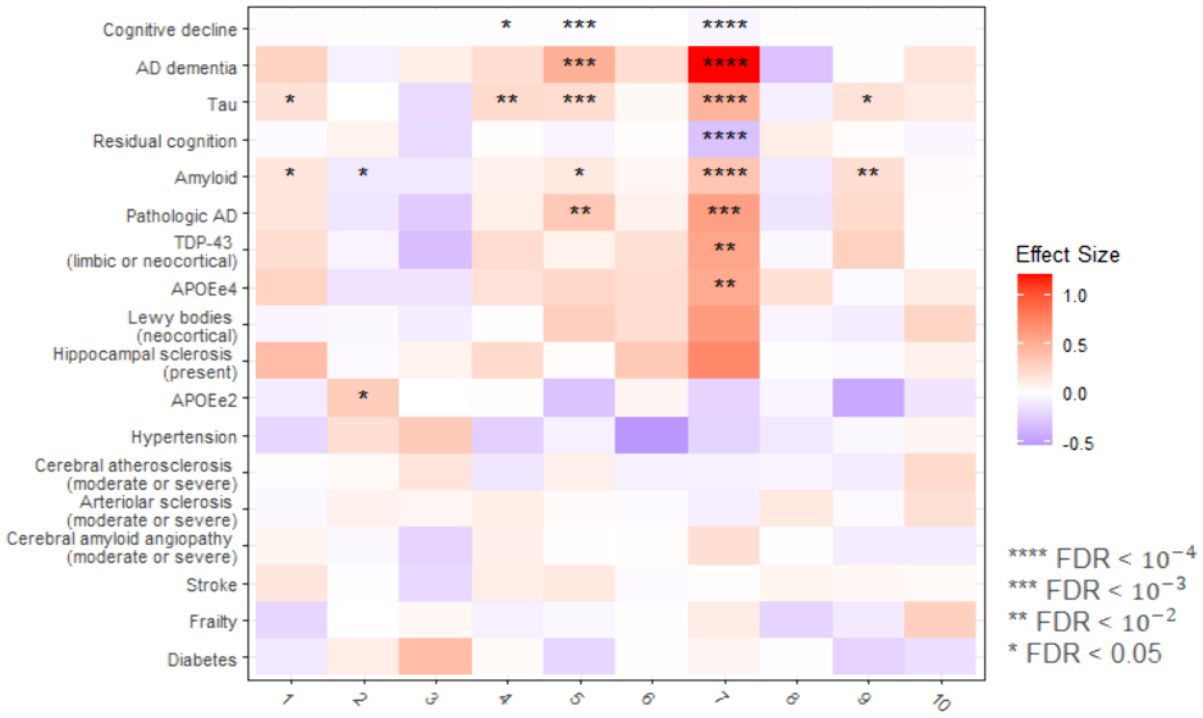

Variance explained per factor
Factor10
Factor9
Factor8
Factor7
Factor6
Factor5
Factor4
Factor3
Factor2
Factor1
Methylation
Transcriptomic
Proteomic
Var. (%)
0
5
10
15

Figure 2. Association between traits (y-axis) and factors (x-axis).



Conclusions: Our unsupervised multi-omics integration approach offers valuable insights into the pathogenesis of AD, highlighting key molecular pathways that contribute to its development and progression.

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AGE-RELATED VARIATION IN THE MAGNITUDE OF COGNITIVE SEX DIFFERENCES: A PSYCHOMETRIC NETWORK ANALYSIS OF INTACT OLDER ADULTS

Anat Rotstein
University of Haifa, Gerontology, Haifa, Israel

Aims: Sex differences in cognition are apparent in late life. Evidence suggests that older females outperform males in general and specific neuropsychological tasks, such as verbal abilities. In contrast, older males perform better than females on tasks that require visuospatial processing. Biological changes associated with aging may partly explain these sex differences, yet evidence suggests that cognitive function is stable across age groups by sex. The current study aims to examine the cognitive networks of older males compared to females, delineated by different age groups, using an alternative approach termed psychometric network analysis.
Methods: The current cohort of community-dwelling adults aged 65 years and older (N=2,802) was derived from the Advanced Cognitive Training for Independent and Vital Elderly study. Late-life cognition was assessed with the Mini-Mental State Examination. Psychometric network analyses were computed on dichotomized items based on bivariate tetrachoric correlation matrixes according to standard guidelines. Analyses were conducted separately for males and females of different age groups (older being >=73 years and younger being <73 years).
Results: Late-life cognition networks clustered into a single subnetwork regardless of sex and age. The older (>=73 years; N=1071) female network had more positive connections (N=52) and fewer negative connections (N=2) than the male (N=350) network (N=49; N=5), whereas the younger (<73 years; N=1054) female network had more negative connections (N=4) than the same-age male (N=326) network (N=0).
Conclusions: Negative network connections between specific cognitive processes may represent neuro-cognitive compensation processes, suggesting that females may compensate earlier than males. By representing cognition as a network or a complex system of internal dynamics, the current study is a step forward in forming a deeper understanding of sex differences in late-life cognition at different ages.

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Virtual EP - 083

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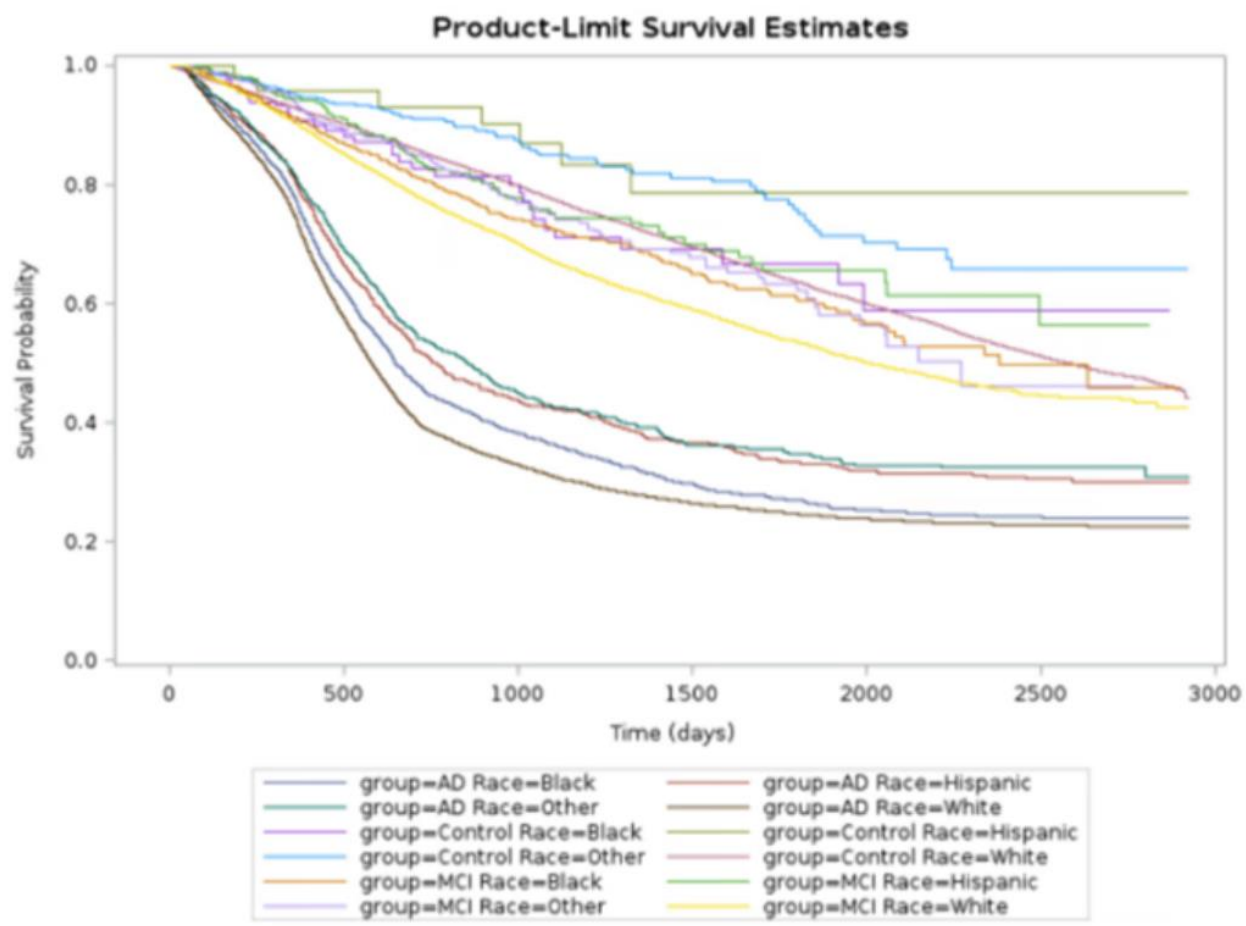
NATURAL HISTORY OF ALL-CAUSE MORTALITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DEMENTIA AMONG UNITED STATES MEDICARE BENEFICIARIES

Raymond Zhang[1], Quanwu Zhang[1], Kavita Nair[2], Ran Gao[1], Babak Haji[1], Amir Tahami Monfared[1]
[1]Eisai, Inc, Nutley, United States of America, [2]University of Colorado Anschutz Medical Capus, Department Of Neurology And Pharmacy, Aurora, United States of America

Aims: Alzheimer's disease is reported as the sixth leading cause of mortality in the US. This study aims to benchmark all-cause mortality in patients 65+ years with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) relative to those without MCI/AD.
Methods: Patients with MCI/AD were randomly selected 1:100 from over 4 million patients identified from the Centers for Medicare and Medicaid fee for service beneficiaries (CMS:2014-2021). A control group without MCI/AD was matched 1:1 by age and sex. All-cause mortality was evaluated through end of 2021 over patient demographics. Poisson regression was used to estimate adjusted rate of mortality rate per 1,000 person-years.
Results: A sample of 48,061 patients with 26% MCI and 74% AD were identified for the study. Mean age at the MCI/AD detection (index date) was 77 years for MCI and 84 years for AD. The combined sample had 65.1% women, 9.8% Black, 3.2% Hispanic, and 82% White. Top 5 comorbidities for the MCI/AD group at index date included hypertension (36.7%), hyperlipidemia (25.3%), mental disorder (21.7%), diabetes (15.5%), and cardiovascular disease (12.2%). Adjusted all-mortality/1,000 patient-years was 278 for MCI and592 for AD compared to 271 for the control group. Mortality/1,000 patient-years were 266 for MCI, 585 for AD, and 262 for control group for women, and 294, 608 and 287, respectively, for men. After statistical adjustment of patient demographics and comorbidities, estimated mortality rates were higher in White relative to Black or Hispanic subgroups across MCI, AD, and control cohorts (*P*'s<0.01) (Figure).


Product-Limit Survival Estimates
Survival Probability
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0.6
0.4
0.2
0.0
0
500
1000
1500
2000
2500
3000
Time (days)
group=AD Race=Black
group=AD Race=Hispanic
group=AD Race=Other
group=AD Race=White
group=Control Race=Black
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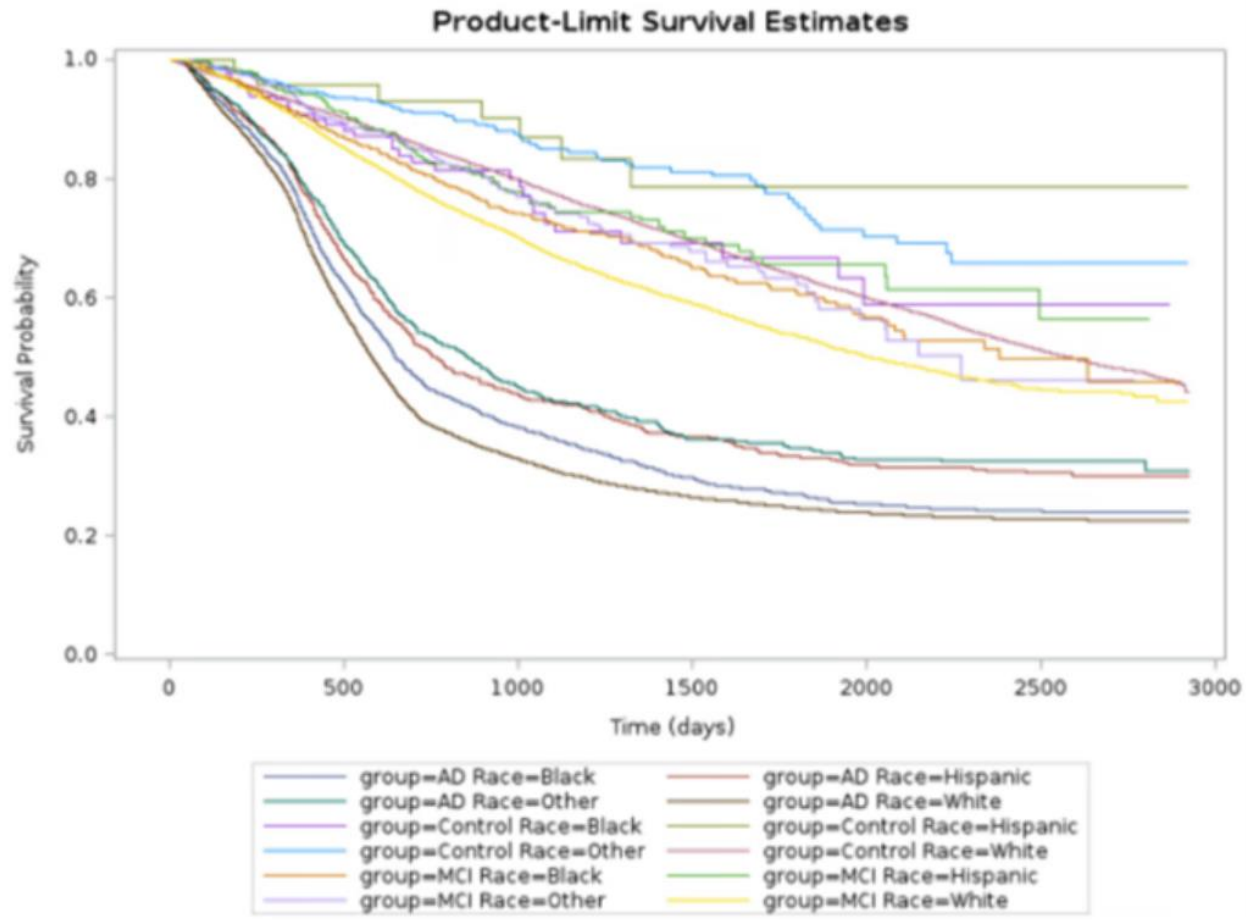

Conclusions: All-cause mortality in MCI is comparable to the matched control cohort from US CMS beneficiaries but doubles with AD. Mortality in White across MCI/AD/control groups is higher relative to Black or Hispanic racial groups.

Virtual EP - 084

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POLYAMINE DYSREGULATION AND NUCLEOLAR DISRUPTION IN AUTOIMMUNE AND NEURODEGENERATIVE DISEASES

Wesley Brooks
University of South Florida, Safety Harbor, United States of America

Aims: This presentation will introduce a new hypothesis, "polyamine dysregulation and nucleolar disruption in autoimmune and neurodegenerative diseases". The hypothesis explains early events common in many autoimmune and neurodegenerative diseases by considering 1) disease tautology, 2) a systems biology approach considering multiple cellular pathways, 3) higher-order epigenetics, and 4) a previously published hypothesis focused on lupus.
Methods: Key word searches (e.g., PubMed, Google Scholar) were used with terms such as "Alzheimer's", "nucleolin", "Alu elements" and key words from an earlier lupus hypothesis "X chromosome-nucleolus nexus". Literature searches identified locations of disease-related genes relative to the nucleolus, peri-nucleolar chromatin, Alu clusters and other pertinent genes.
Results: Correlations emerged between Alzheimer's genes (e.g., tau), Alu elements, and peri-nucleolar chromatin (chromosomes 14, 17, 19, 21 and inactive X), with the possibility that abnormal nucleolar dynamics from cellular stress could disrupt epigenetic control allowing significant Alu expression that disrupts nucleolar functioning. Polyamines drive nucleolar dynamics and the disruption could entail wasteful rounds of polyamine synthesis and recycling, reducing S-adenosylmethionine (SAM) and acetyl-CoA. Low SAM and acetylcholine are reported in Alzheimer's and low SAM triggers p38 kinase phosphorylation of tau. Clusters of Alu elements were found nearby such as the X chromosome's PAR1 (28.8% Alu), chromosome 19 (25.8% Alu), and chromosome 22 long arm (19% Alu).
Conclusions: The hypothesis provides plausible explanations of events that lead to tau and amyloid-β aggregation in Alzheimer's, or autoantigens in other diseases. Central to the hypothesis is nucleolar dynamics driven by polyamines with wasteful rounds of polyamine synthesis and recycling that reduce available SAM and acetyl-CoA. Abnormal nucleolar dynamics can disrupt epigenetic control of Alzheimer's related genes in peri-nucleolar chromatin with opening of Alu elements that further disrupt the nucleolus.

Virtual EP - 085

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PF-04691502, A PI3K/MTOR DUAL INHIBITOR, AMELIORATES AD-LIKE PATHOLOGY IN A MOUSE MODEL OF AD

Marika Lanza, Rossella Basilotta, Giovanna Casili, Salvatore Oddo, Emanuela Esposito
Univesity of Messina, Department Of Chemical Biological Pharmaceutical And Environmental Sciences, Messina, Italy

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder that significantly impacts the lives of patients and their families. The pathological features of AD include the accumulation of amyloid-β (Aβ) and Tau, which disrupt neuronal function and communication, ultimately leading to neuronal loss and brain atrophy. Efforts to understand the molecular mechanisms underlying these pathological changes have led to advancements in diagnostic techniques and potential therapeutic interventions. However, the complexity of AD necessitates further research to develop more effective treatments and, ideally, preventive measures. Extensive research suggests that diminishing mTOR signaling increases lifespan and health span across various species. Increased PI3K/mTOR signaling has been linked to the progression of AD pathology, leading to neuronal degeneration and impairments in cognitive function. In this study, we investigated the effect of PF-04691502, a PI3K/mTOR dual inhibitor, on AD-like pathology in APP/PS1 mice, a widely used animal model of AD.
Methods: 18-month-old APP/PS1 and wild-type mice were dosed orally with 1 mg/kg PF-04691502 for 12 weeks. At the end of the treatment, we assessed changes in spatial learning and memory using the Morris water maze. The mice brains then were processed for neuropathological and biochemical analyses.
Results: We found that PF-04691502 improved learning and memory in APP/PS1 mice and reduced insoluble Aβ brain deposition. Mechanistically, these changes were linked to an increase in autophagy induction.
Conclusions: These results provide preclinical data indicating that PF-04691502 may be a valid therapeutic for AD and other neurodegenerative disorders associated with aging and mTOR hyperactivity.

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SUBCELLULAR SUMO1 AND UBC9 MISLOCALIZATION IN HUMAN POSTMORTMEM TISSUES, BLOOD SAMPLES AND IN VITRO MODELS OF ALZHEIMER'S DISEASE

Marco Cimino[1], Ludovica Zaccagnini[1], Rachele Marino[1], Pamela Cappelletti[2], Jenny Leone[1], Kambiz Hassanzadeh[1], Valeria De Turris[3], Massimo Corbo[2], Melania Filareti[2], Annalisa Davin[4], Emanuele Tino Poloni[4], Vittoria Medici[4], Marco Feligioni[1]
[1]European Brain Research Institute - Rita Levi Montalcini Foundation, Rome, Italy, [2]Casa di Cura Igea, Milan, Italy, [3]Italian Institute of Technology, Rome, Italy, [4]Golgi-Cenci Foundation, Abbiategrasso, Italy

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline of cognitive functions. One of the hallmarks of AD is the formation of cytotoxic protein aggregates, mainly formed by Aβ oligomers and Tau, which lead to neuronal loss. The proteins inside these aggregates often display several aberrant post-translational modifications (PTMs). Nowadays, increasing evidence supports an involvement of the PTM SUMOylation, especially SUMO1-ylation, in AD-related protein aggregation. Therefore, the aim of our work is to gain more insight into the role of SUMO1-ylation in AD.
Methods: By using *in vitro* cellular models, human autoptic brain and peripheral blood samples from patients at different stages of AD, we investigated potential changes in the expression and subcellular distribution of SUMO1 and the SUMO-conjugating enzyme UBC9.
Results: Western blots from AD brains show that while SUMO1-ylation was not affected by the disease severity, Ubc9 expression slightly increased in AD patients. However, in immunofluorescence images, SUMO1 and UBC9 were progressively misplaced from the nucleus to the cytoplasm, where they formed aggregates. SUMO1 and hyperphosphorylated Tau strongly co-localized within these aggregates. Similar findings were also reported in both SH-SY5Y cells and mouse primary neurons exposed to oxidative stress. Interestingly, UBC9 and SUMO1 were detectable in peripheral blood. UBC9, but not SUMO1, expression was higher in peripheral blood monocytes (PBMC) of AD patients, although both proteins were mislocalized to the cytoplasm in AD patients' PBMCs. SUMO1-ylation levels were also modified in neuronal extracellular vesicles purified from the serum of AD subjects.
Conclusions: In conclusion, SUMOylation certainly plays a role in AD-related protein aggregation, making it a candidate therapeutic target. Furthermore, the detection of SUMOylation in blood fractions encourages additional studies to validate it as novel AD biomarker.

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Virtual EP - 087

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TAU PATHOLOGY DIFFERENCES BETWEEN BRAIN REGIONS CHARACTERISED BY QUANTITATIVE MASS SPECTROMETRY

Diana Piotrowska[1], Elena Camporesi[1], Malin Wennström[2], Juan Lantero-Rodriguez[1], Laia Montoliu-Gaya[1], Niklas Mattsson-Carlgren[2], Irena Burmann[3], Johan Gobom[1], Henrik Zetterberg[1], Kaj Blennow[1], Oskar Hansson[2], Gunnar Brinkmalm[1]
[1]Institute of Neuroscience & Physiology, Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry & Neurochemistry, Mölndal, Sweden, [2]Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Faculty of Medicine, Lund University, Lund, Sweden, [3]The Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, Göteborg, Sweden

Aims: Tau alterations are hallmark pathologies of Alzheimer's disease (AD) and other tauopathies. Different phosphorylation sites of soluble tau fragments have been investigated in brain soluble fractions as well as in CSF and plasma. Less is known about the insoluble tau aggregates, especially in other tauopathies like corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP). In the current study, soluble and insoluble fractions from postmortem brain samples, superior temporal gyrus (STG) and fusiform gyrus (FuG), were investigated. Tau from intermediate AD (iAD, n=20), severe AD (sAD, n=20), CBD (n=2), PSP (n=8), and primary age-related tauopathy (PART, n=12) cases was analysed by mass spectrometry (MS) focusing on phosphorylation.
Methods: Soluble (tris-buffered saline, TBS), and sarkosyl-insoluble (SI) brain extracts were immunoprecipitated with the HT7 antibody. Tryptic peptides were monitored by liquid chromatography/high-resolution data-dependent MS using isotope-labelled standards for quantification
Results: The preliminary data shows that phospho-peptide levels, p217, p262, p396, p212+217, p231+235, and p396+404, for the TBS fraction were lowest for PART and CBD/PSP, increased in iAD and further increased in sAD. For p404, the levels were not altered between the groups. The effect was generally more pronounced in FuG than in STG. We did not observe any corresponding significant increase for the non-phosphorylated MTBR peptides, although a trend towards increased levels of these peptides could be observed for iAD and sAD in the FuG region.
Conclusions: The increasingly higher levels of phospho-peptides in iAD and sAD, respectively, is in line with the progression of tau pathology. Moreover, the results suggest that p396 is phosphorylated earlier than p404. STG and FuG are differently affected by tau pathology with FuG being more affected. Data from the SI fraction is currently under analysis and will be presented.

Virtual EP - 088

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DESIGNING AN AAV TO DELIVER TAU TO SPECIFIC INTERNEURON POPULATIONS AND TRACK ITS NEURONAL CELL TO CELL SPREADING IN MURINE MODELS.

Emily Johnson, Yuanyuan Deng, Yazi Ke, Lars Ittner
Macquarie University, Sydney, Australia

Aims: This study aims to develop and validate a method for delivering mutated tau protein to targeted interneuron subsets, like LAMP5, a population implicated in AD. The objective was to validate the AAV in delivering and tracking tau spreading.
Methods: An inducible adeno-associated virus (AAV) delivers genes for human mutant tau and green fluorescent protein (GFP) into all neurons. Initially, these genes remain inactive, integrated behind LOX-P variant recombination sites in the murine genome. Tau and GFP expression occurs only in the presence of CRE-recombinase, which is absent from tissues, keeping the genes silenced until the enzyme is introduced. A second AAV, which expresses CRE-recombinase, activates the genes flanked by LOX-P sites. This enzyme facilitates the necessary recombination to enable tau and GFP expression in targeted neuronal cells. The CRE-AAV is designed to target specific subpopulations of interneurons, ensuring precise activation of the FLEX AAV in these neuronal populations.
Results: Tau expression was successfully induced in targeted neurons, and seen to spread to neighbouring, non-induced populations. Histological analysis validated the accuracy of targeting tau to the intended neurons. Previously validated CRE AAVs were used. GFP expression overlapped with targeted neuron populations tau localisation was similarly observed in these cells. Additionally, cells not directly targeted by the AAV began to show tau expression over time, suggesting tau spreading from initially infected neurons.
Conclusions: This study established a method for the targeted delivery of mutated tau protein to specific interneuron subsets. The primary objectives were to validate the technique for inducing mutated tau in particular interneuron populations, to elucidate how tau spreads from these neurons, and to allow future assessment of specific populations in AD.

Virtual EP - 089

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THE MOLECULAR BASIS FOR DEMENTIA HETEROGENEITY AMONG ALZHEIMER'S PATIENTS.

Sivaprakasam Ramamoorthy
Indian institute of science, Centre For Brain Research, Bangalore, India

Aims: Tau pathology in Alzheimer's disease (AD) patients begins in the transentorhinal cortex and propagates to the limbic system and associated cortical regions. However, there is a heterogeneity in dementia progression in AD patients. The molecular basis of this kind of heterogeneity in dementia is not clear.
Methods: We used human postmortem brain samples with clinical data, western blotting, microscopy (confocal, AFM, and TEM), cell culture, and biochemical and molecular techniques to address the questions.
Results: 1) We report that AD with comorbidities like dementia with lewy bodies (DLB) progresses faster than AD-only. AD-DLB patients had higher levels of soluble oligomeric tau proteins and less insoluble tau proteins compared to AD-only patients. While the frontal lobe is more vulnerable to lewy bodies, tau and α-synuclein aggregate in distinct neurons, indicating selective neuronal and regional vulnerability to tau and α-synuclein pathology. Dysfunctional metabolic pathways are more closely associated with fast-progressing AD-DLB. 2) We found that cognitively resilient AD patients with less tau pathology have preserved V-ATPase expression, suggesting that altered lysosomal pH causes tau proteins to aggregate in cognitively vulnerable AD patients. Lysosomal-degradation-resistant tau fibrils accumulate inside the lysosomes. Lysosomes in Alzheimer's brain contain partially digested, seed-competent pathogenic tau proteins, which are primarily composed of the *amyloidogenic* core, with the peripheral part degraded. We further demonstrate that tau aggregates are secreted via lysosomal exocytosis.
Conclusions: 1) Our study indicates that comorbidities such as α-synuclein aggregation and metabolic dysfunctions are associated with rapidly progressing AD patients, highlighting the importance of subgrouping AD patients for clinical trials. 2) Our data indicates that dysfunctional lysosomes, which contain partially digested secretory tau fibrils in cognitively vulnerable AD patients, secrete the tau proteins extracellularly.

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APOE E4 POTENTIATES TAU-RELATED REACTIVE ASTROGLIOSIS, NEURODEGENERATION AND COGNITIVE DECLINE

Lydia Trudel[1], Joseph Therriault[1], Arthur Macedo[1], Nesrine Rahmouni[1], Etienne Aumont[1], Seyyed Ali Hosseini[1], Stijn Servaes[1], João Pedro Ferrari-Souza[2], Bruna Bellaver[3], Pamela Ferreira[3], Tevy Chan[1], Yi-Ting Wang[1], Jaime Fernandez-Arias[1], Yansheng Zheng[4], Brandon Hall[1], Jenna Stevenson[1], Robert Hopewell[5], Chris Hsiao[5], Thomas Karikari[6], Eduardo Zimmer[2], Andrea Benedet[7], Nicholas Ashton[8], Serge Gauthier[5], Tharick Pascoal[3], Henrik Zetterberg[8], Kaj Blennow[9], Pedro Rosa-Neto[1]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [3]University of Pittsburgh, Pittsburgh, United States of America, [4]McGill University, Neurology And Neurosurgery, MONTREAL, Canada, [5]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada, [6]Department of Psychiatr, University of Pittsburgh, Pittsburgh, United States of America, [7]University of Gothenburg, Gothenburg, Sweden, [8]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, [9]Clinical Neurochemistry Laboratory, Mölndal, Sweden

Aims: Inflammation has been identified as a contributing factor in neurodegenerative processes, with tau pathology often associated with increased inflammatory responses in Alzheimer's disease (AD). The apolipoprotein E (APOE) ε4 allele, a genetic risk factor for AD, is known to modulate both tau pathology and inflammatory cascades in the brain. This study investigated the association between Chitinase-3-like protein 1 (YKL-40), a marker of reactive astrogliosis, and tau burden as measured by positron emission tomography (PET), while exploring the involvement of APOE ε4 carriership.
Methods: We used data from 132 Translational Biomarkers in Aging and Dementia (TRIAD) cohort participants that underwent magnetic resonance imaging (MRI), [^{18}F]MK6240-PET, [^{18}F]AZD4694-PET, APOE genotyping, cerebrospinal fluid (CSF) measurement of YKL-40 and cognitive assessments. We assessed the topographical distribution of YKL-40 mRNA expression using *postmortem* data from the Allen Human Brain Atlas.
Results: Analyses revealed a significant relationship between tau pathology and CSF YKL-40 concentrations, which mirrored the pattern of YKL-40 mRNA distribution in the human brain, indicating an association between AD pathology and reactive astrogliosis. Importantly, the association between tau pathology and YKL-40 was stronger and more widespread in individuals carrying the APOE ε4 allele, suggesting a genotype-specific modulation of the neuroinflammatory response. Finally, we found that higher YKL-40 levels were associated with reduced hippocampal volume cross-sectionally and predicted longitudinal increases in Clinical Dementia Rating Sum of Boxes (CDR SoB) over a median of 2.4 years.

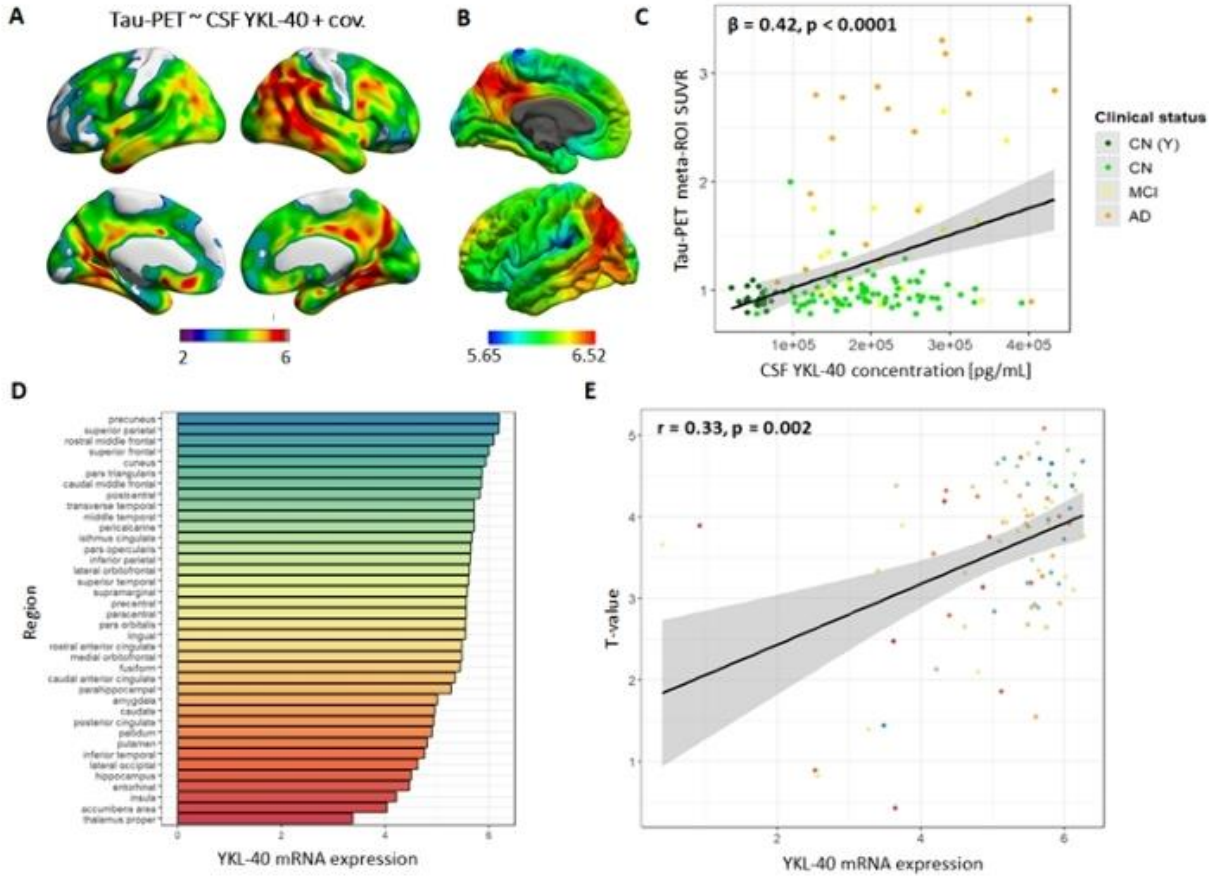

Figure 1. Tau-PET is associated with CSF YKL-40 in regions that resemble those of YKL-40 mRNA expression. (**A**) Voxelwise association between CSF YKL-40 and tau-PET corrected for age, sex and global amyloid-β. Results survived random field theory correction for multiple comparisons at $p < 0.001$. Color bar indicates t-values. (**B**) Brain map of the topographical distribution of YKL-40 mRNA expression in six cognitively unimpaired individuals obtained from the Allen Human Brain Atlas. (**C**) Association between CSF YKL-40 and meta-ROI tau-PET SUVR across clinical diagnoses. We employed a regression model controlling for age, sex and amyloid-β. Beta coefficient represents standardized beta value. (**D**) Bars show average mRNA expression in each DKT brain region. (**E**) Spearman correlation between YKL-40 mRNA expression and uncorrected t-value extracted from association in (**A**). Each dot represents a different DKT brain region.

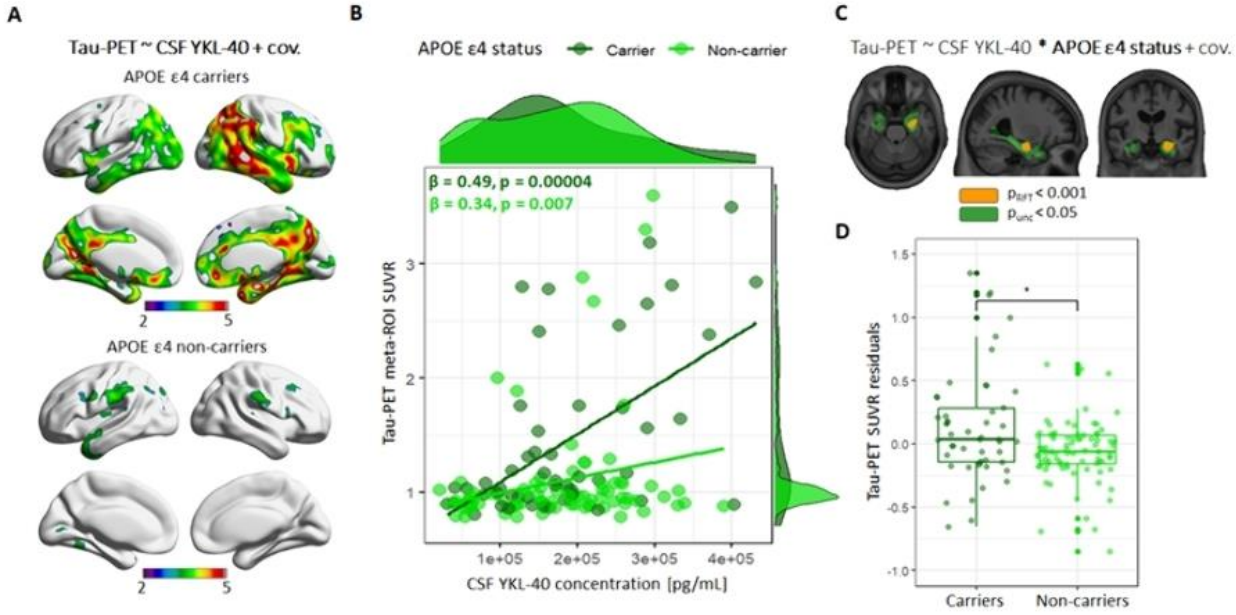

Figure 2. Tau-PET is strongly associated with CSF YKL-40 in APOE ε4 carriers. (**A**) Voxelwise association between CSF YKL-40 and tau-PET in APOE ε4 carriers and non-carriers. Results survived random field theory correction for multiple comparisons at $p < 0.001$. Color bar indicates t-values. (**B**) Association between CSF YKL-40 and tau-PET SUVR in APOE ε4 carriers and non-carriers, correcting for age, sex and global amyloid-β. Beta coefficients represent standardized beta values. (**C**) Voxelwise interaction between CSF-YKL-40 and APOE ε4 status on tau-PET. Orange shows results of interaction corrected for multiple comparisons ($p < 0.001$), green shows uncorrected results ($p < 0.05$). (**D**) Tau-PET SUVR controlling for global amyloid-β in regions of interaction displayed in orange in (**C**), in APOE ε4 carriers and non carriers. Stars show level of significance of Wilcoxon signed-rank test (* = 0.05).

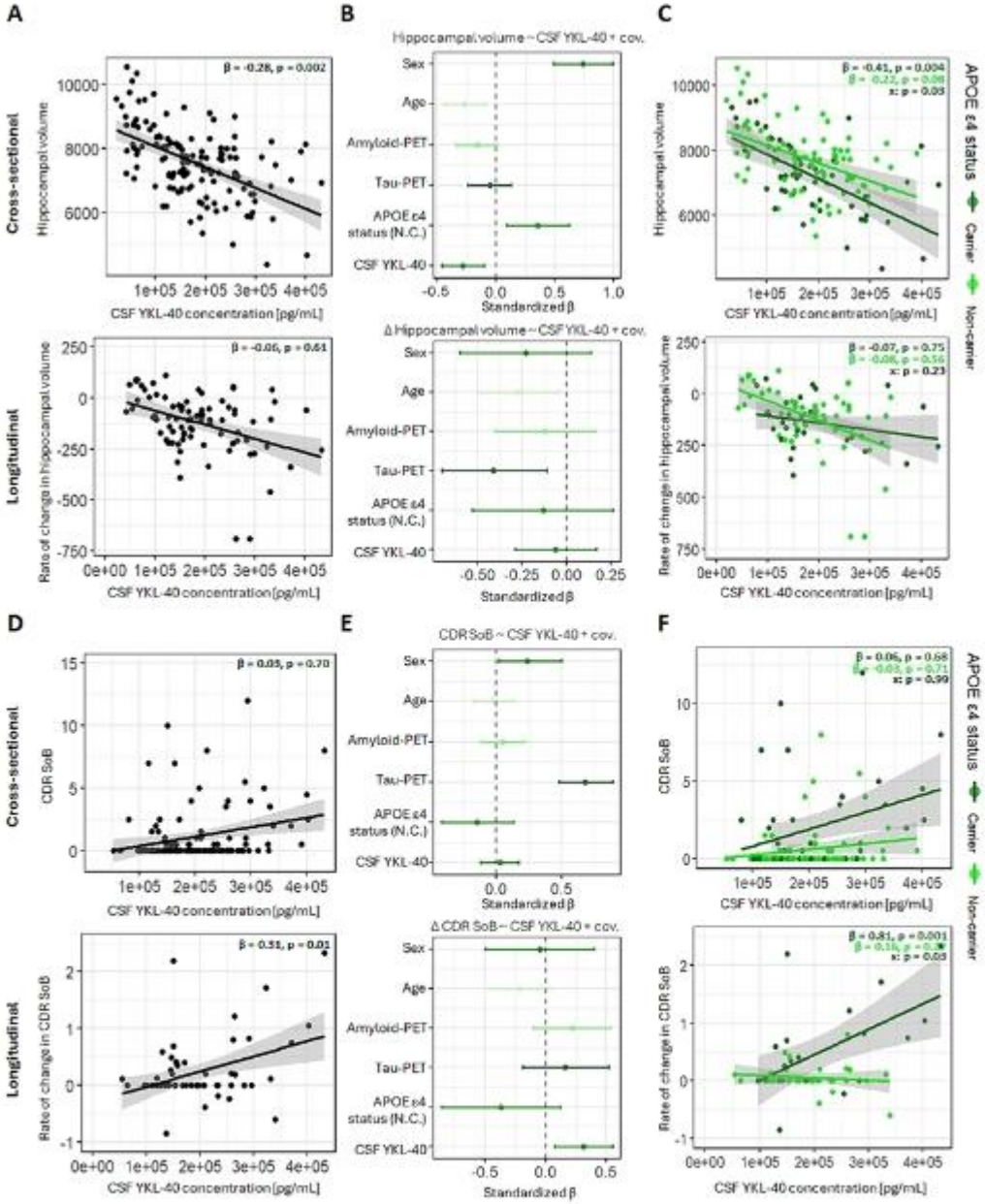

Figure 3. APOE ε4 modulates the relationship between CSF YKL-40 and hippocampal volume and its predictive value for longitudinal clinical impairment. (**A**) Associations between CSF YKL-40 and hippocampal volume (mm^3) and cross-sectionally and longitudinally. (**B**) Forest plots displaying standardized β and 95% confidence intervals of the models. (**C**) Associations in (A), in APOE ε4 carriers and non-carriers. (**D**) Associations between CSF YKL-40 and CDR SoB and cross-sectionally and longitudinally. (**E**) Forest plots displaying standardized β and 95% confidence intervals of the models. (**F**) Associations in (D), in APOE ε4 carriers and non-carriers. Beta coefficients represent standardized beta values.

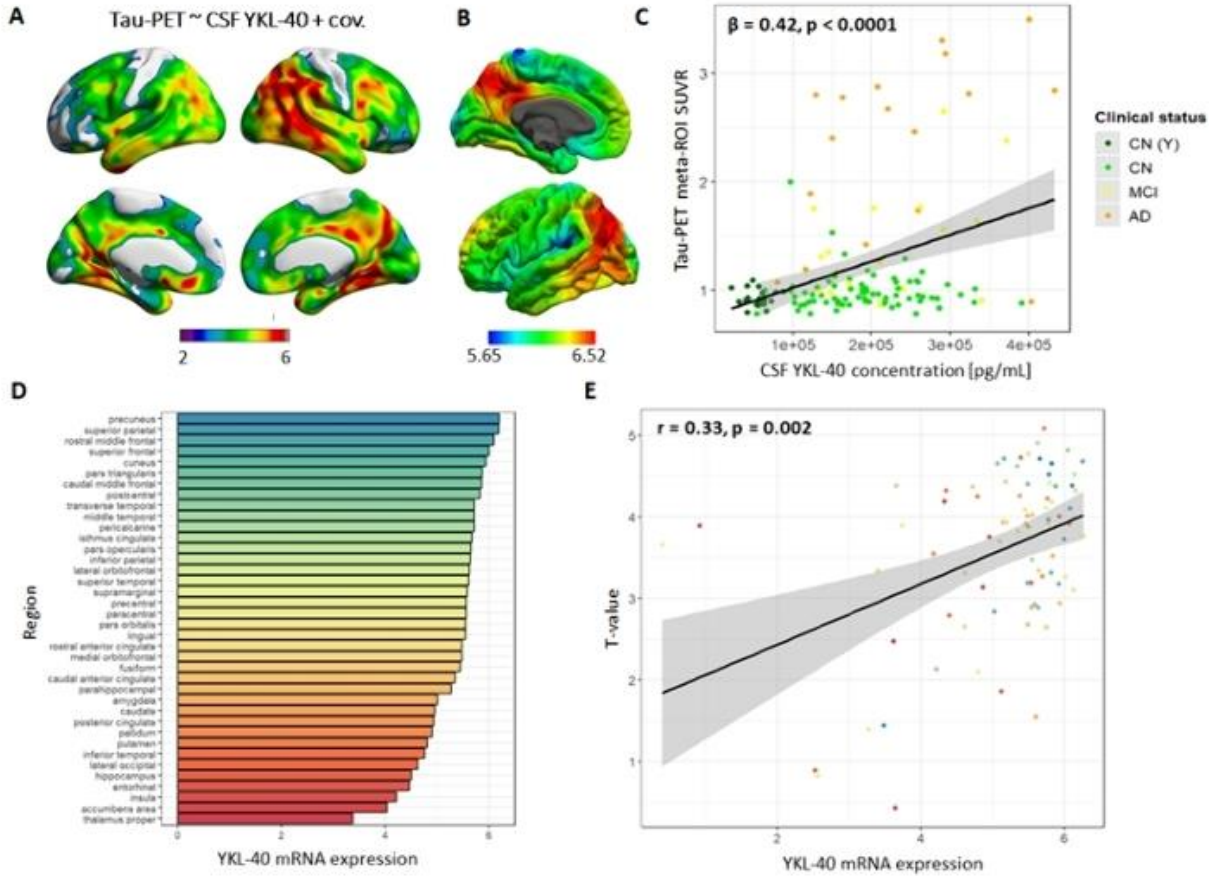

Figure 1. Tau-PET is associated with CSF YKL-40 in regions that resemble those of YKL-40 mRNA expression. (**A**) Voxelwise association between CSF YKL-40 and tau-PET corrected for age, sex and global amyloid-β. Results survived random field theory correction for multiple comparisons at $p < 0.001$. Color bar indicates t-values. (**B**) Brain map of the topographical distribution of YKL-40 mRNA expression in six cognitively unimpaired individuals obtained from the Allen Human Brain Atlas. (**C**) Association between CSF YKL-40 and meta-ROI tau-PET SUVR across clinical diagnoses. We employed a regression model controlling for age, sex and amyloid-β. Beta coefficient represents standardized beta value. (**D**) Bars show average mRNA expression in each DKT brain region. (**E**) Spearman correlation between YKL-40 mRNA expression and uncorrected t-value extracted from association in (**A**). Each dot represents a different DKT brain region.

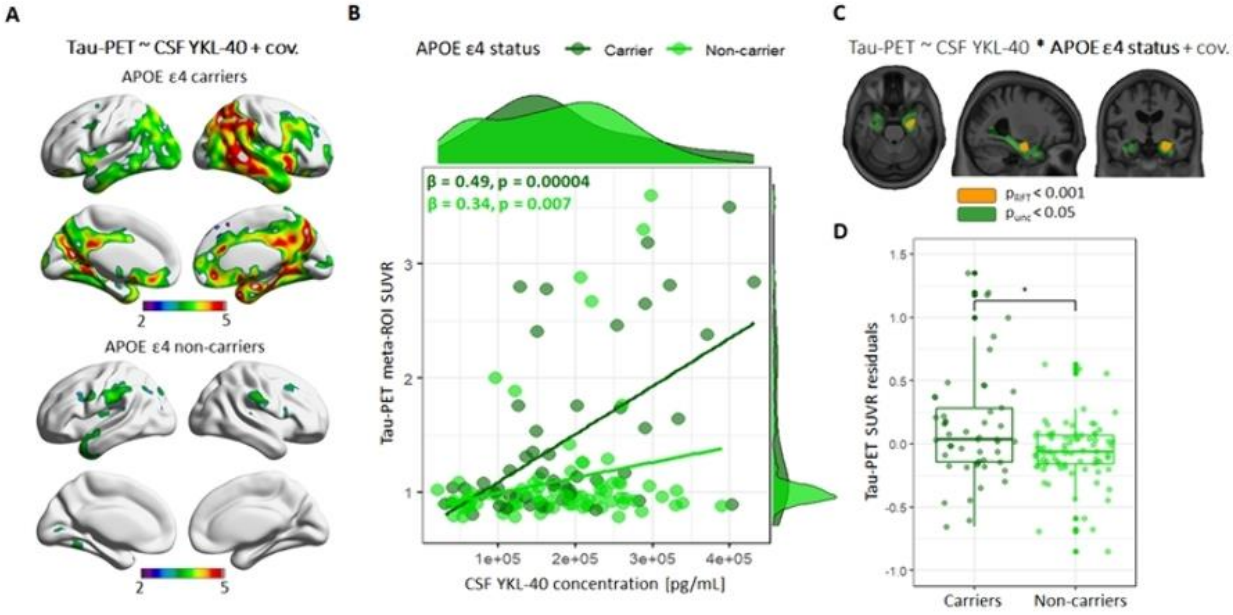

Figure 2. Tau-PET is strongly associated with CSF YKL-40 in APOE ε4 carriers. (**A**) Voxelwise association between CSF YKL-40 and tau-PET in APOE ε4 carriers and non-carriers. Results survived random field theory correction for multiple comparisons at $p < 0.001$. Color bar indicates t-values. (**B**) Association between CSF YKL-40 and tau-PET SUVR in APOE ε4 carriers and non-carriers, correcting for age, sex and global amyloid-β. Beta coefficients represent standardized beta values. (**C**) Voxelwise interaction between CSF-YKL-40 and APOE ε4 status on tau-PET. Orange shows results of interaction corrected for multiple comparisons ($p < 0.001$), green shows uncorrected results ($p < 0.05$). (**D**) Tau-PET SUVR controlling for global amyloid-β in regions of interaction displayed in orange in (**C**), in APOE ε4 carriers and non carriers. Stars show level of significance of Wilcoxon signed-rank test (* = 0.05).

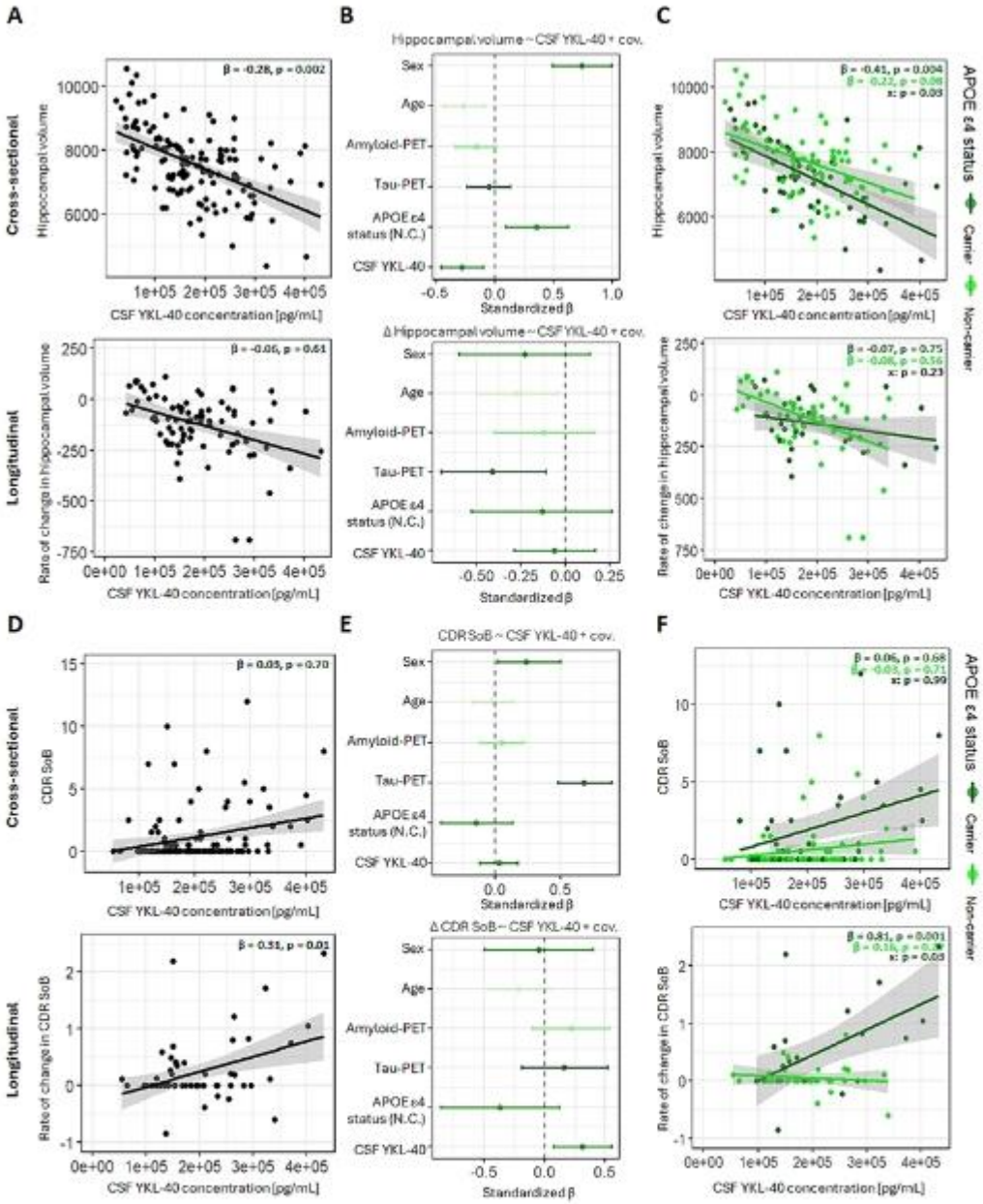

Figure 3. APOE ε4 modulates the relationship between CSF YKL-40 and hippocampal volume and its predictive value for longitudinal clinical impairment. (**A**) Associations between CSF YKL-40 and hippocampal volume (mm^3) and cross-sectionally and longitudinally. (**B**) Forest plots displaying standardized β and 95% confidence intervals of the models. (**C**) Associations in (A), in APOE ε4 carriers and non-carriers. (**D**) Associations between CSF YKL-40 and CDR SoB and cross-sectionally and longitudinally. (**E**) Forest plots displaying standardized β and 95% confidence intervals of the models. (**F**) Associations in (D), in APOE ε4 carriers and non-carriers. Beta coefficients represent standardized beta values.

Conclusions: We observed that APOE ε4 potentiates the association of reactive astrogliosis with tau pathology, downstream neurodegeneration and clinical deterioration. These findings help inform the multifaceted role of tau-associated neuroinflammation in the progression of AD, especially in the presence of genetic risk factors such as APOE ε4.

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Virtual EP - 091

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AGING AND NEURODEGENERATION: USING CANINE COGNITIVE DYSFUNCTION TO EXPLORE BIOMARKERS AND INFLAMMATORY PATHWAYS IN ALZHEIMER'S DISEASE

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Aims: Aging is a significant risk factor for neurodegenerative diseases, such as Alzheimer's Disease and related dementias (AD/ADRD), as well as Canine Cognitive Dysfunction Syndrome (CCD) in dogs. Given the limitations of traditional models in reflecting age-related changes in humans, senior dogs provide a promising natural model for studying neurodegeneration. This research investigates the relationship between behavioral changes and pathological mechanisms of neuroinflammation in geriatric dogs with CCD, utilizing biomarkers relevant to human neurodegeneration, including neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), and amyloid-beta (Aβ) ratios.
Methods: Our study enrolled senior dogs and assessed cognitive and behavioral changes alongside neuropathological and inflammatory events associated with CCD. We *hypothesize* that the toxic signaling events that cause CCD include the accumulation of neurotoxic proteins, which trigger neuroinflammation through the activation of glial inflammatory responses. We address this hypothesis using canines cognition and behavior as they age and CCD progresses prior to analysis of postmortem pathological analyses.
Results: indicate that aging significantly impacts biomarker levels, with reduced Aβ ratios and elevated NfL, correlating with cognitive decline and age. NfL, in particular, demonstrated strong positive correlations with cognitive impairment, suggesting its utility as a non-invasive diagnostic tool. Furthermore, we found that toxic protein accumulation and activation of glia leads to neuroinflammatory responses. We then correlated clinical neurological findings with pathological protein buildup and glial inflammation, as well as analyzing inflammatory signaling through transcriptomic approaches.
Conclusions: Data from canine models will be aligned with existing human ADRD datasets, enhancing the translational value of findings. This work not only highlights the utility of CCD as a model for AD/ADRD but also suggests potential diagnostic and therapeutic targets for neurodegeneration in both humans and dogs.

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COMPARATIVE ANALYSIS OF HUMANIZED TAU MOUSE MODELS IN ALZHEIMER'S DISEASE: UNRAVELING TAU PATHOLOGY

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Aims: Tau pathology is a critical factor in the progression of neurodegenerative diseases, including Late Onset Alzheimer's Disease (LOAD). This study aims to investigate the impact of human tau protein on mouse brain physiology by utilizing genetically modified mouse models that express the human MAPT-GR gene. Specifically, the objectives are to: Evaluate the biochemical and histopathological changes associated with tau pathology in different mouse models. Compare the phenotypic expressions of three humanized tau mouse models: MAPT-GR wild-type, MAPT-GRIVS10+16, and MAPT-GRN279K. Elucidate the spatial and temporal development of tau-related abnormalities to better understand tau's role in neurodegenerative processes.
Methods: To achieve these aims, we employed a comprehensive approach combining biochemical and histopathological techniques. The study examined three distinct mouse models—MAPT-GR wild-type, MAPT-GRIVS10+16, and MAPT-GRN279K—at 4 and 12 months of age. We profiled tau isoforms, assessing post-translational modifications, and studying tau interactions with other cellular constituents to capture the molecular environment of tau pathology.
Results: Differences in tau isoforms and post-translational modifications were noted across the models, reflecting complex tau interactions that resemble human pathology. These variations highlighted the impact of specific genetic modifications on tau behavior and its interaction within the cellular environment. Pathological analysis is ongoing.
Conclusions: This study provides critical insights into how human tau protein influences brain physiology in a murine context, offering a detailed understanding of tau's role in neurodegenerative diseases like Alzheimer's. The observed differences among the mouse models underscore the impact of specific tau mutations on disease progression. These results contribute valuable knowledge that could inform the development of targeted therapeutic interventions aimed at mitigating tau pathology in Alzheimer's disease and related disorders.

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THE IMPACT OF EMPLOYMENT STATUS ON ALZHEIMER'S DISEASE AND COGNITIVE IMPAIRMENT IN AFRICAN AND AFRICAN AMERICAN ADULTS: A GENDER AND AGE STRATIFIED ANALYSIS

Azizi Seixas[1], Carolina Scaramutti[1], Farid Rajabli[2], Larry Adams[2], Michael Cuccaro[2], Joshua Akinyemi[3], African Dementia Consortium (Afdc)[4], Jeffery Vance[2], Margaret Pericak-Vance[2]
[1]Department of Psychiatry and Behavioral Sciences, Miller School of Medicine, University of Miami, Miami, USA, Miami, United States of America, [2]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [3]University of Ibadan, Department Of Epidemiology And Medical Statistics, College Of Medicine, Ibadan, Nigeria, [4]University of Ibadan, College Of Medicine, Ibadan, Nigeria

Aims: Employment status is a recognized social determinant of health that can impact various health outcomes, including cognitive function. However, there is limited research on the relationship between employment status and Alzheimerdisease (AD) or cognitively unimpaired (CU) among African and African American populations. This study aims to examine the association between employment status and AD/CI (cognitively impaired) in these populations, stratified by age and gender, to provide insights into how employment may influence cognitive health, particularly in older adults.
Methods: Data were derived from the READD-ADSP(DAWN) study, comprising 643 participants from 5 African countries and 736 African American participants in the United States. AD status was defined based on clinical diagnoses and AD pathology, while CI was assessed using established diagnostic criteria. Participants were stratified into two age subsets: those aged 65 years and older, and those under 65. Employment status was categorized as currently employed, retired, or not working. Fisher's exact test was used to assess differences in AD and CU status across employment categories, with additional stratification by gender.
Results: The results showed that women, 65 and older, who were currently employed demonstrated a lower likelihood of AD or CI compared to their retired or non-working counterparts (α =.03). No statistically significant associations or trend between employment status and AD/CI were observed among men or younger participants and among African Americans.
Conclusions: Employment status is associated with cognitive health, particularly among older African women.Continued employment in later life appears protective against AD and cognitive impairment.These findings underscore the importance of considering employment as a potential modifiable factor in cognitive health interventions, particularly in aging African and African American populations.Further research should explore the mechanisms behind this association and its implications for health strategies.

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DUPLEX-STRAND SINGLE-NEURON SEQUENCING REVEALS NEURONS ACCUMULATE SOMATIC MUTATIONS INDEPENDENTLY OF TAU IN ALZHEIMER'S DISEASE

Katherine Brown[1], Bowen Jin[1], Denis Smirnov[1], Samantha Kirkham[2], Elizabeth Hennessey[1], Samuel Naik[1], Matthew Frosch[3], Derek Oakley[1], Bradley Hyman[4], August Huang[5], Michael Miller[6]
[1]Brigham and Women's Hospital, Boston, United States of America, [2]Boston Children's Hospital, Boston, United States of America, [3]Massachusetts General Hospital, Neuropathology, Boston, United States of America, [4]Massachusetts General Hospital, Neurology, charlestown, United States of America, [5]Boston Children's Hospital, Genetics And Genomics, Boston, United States of America, [6]Brigham and Women's Hospital, Pathology, Boston, United States of America

Aims: Recent studies have found that neurons accumulate somatic mutations with age, and that mutational accumulation is elevated in Alzheimer's disease (AD) neurons. Pathological deposition of phosphorylated-tau is a hallmark of AD. While only a subset of neurons within affected brain regions exhibit tau pathology in AD, the etiology and pathological consequences of this heterogeneity remain unclear. Comparing the somatic genomic landscape of AD neurons with distinct tau states may reveal whether the accumulation of somatic mutations in AD are driven by disease pathology.
Methods: We developed and applied a fluorescence-activated nuclear sorting method to separate neuronal nuclei by their tau cytopathology. We then employed duplex-strand single-cell genome sequencing to compare the genomes of neurons with distinct tau pathology from AD postmortem brain prefrontal cortex.
Results: We found that tau+ and tau- AD neurons exhibit elevated somatic single nucleotide variants (sSNV) and insertion/deletion (indel) burdens compared to neurotypical controls, in which double-stranded sSNV and single-stranded DNA lesions accumulate with age. Mutational signature analyses implicate disease-associated oxidative damage as a contributor to the elevated AD sSNV burden and reveal a novel indel signature specific to AD. Surprisingly, we observed similarly elevated sSNV and indel burdens in both tau+ and tau- neurons in AD, with abundant oxidative damage signatures.
Conclusions: We observed no significant difference in sSNV or indel burdens between tau+ and tau- neurons in AD, though AD neurons in general accumulated more mutations than controls, regardless of tau pathology. These findings suggest that tau aggregation and somatic mutation accumulation occur independently, pointing to an upstream pathological event driving both processes. Furthermore, our results indicate that tau aggregation may not harm neurons in a cell-autonomous fashion, with implications for tau-targeted therapy.

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EXPLORING THE EFFECT OF GUT MICROBIOME ON INSOMNIA AMONG PATIENTS' WITH PARKINSON'S DISEASE

Shih-Chen Fu
National Dong Hwa University, Department of Biochemical and Molecular Medical Sciences, Hsinchu, Taiwan

Aims: Background: Parkinson's disease (PD) is a neurodegenerative disorder often accompanied by insomnia. The gut microbiome may play a role in these sleep disturbances. **Objective:** To explore the relationship between gut microbiome profiles and insomnia in PD patients, compared with healthy controls. **Methods:** We analyzed the gut microbiome of 299 participants (176 PD patients, 123 controls) categorized by insomnia status. Demographic variables showed no significant differences between insomnia and non-insomnia groups, so they were not controlled. Alpha and beta diversity indices were calculated, and key bacterial taxa linked to insomnia were identified.
Results: PD patients with insomnia showed significant reductions in alpha diversity indices, especially Observed and Chao1 ($p<0.05$). Beta diversity showed significant differences between insomnia and non-insomnia groups in PD ($p=0.001$) and controls ($p=0.036$). In both groups, Bacteroidota significantly increased with insomnia. In PD, insomnia-associated bacteria included Alistipes and Bacteroides.
Conclusions: Gut microbiome profiles differ in PD patients with insomnia, suggesting potential for microbiome-targeted therapies.

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A STUDY PROTOCOL WITH PRELIMINARY RESULTS ON COGNITION, NEUROIMAGING, AND BIOMARKERS AFTER HERPES SIMPLEX ENCEPHALITIS

Eske Gertje[1,2], Danielle Van Westen[3,4], Erik Stomrud[1,5], Shorena Janelidze[1], Laura Wisse[3], Gustav Torisson[6], Sebastian Palmqvist[1,5], Oskar Hansson[1,5], Niklas Mattsson-Carlgren[1,7,8]
[1]Clinical Memory Research Unit, Department Of Clinical Sciences, Malmö, Sweden, [2]Skåne University Hospital, Department Of Internal Medicine, Lund, Sweden, [3]Diagnostic Radiology, Department Of Clinical Sciences, Lund, Sweden, [4]Skåne University Hospital, Imaging And Function, Lund, Sweden, [5]Skåne University Hospital, Memory Clinic, Malmö, Sweden, [6]Skåne University Hospital, Department Of Infectious Diseases, Malmö, Sweden, [7]Lund University, Wallenberg Center For Molecular Medicine, Lund, Sweden, [8]Lund University, Neurology, Lund, Sweden

Aims: Herpes simplex encephalitis (HSE) is a serious infection of the brain and can lead to cognitive impairment. HSE predominantly affects the medial temporal lobes (MTL), which are critical for memory functions. We therefore aim to study effects of encephalitis caused by herpes simplex virus 1 (HSV-1) or human herpes virus 6 (HHV-6) on long-term cognition and function as well as structural brain changes after infection. Finally, we also aim to study associations with fluid biomarkers of amyloid and tau pathologies, and test if these are linked to changes in cognition and function.
Methods: Patients from southern Sweden diagnosed during 2001-2024 with HSE have been identified retrospectively using the clinical laboratory database on CSF samples that have tested positively for HSV-1 or HHV-6 virus PCR. Healthy controls (CU) and Alzheimer's Disease (AD) patients were enrolled from the BioFINDER study and age-matched to the HSE cohort. All participants underwent neuropsychological examination, 7 Tesla MRI scan (if no contraindications), and CSF and blood collections. CSF Aβ42/40 ratio, p-tau and t-tau levels were determined. An automatic segmentation method of hippocampal subfields (ASHS) will be applied to T2 weighted MRI scans and medial temporal lobe subfield volumes will be measured.
Results: The population includes participants with HSE (due to HSV-1 or HHV-6), CU, and AD. Most participants had MRI scans and all underwent cognitive testing and blood collection. Results of group-wise comparisons will be presented at ADPD.
Conclusions: Study results might give insights into the degree of involvement of AD pathobiological changes in a HSE-population.

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PROTECTIVE EFFECTS OF COFFEE ON PARKINSON'S DISEASE: THE ROLE OF GUT MICROBIOME MODULATION

Sheng-Hsuan Lin[1,2]
[1]Institute of Statistics, Hsinchu, Taiwan, [2]National Yang Ming Chiao Tung University, Institute Of Statistics, Hsinchu, Taiwan

Aims: Background: This study investigates the potential protective effects of coffee consumption against Parkinson's Disease (PD) through its impact on gut microbiome composition. **Objectives:** To assess whether regular coffee consumption is associated with a reduced incidence of PD and whether these effects are mediated by changes in gut microbiota.
Methods: Methods: Participants were recruited, and coffee consumption data were collected. Gut microbiome composition was analyzed using 16S rRNA sequencing. Statistical comparisons between coffee consumption groups were conducted to evaluate differences in microbiota and PD incidence.
Results: Results: Participants consuming >1 cup/day of coffee exhibited a significantly lower PD incidence compared to non-coffee drinkers (53% vs 66%, $p<0.05$). Significant alterations were observed in 2 bacterial genera and 1 species among participants consuming >3 cups/day. No significant differences were noted in α or β diversity indices between the groups. Gut microbiome changes accounted for 5.06% of the protective effect of coffee against PD.
Conclusions: Conclusion: Regular coffee consumption may offer protection against PD through multiple mechanisms, including modulation of the gut microbiome. Further research is warranted to explore the underlying pathways and implications for PD prevention.

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COMPOUND SCREENING FOR ALPHA-SYNUCLEIN DIRECTED SMALL MOLECULES

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[1]Newcastle University, Campus for Ageing and Vitality, Newcastle, United Kingdom, [2]Newcastle University, Newcastle, United Kingdom

Aims: A significant feature of dementia with Lewy bodies and Parkinson's disease with dementia is the eventual spread of oligomeric and aggregated alpha-synuclein into anatomically connected cortical areas. This is seen clinically as increasing severity of dementia due to increasing severity of underlying alpha-synuclein pathology impacting previously unaffected areas. Preventing the spread of alpha-synuclein would be expected to delay the onset of specific clinical features, reduce the severity of symptoms, or prevent disease progression. Identifying compounds that can prevent the aggregation of alpha-synuclein would be a step forward in preventing disease progression in Lewy-body disorders.
Methods: We have begun screening a series of small molecules for their activity in preventing aggregation of alpha-synuclein in DLB and PDD using an approach used for compound screening. Recombinant wild type alpha-synuclein has been primed to aggregate by seeding with preformed fibrillar alpha-synuclein in the presence of Thioflavin-T to monitor aggregation of monomers with time.
Results: Our findings indicate that choice and concentration of solvent used for solubilising small-molecules has a measurable effect on alpha-synuclein aggregation rates. Typical solvents such as dimethyl-sulfoxide or ethanol used at standard concentrations, 128mM/1% or 217mM/1% respectively, can promote or delay aggregation, potentially masking any effects of the compounds being screened. Since reactions are performed in an aqueous environment, compound solubility becomes critical with precipitation of compounds at micromolar concentration potentially promoting alpha-synuclein aggregation. As Thioflavin-T fluorescence is used as a readout for aggregation of alpha-synuclein, compounds that interfere with the low affinity binding of Thioflavin-T to alpha-synuclein can produce false positive reactions without preventing aggregation.
Conclusions: Our results indicate that careful selection of compound concentration, solvent type and concentration, are needed for the identification of much needed small molecules targeting alpha-synuclein aggregation.

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MODULATING TAU: EXPLORING NOVEL ASOS IN NEURODEGENERATIVE DISEASES

Carlos Marques[1], Bruno Godinho[2], Jonathan Watts[3], Nuno Sousa[1], Ioannis Sotiropoulos[4], Joana Silva[1]
[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal, [2]Atalanta Therapeutics, Boston, United States of America, [3]RNA Therapeutics Institute, University of Massachusetts Medical School, Worcester, United States of America, [4]Institute of Biosciences & Applications, NCSR Demokritos, Athens, Greece

Aims: Considering recent evidence from Alzheimer's disease (AD) field about the essential role of Tau in AD brain pathology, we aimed to screen novel antisense oligonucleotides (ASOs) designed for lowering total Tau or 4R-Tau levels, addressing these objectives: i.Design, generate and test *in vitro* novel ASOs against mouse or human Tau, using cell lines; ii. Select and test the most efficient ASOs in primary neurons; and iii.Test the efficiency of the selected ASOs in mouse brain.
Methods: This project tested several ASOs with different chemical modifications against Tau protein in cell lines and primary neurons, identifying novel ASOs with high efficiency reducing Tau levels or 4R-Tau, measured by qRT-PCR, Western blot and immunofluorescence. After selecting the most potent ASOs from *in vitro* studies, we performed a pilot study to assess the efficiency of ASOs *in vivo*.
Results: Firstly, mouse-Tau ASOs and human-Tau ASOs were tested on mouse and human neuroblastoma cells, respectively. After qRT-PCR analysis, 13 of each were re-tested for protein level assessment, through Western blot. Next, the 4 most efficient mouse-Tau and human-Tau ASOs were tested in primary neurons. Their efficiency on reducing Tau levels was confirmed, and we evaluated their impact on neuronal morphology, revealing significant alterations in complexity. Finally, mouse-Tau ASOs were tested in a pilot in vivo study using wild-type mice, whereas human Tau-ASOs were tested in THY-Tau22 mice, revealing significant reductions in both mRNA and protein levels of Tau.
Conclusions: Altogether, these data provide the first *in vitro* and *in vivo* confirmation of the efficiency of novel ASOs against Tau, that can further support future studies focusing on ASOs as an innovative RNA-based therapeutic approach against AD, Down Syndrome, and other Tau-related brain pathologies.

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DIGITAL NEUROREHABILITATION IN THE TREATMENT OF PROPER NAME ANOMIA IN PEOPLE WITH DEMENTIA

Aygun Badalova
University College London, London, United Kingdom

Aims: The Gotcha!aims to provide practice-based therapy for PWD to relearn the names of key people in their lives. It has been developed according to the principles of errorless learning, which have previously been shown to improve the remembering the familiar people's names and benefit the relationship between the PWD and their loved ones. (Clare et al, 1999, 2000, 2003)
Methods: Methods: Gotcha! is a digital confrontation naming therapy app which enables patients to train one face per day by using photos that the app represents. During the development phase we carried our qualitative research (thematic analysis) on why PWD get involved in research projects such as ours. Gotcha! therapy block lasts for six weeks and prior to the therapy patients complete a multiple baseline paradigm with eight weekly tests of free naming of the to-be trained faces. During the therapy, a novel speech verifier is used to provide real-time feedback (Barbera et al. 2020). Two analyses method is used to investigate the behavioural data: 1) within-subject non-parametric analysis using Tau-U metric (Parker et al. 2011); 2) a parametric group analysis using an ANOVA.
Results: In terms of the quantitative data, our results from the first 20 subjects showed: **Within-subjects, non-parametric results** 1) Tau-U. 80% showed a positive trend with better naming during the training phase with 8/20 reaching statistical significance. **Parametric group results** 2) ANOVA demonstrated a significant effect at the group level of training>baseline phase, $F(1,19) = 13.18$, $p = 0.01$
Conclusions: App-based proper name anomia retraining works for the majority of PWD in our trial thus far. Being able to freely recall and produce the name of a relative or loved one has a big impact on people's lives.

Virtual EP - 101

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AN OPTIMIZED NURR1 AGONIST EXERTS TIMEPOINT-DIFFERENT EFFECTS ON MITIGATION OF L-DOPA-INDUCED DYSKINESIA IN PARKINSON'S DISEASE MODEL MICE

Woori Kim, Kwang-Soo Kim
McLean Hospital, Psychiatry, Belmont, United States of America

Aims: This study was performed to validate whether the optimized and advanced Nurr1 agonist can prevent or attenuate L-DOPA-induced dyskinesia (LID) in Parkinson's disease (PD) model mice, eventually for the development of a side-effect-free drug for treating patients with PD.
Methods: The final candidate, 4A7C-203 was selected via extensive high-throughput analyses (Nurr1 transcriptional activity, binding affinity, cytotoxicity) and pharmacokinetic study. To validate its effects on neuroprotection and neuroinflammation, 4A7C-203 was tested in midbrain dopaminergic (mDA) neuron-glia co-cultures in the absence or presence of MPP^+ or LPS stimulation. Next, 4A7C-203 was administered in MPTP-induced PD mice to verify its efficacy in PD-like behaviors changes. Finally, we setup different remedies in combination with L-DOPA, including pre-treatment (administrate 4A7C-203 prior to L-DOPA), co-treatment (administrate 4A7C-203 along with L-DOPA), addition (add 4A7C-203 after L-DOPA), and substitution (switch to 4A7C-203 after L-DOPA discontinuation), to verify whether 4A7C-203 can prevent or attenuate LID at different timepoint administered. Serotonin receptor 1B ($5\text{-}HT_{1B}$) agonist CP-94253 was added together with 4A7C-203 in the substitution remedy to confirm the synergetic effect of serotonergic regulation on LID.
Results: We demonstrated that 4A7C-203 improves behavioral deficits of MPTP-induced PD model mice. Notably, 4A7C-203 did not develop dyskinetic side-effect at all and was also able to attenuate LID at different degrees depending on the timepoint administered. Besides, 4A7C-203 cut down striatal serotonergic hyperinnervation and normalized dopamine turnover rate by protecting dopaminergic neurons and suppressing glial activation in the striatum. Furthermore, we identified that 4A7C-203 induces synergism with CP-94253 on LID mitigation in our PD model mice.
Conclusions: These findings suggest 4A7C-203 as a promising drug not only improves PD-like deficits, also has the potential to prevent or mitigate dyskinetic side-effect when it is introduced to the PD patients with LID.

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ASSOCIATION OF IRON LEVEL IN THE NUCLEUS ACCUMBENS WITH COGNITIVE IMPAIRMENT IN PREECLAMPSIA : A PROSPECTIVE COHORT STUDY

Boyao Chen[1], Linfeng Yang[2], Tao Chen[2], Meng Li[3], Lingfei Guo[1], Na Wang[1,4], Xinyue Zhang[1], Zhenyu Cheng[4], Yiwen Chen[1], Pengcheng Liang[1], Xinxin Huo[1], Fushuai Zhang[1]
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Aims: To investigate alterations in susceptibility values obtained from quantitative susceptibility mapping (QSM) of the striatum in patients with preeclampsia, focusing on the correlation between these alterations and cognitive impairment.
Methods: This study enrolled 292 participants aged 20 to 40 years, comprising 112 nonpregnant healthy controls (NPHC), 60 pregnant healthy controls (PHC), and 120 patients with preeclampsia. All participants were scanned on a 1.5-T MR scanner. And results of clinical characteristics and cognitive tests were collected from all the participants. One-way ANOVA tests and two-sample T-tests were used to analyze the differences in susceptibility values of the striatum among the three groups. Partial Pearson correlation analysis was used to detect the relationships between variables and the scores of cognitive tests. In addition, receiver operating characteristic (ROC) analysis was employed to evaluate the diagnostic performance of susceptibility values, by incorporating other clinical variables, various models were constructed in order to identify the optimal model.
Results: Preeclampsia patients exhibited higher susceptibility values of the NAc compared to the other groups (P=0.020). A significant positive correlation was observed between susceptibility values of the NAc and hematocrit levels after controlling for age and gestational week(r=0.154, P=0.040) in the two pregnant groups. Additionally, susceptibility values correlated with cognitive performance on the TMT(R=0.156, P=0.037). Compared to other models, the combination of NAc susceptibility values with hematocrit and gestational week more effectively distinguished preeclampsia from healthy pregnancy group.

Table 1. Clinical characteristics of the participants.

Variables	NPHC n 112	PHC n 60	Preeclampsia n 120	F/t/ χ^2 value	P value	P value (post hoc)		
						NPHC vs.Preeclampsia	PHC vs. Preeclampsia	NPHC vs. PHC
Age (years)	31.73±4.31	29.73±3.86	31.70±4.33	1.29	0.278[a]	-	-	-
Gestational week (week)	-	30.90±6.38	34.08±3.35	35.54	<0.001 [t]	-	-	-
Weight(kg)	58.89±7.80	69.80±9.17	81.23±11.49	146.30	<0.001[a]	<0.001	<0.001	<0.001
Body Mass Index (kg/m²)	22.33±2.97	26.97±3.59	30.96±4.04	22.14	<0.001[a]	<0.001	<0.001	<0.001
Systolic pressure (mmHg)	111.25±9.63	112.13±10.88	157.80±12.73	597.62	<0.001[a]	<0.001	<0.001	0.624
Diastolic pressure (mmHg)	69.17±8.39	71.42±7.97	100.89±8.82	470.76	<0.001[a]	<0.001	<0.001	0.099
Mean atrial pressure (mmHg)	83.17±8.09	85.00±8.00	119.86±8.79	656.02	<0.001[a]	<0.001	<0.001	0.182
Hemoglobin (g/L)	128.13±10.63	115.40±12.16	124.46±11.83	24.27	<0.001[a]	0.015	<0.001	<0.001
Hematocrit	39.55±2.90	35.25±3.33	37.80±3.34	36.03	<0.001[a]	<0.001	<0.001	<0.001
Platelet (*10^9/L)	250.16±69.74	214.95±51.84	197.53±58.89	21.27	<0.001[a]	<0.001	0.077	<0.001
Glucose (mmol/L)	4.65±0.50	4.51±0.45	4.82±1.02	3.58	0.030[a]	0.097	0.237	0.010
Creatinine (μmol /L)	49.78±10.59	44.25±13.55	54.88±16.28	12.35	<0.001[a]	0.005	<0.001	0.013
ACR (mg/g)	-	0.02±0.02	14.59±80.12	1.02	0.315	-	-	-
ALT (U/L)	13.85±7.54	12.45±5.64	21.91±30.27	6.47	0.002	0.003	0.003	0.665
AST (U/L)	17.59±6.33	16.00±5.41	24.83±19.39	12.52	<0.001[a]	<0.001	<0.001	0.456
MoCA*	30(30-30)	30(29-30)	29(27-29)	51.05	<0.001[a]	<0.001	<0.001	0.035
SCWT	103.74±20.19	117.67±21.40	122.00±24.89	20.04	<0.001[a]	<0.001	0.223	<0.001
TMT	108.83±36.87	115.35±41.72	150.24±39.88	26.06	<0.001[a]	<0.001	0.411	<0.001

The data are presented as the means ± standard deviations. [a]: ANOVA test; [t]: two-sample t test; *: data are median, and data in parentheses are the interquartile range; NPHC: nonpregnant healthy control; PHC: pregnant healthy control; kg: kilograms; MoCA: Montreal Cognitive Assessment; SCWT: Stroop Color and Word Test; TMT: Trail Making Test (A sum B); SDMT: Symbol Digit Modalities Test.

Table 2. Susceptibility value differences [ppb($\times 10^{-9}$)] in striatum (avergae of left and right)

Variables	NPHC (n=112)	PHC (n=60)	Preeclampsia (n=120)	F	P*	P value (post hoc)		
						NPHC **vs.** Preeclampsia	PHC **vs.** Preeclampsia	NPHC **vs.** PHC
Nucleus Accumbens	14.60±18.11	15.59±20.93	22.49±19.57	5.398	**0.020**	**0.002**	**0.027**	0.725
Globus Pallidus	98.60±29.72	108.14±32.52	102.73±30.74	1.909	0.300	0.307	0.266	0.053
Putamen	44.53±31.26	42.73±26.07	47.70±29.65	0.652	0.696	0.417	0.290	0.704
Caudate Nucleus	58.56±15.83	50.09±17.33	49.85±19.45	0.209	0.811	0.580	0.933	0.591

*FDR correction, P < 0.05. NPHC: nonpregnant healthy control; PHC: pregnant healthy control.

Table 3. Determinants of susceptibility values: results of multiple linear stepwise regression analysis in two pregnant groups.

	Factors	β	Standardized β	T	P	R of Model	P of Model
Nucleus Accumbens	Hematocrit(HCT)	0.869	0.152	2.069	0.040	0.226	0.010
	Age	0.751	0.156	2.117	0.036		
Putamen	Age	0.481	0.302	4.273	<0.001	0.342	<0.001
	BMI	0.498	0.148	2.087	0.011		
Caudate	Age	1.234	0.276	3.836	<0.001	0.276	<0.001

Significant p values < 0.05.

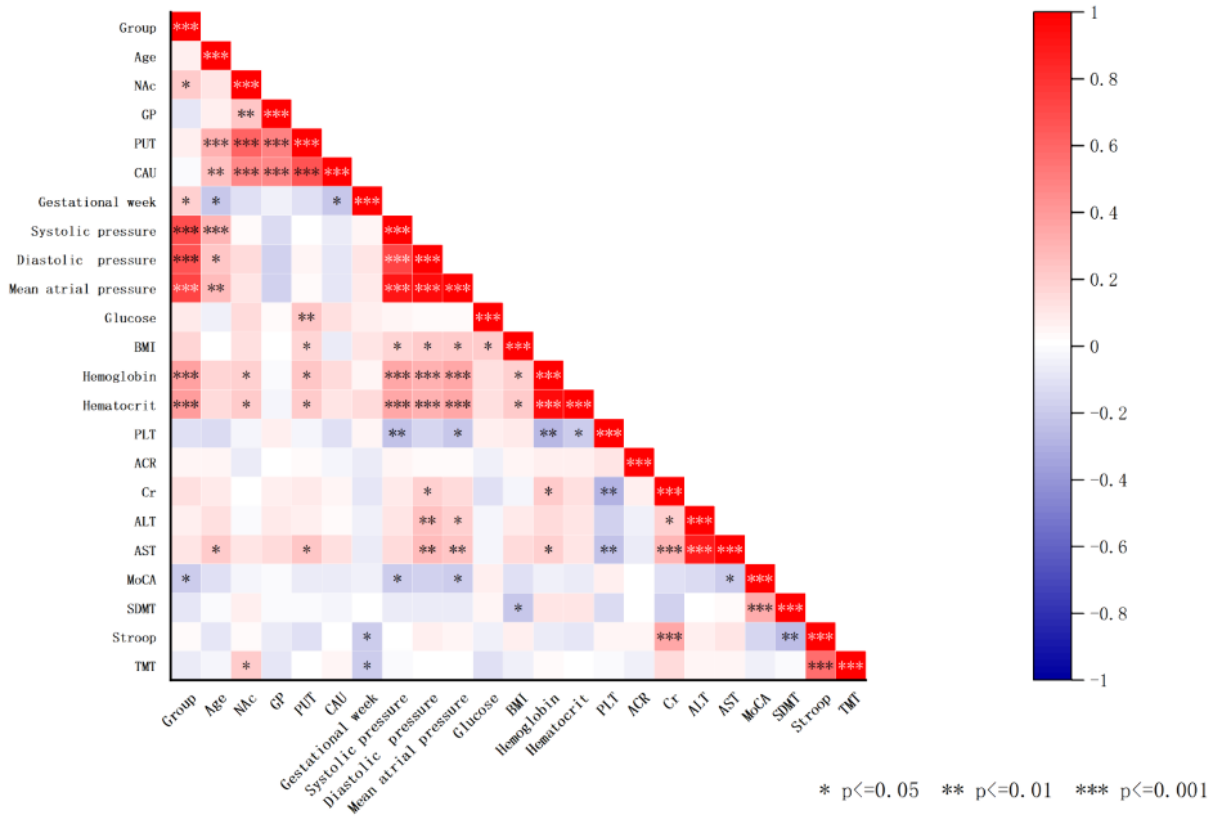

Figure1. Heat maps of clinical characteristics and cognitive tests in relation to susceptibility value in striatum.

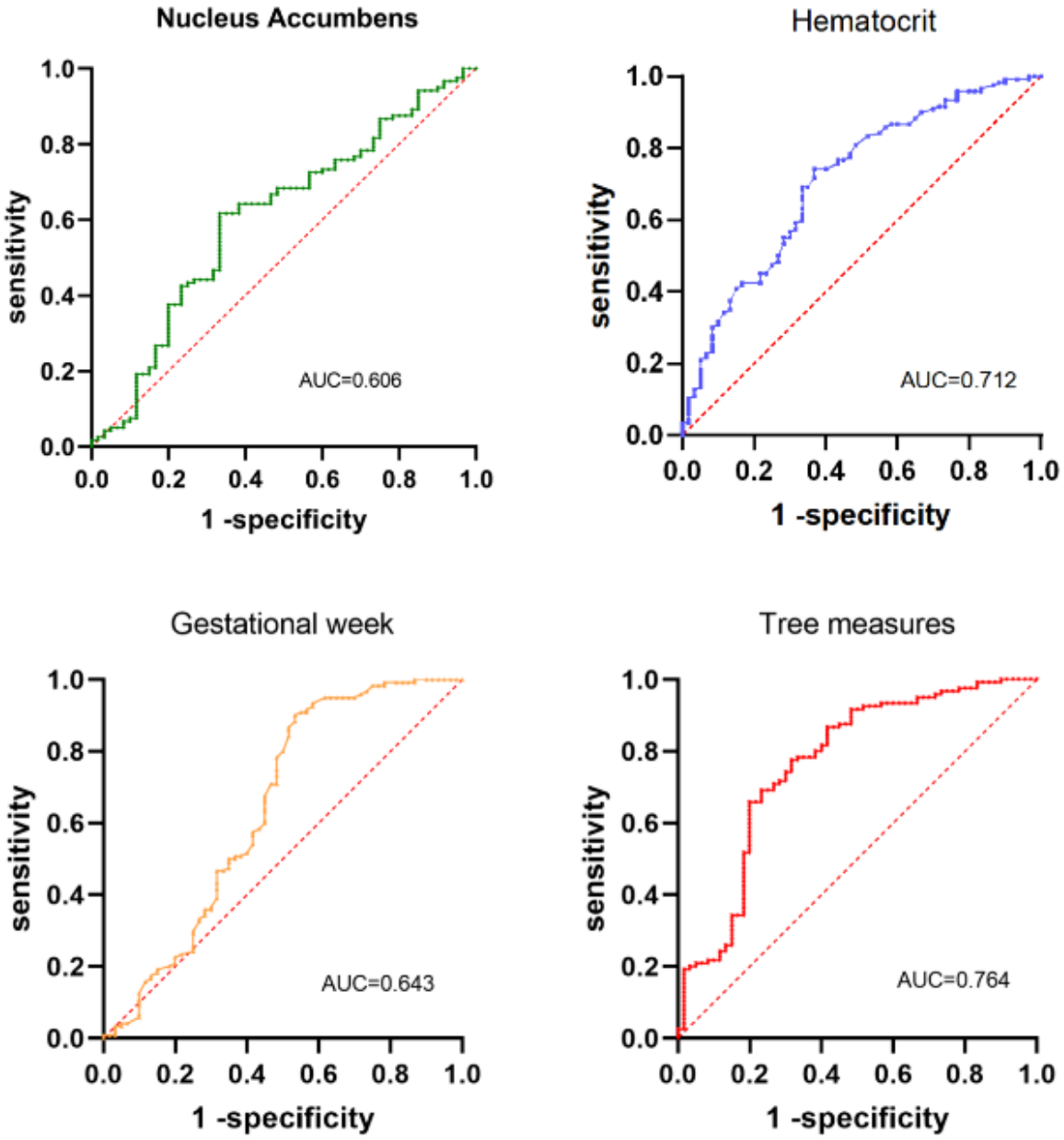

Figure3. Receiver operating characteristic (ROC) curves of the three measures for discriminating the preeclampsia from pregancy. The area under the curve (AUC) for the combination of three measures using logistic regression (NAc susceptibility values, hematocrit, gestational week) is greater than that for the NAc susceptibility values alone (AUC 0.764 vs.0.606, Z = -3.221, p = 0.001).

Table4. Diagnostic accuracy of susceptibility value of nucleus accumbens, gestational week and hematocrit to detect preeclampsia from pregancy

Test result variable(s)	AUC(95% CI)	p value	Cutoff value (%)	Sensitivity	Specificity
NAc	0.604 (0.515 - 0.694)	0.022	-3.868	0.858	0.850
Gestational week	0.643 (0.547 -0.739)	0.002	34.500	0.658	0.450
Hematocrit	0.712 (0.631 - 0.793)	<0.001	36.700	0.767	0.333
Tree measures	0.764 (0.685 - 0.844)	<0.001	0.542	0.658	0.450

AUC, area under the curve; CI, confidence interval

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Variables	NPIIC n 112	PIIC n 60	Preeclampsia n 120	F/t/ χ^2 value	P value	P value (post hoc)		
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Age (years)	31.73±4.31	29.73±3.86	31.70±4.33	1.29	0.278[a]	-	-	-
Gestational week (week)	-	30.90±6.38	34.08±3.35	35.54	<0.001 [t]	-	-	-
Weight(kg)	58.89±7.80	69.80±9.17	81.23±11.49	146.30	<0.001[a]	<0.001	<0.001	<0.001
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ACR (mg/g)	-	0.02±0.02	14.59±80.12	1.02	0.315	-	-	-
ALT (U/L)	13.85±7.54	12.45±5.64	21.91±30.27	6.47	0.002	0.003	0.003	0.665
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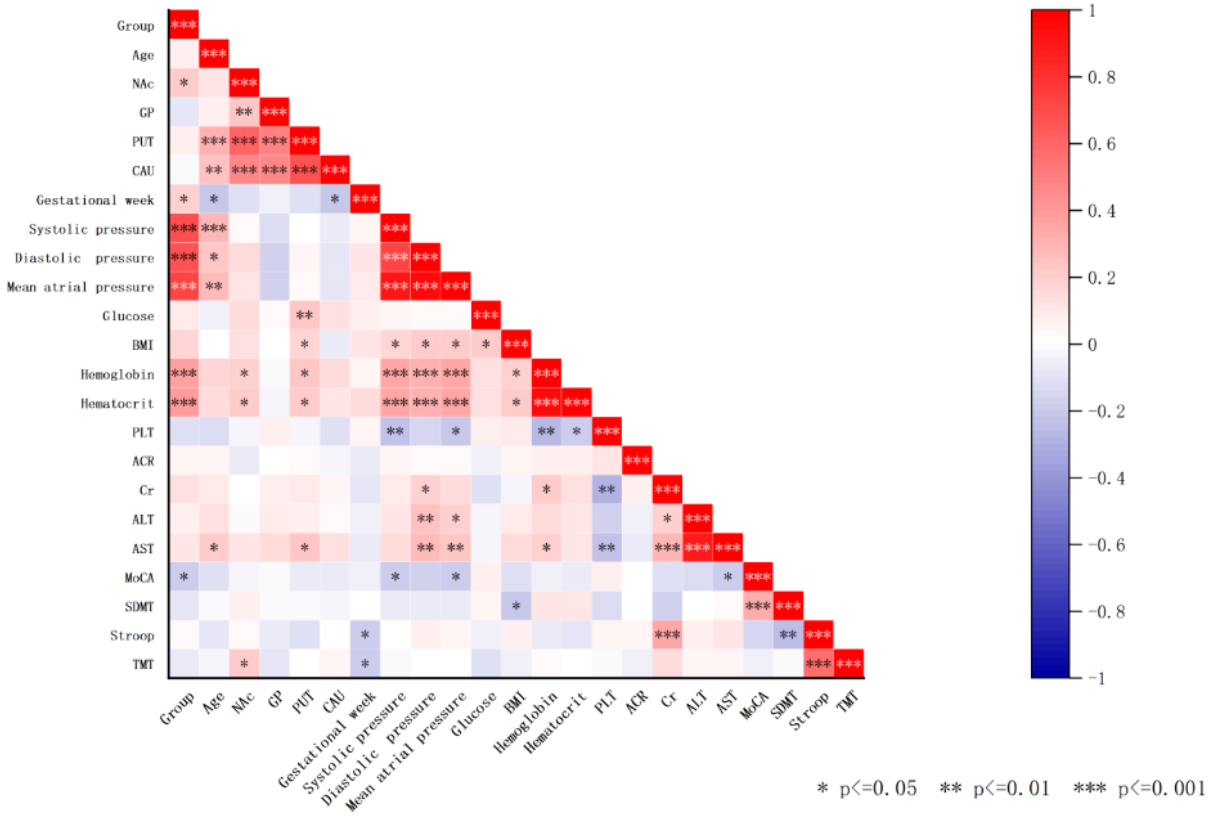

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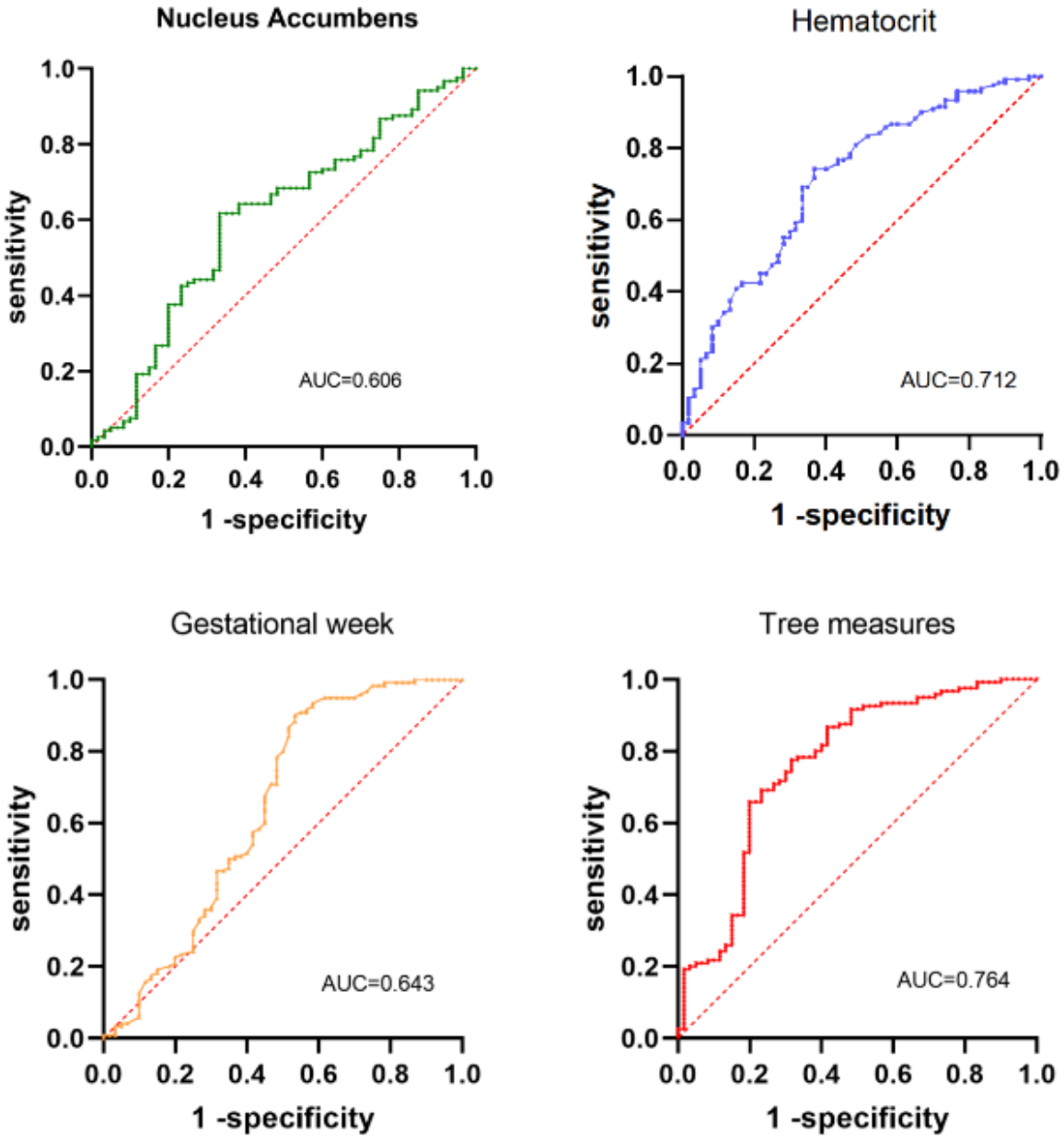

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AUC, area under the curve; CI, confidence interval

Conclusions: We found that the iron level in nucleus accumbens increased in preeclampsia, and this is significantly correlated with higher hemoglobin and poorer task processing speed. Additionally, we developed a classification model for preeclampsia that not only facilitates early diagnosis but also provides a theoretical foundation for subsequent treatment.

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NOVEL SCREENING METHODS USING COGNITIVE MEASURES IN AUTONOMY, A MULTICENTER PHASE 2 TRIAL OF ANTI-PHOSPHORYLATED TAU ANTIBODY POSDINEMAB IN EARLY ALZHEIMER'S DISEASE

Maggie Fedgchin[1], Amy Veroff[2], David Henley[1], Janice Wong[1], Jennifer Bogert[3]
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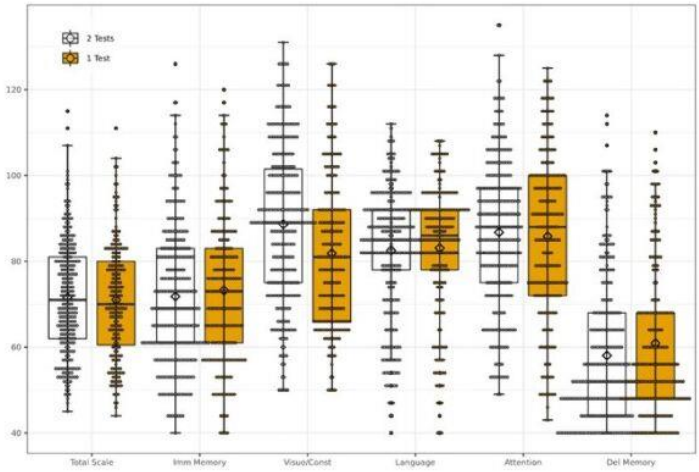
Aims: Assess impact of 1) administering two vs one screening practice tests on baseline variability of cognitive measures, and 2) allowing flexibility in a screening cognitive severity cutoff on baseline characteristics of participants with early Alzheimer's disease (AD; mild cognitive impairment [MCI]/mild dementia) enrolled in the phase 2 Autonomy trial of posdinemab, an anti-phosphorylated tau (mid-domain epitope) antibody.
Methods: Baseline characteristics of the two practice test cohorts (two vs one practice administrations of RBANS and ADAS Cog 13) were compared to assess variability. The Autonomy study (NCT04619420) enrolled participants with RBANS DMI ≤85 or >85. While participants with RBANS DMI >85 are usually excluded from AD trials, they could be enrolled in this study with evidence of high premorbid cognitive function. The baseline characteristics – including overall clinical severity of AD – of RBANS DMI ≤85 vs >85 cohorts, and the total population are described.
Results: Baseline characteristics of the two vs one practice test cohorts were comparable **(Table 1)**. Of the baseline mean RBANS total score and indices, only the difference between cohorts in the visuospatial index was statistically significant (one test was worse than two tests; **Fig 1**). A similar analysis for ADAS-Cog13 will be presented. Analysis of baseline characteristics of the RBANS DMI ≤85 vs >85 cohorts showed that inclusion of less impaired participants (RBANS DMI ≥85) did not impact the overall clinical severity of AD in the total population at baseline (**Table 2**).
Conclusions: Novel screening methods using cognitive measures in the Autonomy study can inform future study designs. One practice test prior to baseline was sufficient to minimize learning effects. Flexibility with RBANS DMI allowed enrollment of less impaired participants without impacting overall population characteristics.

Table 1. Baseline characteristics of the participants who underwent two tests versus those who underwent one test

Baseline characteristics	Two tests n=274	One test n=207
Age, years, mean ± SD	71.1 ± 5.9	71.6 ± 5.8
Female, %	53.7	51.2
Race, %		
Caucasian	70.8	90.3
Others	29.2	9.7
Education, %		
Less than high school education	12.4	15.9
At least some high school or greater	87.6	84.1
Baseline tau burden on Tau PET (in intermediate tau population)		
Low Stratum	41.6	46.4
High Stratum	58.4	53.6
Baseline RBANS score, mean ± SD		
Total Score	71.6 ± 13.0	71.0 ± 13.3
Delayed Memory Index	58.0 ± 17.0	60.9 ± 17.8

PET: Positron Emission Tomography; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; SD: Standard deviation.

Figure 1. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score in the one versus 2 tests



Del Memory: Delayed memory; Imm Memory: Immediate memory; Visuo/Const: Visuospatial/constructional abilities

Table 2. Baseline characteristics of the participants in RBANS DMI ≤85 versus >85 cohorts

Participants with Screening RBANS V1	Screening V1 RBANS DMI ≤85 N=483	Screening V1 RBANS DMI >85 N=39	Total N=522
Age, years, mean ± SD	71.5 ± 5.8	71.0 ± 6.1	71.4 ± 5.9
Female, %	52.6	48.7	52.3
Race, %			
Caucasian	78.5	76.9	78.4
Others	21.5	23.1	21.6
Education, %			
Less than high school education	14.9	7.7	14.4
At least some high school or more	85.1	92.3	85.6
Baseline tau burden on Tau PET (in intermediate tau population)			
Low Stratum	42.0	69.2	44.1
High Stratum	58.0	30.8	55.9
Baseline RBANS score, mean ± SD			
Total Score	70.0 ± 12.1	91.1 ± 11.7	71.6 ± 13.3
Delayed Memory Index	56.4 ± 14.6	93.0 ± 11.9	59.1 ± 17.4
Baseline ADAS-Cog13 score, mean ± SD	26.1 ± 7.4	13.9 ± 5.6	25.2 ± 8.0
Baseline ADCS-ADL-MCI score, mean ± SD	41.6 ± 6.4	45.5 ± 3.9	41.9 ± 6.3
Baseline CDR-SB, mean ± SD	3.0 ± 1.1	2.2 ± 1.0	2.9 ± 1.2
Baseline CDR-GS, %			
0-0.5	90.5	97.4	91.0
1.0	9.5	2.6	9.0

ADAS-Cog13: Alzheimer's Disease Assessment Scale cognitive subscale 13; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study - Activities of Daily Living for Mild Cognitive Impairment; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of boxes; PET: Positron Emission Tomography; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RBANS DMI: Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index; SD: Standard deviation; V1: Visit 1.

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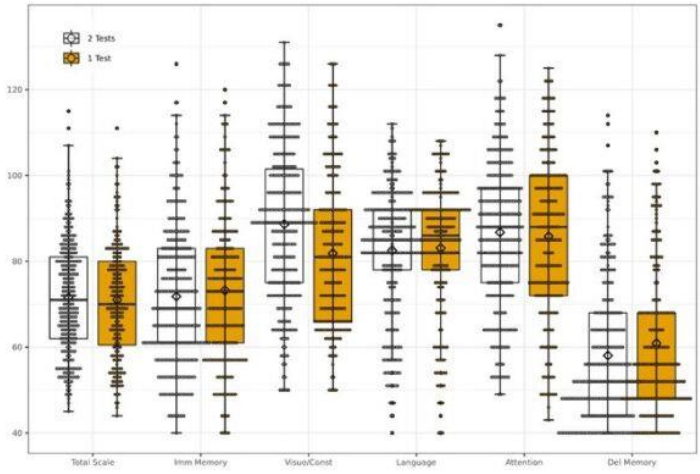

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0-0.5	90.5	97.4	91.0
1.0	9.5	2.6	9.0

ADAS-Cog13: Alzheimer's Disease Assessment Scale cognitive subscale 13; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study - Activities of Daily Living for Mild Cognitive Impairment; CDR-GS: Clinical Dementia Rating-Global Score; CDR-SB: Clinical Dementia Rating-Sum of boxes; PET: Positron Emission Tomography; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RBANS DMI: Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index; SD: Standard deviation; V1: Visit 1.

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Virtual EP - 104

Virtual E-Posters and Oral On-Demand
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THE ASSESSMENT OF CCL-2 AND CX3CL1 CONCENTRATIONS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT

Daria Krawczuk[1], Agnieszka Kulczyńska-Przybik[1], Jan Mroczko[1], Borawska Renata[1], Agnieszka Słowik[2], Barbara Mroczko[1]
[1]Medical University in Bialystok, Department Of Neurodegeneration Diagnostics, Bialystok, Poland, [2]Jagiellonian University in Krakow, Neurology Clinic, Kraków, Poland

Aims: Mild cognitive impairment (MCI) is a condition characterized by noticeable cognitive decline that is greater than expected for a person's age but not severe enough to interfere significantly with daily life. Neuroinflammation is increasingly recognized as an important factor in the pathophysiology of MCI and related neurodegenerative conditions, such as Alzheimer's disease. CCL-2 and CX3CL1 can trigger the activation of microglia, the resident immune cells in the brain. While microglial activation can have protective functions, excessive or chronic activation may lead to neurotoxicity and contribute to the pathogenesis of AD. Given their roles in inflammation, CCL-2 and CX3CL1 have been considered as potential biomarkers targeting the earliest stages of Alzheimer's disease, such as MCI. The purpose of this study was to evaluate CCL-2 and CX3CL1 concentrations in the CSF of MCI patients and subjects without cognitive decline and verify the potential clinical utility of these chemokines.
Methods: The concentrations of CCL-2 and CX3CL1, Aβ1-42, Aβ1-40, Tau, pTau181 were analyzed in the CSF of 37 patients with MCI and without cognitive decline using ELISA method. Moreover, parameters evaluating the integrity of the blood-CSF barrier such as CSF/serum albumin (Qalb) and CSF/serum immunoglobulin G quotient (QIgG) were assessed.
Results: CSF concentrations of CCL-2 and CX3CL1 were significantly higher in MCI patients compared to controls. Moreover, a positive correlation was observed between these two chemokines. Additionally, there were positive correlations among both chemokines and total Tau as well as pTau181 in CSF.
Conclusions: Our findings suggest that CCL-2 and CX3CL1 present high discriminatory value in differentiating MCI from controls. Thus, most likely those chemokines are connected with neuroinflammatory background of the disease and may be applied as potential biomarker in early stages of AD.

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Virtual EP - 105

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TAU AND PHOSPHO-TAU PROTEIN QUANTIFICATION IN CNS-DERIVED CIRCULATING EXOSOMES

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Aims: Parkinsonian syndromes are a group of progressive neurodegenerative disorders affecting various parts of the central nervous system (CNS). These disorders are classified based on protein accumulation: synucleinopathies (e.g., Parkinson's disease and Multiple System Atrophy) involve alpha-synuclein aggregation, while tauopathies (e.g., Progressive Supranuclear Palsy and Corticobasal Syndrome) involve tau protein accumulation. Each syndrome has unique clinical features, affecting different brain regions and cell types. While definitive diagnosis relies on postmortem histopathological examination, distinguishing between these disorders during life is challenging due to symptom overlap, leading to frequent misdiagnosis. Recent studies have explored CNS-derived exosomes as potential biomarkers for neurodegenerative diseases. These extracellular vesicles can cross the blood-brain barrier, entering the bloodstream and offering insights into CNS biochemistry. The accessibility of Exosomes through a simple blood draw has generated significant interest for their use in developing new diagnostic tools and monitoring disease progression.
Methods: In this study we isolated neuron-derived exosomes using immunoaffinity capture with the neural cell adhesion molecule L1CAM. Tau protein content in the purified exosomal fraction was quantified using the highly sensitive SIngle MOlecule Array (SIMOA) immunoassay.
Results: The L1CAM-positive exosome subpopulation showed enrichment for neuronal cell markers. Comparative analysis of total Tau and specific phosphorylated Tau protein concentrations within this exosomal fraction was used to create unique molecular signatures for different Parkinsonian syndromes.
Conclusions: This research characterizes the quantitative differences in Tau and phospho-Tau proteins within CNS-derived, circulating exosomes, establishing specific molecular profiles for distinct Parkinsonian syndromes.

Virtual EP - 106

Virtual E-Posters and Oral On-Demand
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MONITORING TREATMENT EFFECTS OF SODIUM SELENATE IN ALZHEIMER'S DISEASE USING FLUID BIOMARKERS

Jakub Vavra[1], Cassandra Marotta[2], Fernando Gonzalez Ortiz[1], Christopher Hovens[2], Terence O'Brien[2], Laia Montoliu-Gaya[1], Henrik Zetterberg[1], Lucy Vivash[2], Kaj Blennow[1]
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Aims: Sodium selenate is a potential disease-modifying anti-tau therapy for Alzheimer's disease (AD) which reduces hyperphosphorylated tau through activation of the protein phosphatase 2A enzyme. Here we aimed to determine if cerebrospinal fluid (CSF) levels of brain-derived tau (BD-tau) and p-tau217 could be potential biomarkers of treatment effect in clinical trials of sodium selenate (Trial Registration: ACTRN12611001200976).
Methods: Participants (n=21) received either sodium selenate at 10mg (n=10), 320µg (n=5) or placebo (n=6) three times a day for 24 weeks. CSF samples included in this study are from the baseline and week 24 visits. CSF BD-tau and p-tau217 were measured using Simoa. CSF T-tau, p-tau181 and Amyloid-beta42 analyses were performed using ELISA.
Results: We observed the following changes in CSF BD-tau after 24 weeks compared to baseline: the placebo group from 277.0 (210.6 – 425.5) pg/ml to 297.5 (249.9 – 380.5) pg/ml ($p>0.8$); the group receiving 320µg from 319.2 (259.7 – 434.2) pg/ml to 296.1 (257.1 – 373.4) pg/ml ($p>0.06$) and from 410.5 (265.3 – 530.4) pg/ml to 349.6 (239.6 – 433.3) pg/ml ($p<0.01$) in the 10mg group. Moreover, we found a significant correlation between CSF BD-tau and change in right hippocampal volume in participants treated with sodium selenate (Spearman's rho = -0.4541, p-value = 0.04428). There were no significant changes in T-tau, p-tau181, AB-42 or p-tau217 in any of the treatment groups.
Conclusions: The decrease in concentrations of CSF BD-tau agrees with our previous findings where we observed reduced neurodegeneration on diffusion-weighted MRI in AD patients after treatment with sodium selenate. CSF BD-tau demonstrated potential as an effective biomarker for assessing treatment effects in AD patients. Additional research is required to explore the viability of plasma BD-tau and its applicability in other drug trials.

Virtual EP - 107

Virtual E-Posters and Oral On-Demand
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RELEVANCE OF SUBCLINICAL EPILEPTIFORM ACTIVITY IN CLINICALLY HEALTHY ELDERLY POPULATION

Emoke Csernus[1], Andras Horvath[2], Anita Kamondi[2], Dalida Berente[3], Gergo Bolla[3]
[1]Semmelweis University, Medical Imaging Centre, Budapest, Hungary, [2]National Institute of Mental Health, Neurology And Neurosurgery, Budapest, Hungary, [3]Semmelweis University, ., Budapest, Hungary

Aims: Subclinical epileptiform activity(SEA) has been considered of benign etiology and an EEG variant in elderly population. However, epileptiform activity has been associated with decreased cognitive performance, and is a proven marker of progression in Alzheimer's disease. We investigated the relevance of SEA in clinically healthy elderly population with regard to neuropsychological performance and structural neuroimaging.
Methods: We studied 62 elderly subjects determined as healthy based on physical, neuropsychology, neuroimaging(MRI), and serological workup. All subjects underwent 24-h Holter electroencephalography(EEG), visual analysis was conducted by two independent raters. Subjects were classified into EEG positive(EEG+) and negative(EEG-) groups based on detecting epileptiform activity on their EEG. Neuropsychology battery and structural MRI results were compared between the groups.
Results: We studied 62 elderly subjects determined as healthy based on physical, neuropsychology, neuroimaging(MRI), and serological workup. All subjects underwent 24-h Holter electroencephalography(EEG), visual analysis was conducted by two independent raters. Subjects were classified into EEG positive(EEG+) and negative(EEG-) groups based on detecting epileptiform activity on their EEG. Neuropsychology battery and structural MRI results were compared between the groups.
Conclusions: Presence of SEA among healthy elderly shows a discrete but significant association with decreased cognitive performance in certain subdomains, as well as bilateral increased brain volume in several temporal areas. Our results underscore the relevance of data suggesting presence of a hippocampal sparing phenotype in Alzheimer's disease and its potential connection to epileptiform activity.

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DCTCLOCK DETECTS COGNITIVE AND MOTOR IMPAIRMENT IN PARKINSON'S DISEASE AND QUANTIFIES DRAWING TREMOR

Ali Jannati, William William Soulliard-Mandar, John Showalter, David Bates, Sean Tobyne, Alvaro Pascual-Leone
Linus Health, Boston, United States of America

Aims: To assess the utility of DCTclock for identifying cognitive and motor impairments in Parkinson's disease (PD) and quantifying drawing tremors.
Methods: The relationship between DCTclock metrics and idiopathic PD was studied in 165 PD subjects as well as 1528 cognitively unimpaired (CU) subjects. A cross-sectional analysis was conducted looking for differences between CU, PD with MMSE ≥ 28, and PD with MMSE ≤ 27, followed by a second cross-sectional analysis stratified by CU, PD Surgical (referred for standard pre-surgical cognitive workup), and PD Non-Surgical (referred for cognitive problems). DCTclock metrics were compared to standard neuropsychological tests in the PD group. Additionally, a novel tremor detection and quantification metric of DCTclock, Oscillatory Motion (OM), was extracted. Three movement disorder specialists independently rated the tremor severity of 93 DCTclock tests (186 drawings, command/copy conditions) using the Overall Tremor Rating Scale. Drawings were selected from patients diagnosed with Essential Tremor (ET, N=23), PD (N=24), mild cognitive impairment (N=29), and Healthy Control (HC, N=17) (age= 68.24±11.6, education = 14.47±2.1, MMSE = 26.34±2.7).
Results: DCTclock metrics differentiated between CU and PD subjects with MMSE ≥28 groups, between PD subjects with MMSE≥28 and those with MMSE≤27, as well as between PD Surgical and PD Non-Surgical groups, and correlated to standard neuropsychological metrics. OM score had moderate to high agreement (Spearman) with clinician raters with correlations of 0.80 (command), 0.74 (copy), and 0.75 (average). The OM metric of DCTclock differentiated ET and HC groups with high accuracy (AUC=0.94).
Conclusions: DCTclock metrics can detect cognitive impairment due to PD, differentiate between cognitive and motor impairments in PD individuals, and successfully quantify drawing tremors.

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PSP PHENOTYPES IN REAL CLINICAL PRACTICE

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Research Center of Neurology, Neurogenetics, Moscow, Russian Federation

Aims: According MDS criteria 2017 there are many clinical PSP phenotypes admitted. Clinical data of other except PSP-RS phenotype have never assessed on large Russian cohort of PSP patients.
Methods: We evaluated local archive clinical data of PSP patients from 2018 to August 2024. Clinical phenotypes of PSP were established on criteria MDS.
Results: 94 patients with available clinical data were analyzed. There were six clinical phenotypes: PSP-RS (51%), PSP-P (21%), PSP-CBS (9%) PSP-F (9%), PSP-PGF (5%), PSP-SL (4%). For further comparisons three groups were formed (Table): PSP-RS, PSP cortical (PSP-CBS, PSP-F, PSP-SL) and PSP subcortical (PSP-P, PSP-PGF). It was found that subcortical group present more long disease duration in comparison with PSP-RS and PSP cortical groups ($p < 0,05$). There were no significant differences in age of onset, cognitive function and disease severity.

Table. Clinical data of three PSP groups.

Phenotype	PSP-RS	PSP cortical	PSP subcortical	All	p
Number	48 (51%)	20 (21%)	26 (28%)	94 (100%)	-
Age of onset, y	64±7	66±6	63±10	64±8	>0,05
Duration, y	3±1*	3±1§	5±2*§	3±2	* <0,00001 § <0,00001
PSP-RS score	35±11	34±13	27±10	33±12	>0,05
PSP-CDR score	9±2	9±3	9±3	9±2	>0,05
MOCA score	21±6*	17±8§	24±3*§	21±6	* 0,03236 § 0,01778

Conclusions: This data presents one of the first clinical analysis rare PSP phenotypes in Russian cohort of patients using criteria MDS. Distribution by phenotypes is comparable with other authors. Longer disease duration subcortical group may reflect the difficulty of early PSP diagnosis in PD-like phenotypes as PSP-P and PSP-PGF.

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FAST AND ACCESSIBLE ORGANOTYPIC BRAIN SLICE CULTURE MODEL OF TAU PATHOLOGY MIMICS MOUSE MODEL OF TAU PATHOLOGY EX VIVO

James Scott-Solache, Karen Duff
University College London, Uk Dementia Research Institute, London, United Kingdom

Aims: Modelling tau pathology is crucial for advancing our understanding of human neurodegenerative diseases, particularly those like Alzheimer's disease and Frontotemporal Dementia. The current tauopathy mouse model, which carries the Frontaltemporal Dementia-associated MAPT mutations (S305N; 10+3), successfully replicates hyperphosphorylated tau but requires at least six months to develop substantial pathology. This lengthy process results in high costs, logistical challenges, and difficulties in administering experimental interventions.
Methods: To address these limitations, we have developed an organotypic brain slice culture (OBSC) model from human MAPT Knock-in (MAPT-KI) and MAPT-S305N; 10+3 mice.
Results: The MAPT-S305N; 10+3 OBSCs recapitulates key features of tau pathology observed *in vivo*, including intraneuronal hyperphosphorylated tau, within just five weeks of culture that are not present in the control MAPT-KI OBSCs. In addition to accelerating disease modelling, this *ex vivo* system offers a robust and accessible platform for testing therapeutic compounds, viral transduction, and other experimental manipulations.
Conclusions: Its potential for drug screening and mechanistic studies makes this OBSC model a valuable tool for exploring tau-targeted therapies and understanding tau pathology more rapidly and cost-effectively.

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NON-HUMAN PRIMATE MODELS OF AD/PD AND PHOSPHOR-TAU TARGETED DRUG DEVELOPMENT

Jian-Zhi Wang
1 Research Institute of Hubei Topgene Biotechnology; 2 Tongji Medical College, HUST, Wuhan, China

Aims: To volume-producing non-human primate models of AD and PD, which simultaneously display the AD-or PD-like behavioral abnormalities and hallmark pathologies, for evaluating the efficacy of new drugs. To design novel disease-modifying drugs specifically targeting tau hyperphosphorylation and accumulation.
Methods: Aβ or/and AAV-p301l-tau gene and MPTP were infused into brains or intramuscularly into the monkeys. Biochemical assays,PET-CT/ MRI and behavioral paradigms were employed for pathologies/biomarker changes and cognitive/motor functions.
Results: The AD monkey models we produced showed learning and memory deficits, accompanied by the accumulated or increased levels of amyloid-beta, tau proteins, and neurofilaments (NFL, marker of neurodegeneration) in different brain regions, CSF and/or plasma. Microglial activation and a chronic inflammation were also detected in the brain of the AD models. The PD monkey models we produced not only displayed typical PD-like motor- dysfunctions for at least 64 weeks, they also exhibited sleep disorders, anxiety, depression, and cognitive impairments. The MPTP-induced motor deficits were remarkably attenuated by L-dopa treatment, whereas the influence of L-dopa on the non-motor dysfunctions showed paradigm-dependence. By metabolomic analysis, 89 significantly different metabolites in the periphery plasma of PD monkeys were identified. Our systemic studies have demonstrated the abnormal hyperphosphorylation of tau proteins plays a crucial role in AD neurodegeneration and memory loss. Based on this, we developed the dephosphorylation targeting chimera (DEPTAC) to specifically increasing tau dephosphorylation without changing the activities of kinases and phosphatases. By screening and in vitro/in vivo testing, we have received effective/brain-penetrable DEPTAC peptides and small molecules for AD.
Conclusions: Monkey models simultaneously display the AD-or PD-like behavioral deficits and hallmark pathologies are produced and can be used for evaluating the efficacy of new drugs. Novel disease-modifying DEPTACs can specifically target tau hyperphosphorylation.

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PARKINSON'S DISEASE NEURODEGENERATIVE IMAGING BIOMARKERS DIAGNOSTICS

Hilola Daminova
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Aims: Parkinsonism is one of the most significant problems of clinical neurology, both due to its high prevalence in the world's populations and due to the significant disability of patients. The work analyzes the diagnosis of Parkinson's disease (as well as other neurodegenerative diseases) at the prodromal stage. A review of methods for preclinical and early clinical diagnosis of PD shows that the study of prodromal markers and criteria for the premotor phase of PD will make it possible in the future to significantly change the course of the disease using neuroprotective therapy at the stage preceding the death of a significant number of dopaminergic neurons of the substantia nigra.
Methods: Features of course of the neurodegenerative process in PD, rapid loss of dopamineproducing neurons of the substantia nigra in the prodromal period lead to the fact that the first clinical manifestations appear with death of more than 70–80% of nigrostriatal neurons and a significant decrease in level of dopamine in the striatum .
Results: Detection of alpha- synuclein and Lewy bodies in autopsysamples from an extensive brain bank . According to the author, at stage 1, damage occursto the olfactory bulb, anterior olfactory nucleus and dorsal motor nucleus of the vagus nerve,
peripheral ganglia of the autonomic nervous system, H. Braak's double-whammy hypothesis suggests that the trigger that triggers a
cascade of neurodegenerative changes in the brain is a slow virus that enters the nervous system through the nasal and intestinal mucosa.
Conclusions: That is why, at present, the creation and improvement of diagnostic algorithms for PD (as well as other neurodegenerative diseases) at the prodromal stage is considered extremely relevant; today it is recognized as one of the most pressing challenges facing neurology.

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THE IMPACT OF FDG-PET ON THE CLINICAL DIAGNOSIS OF LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY (LATE)

Karen Elrayes[1], Alexander Fish[1], Ava Western[1], Alexandra Freedland-Wolford[1], Ceylan Cankurtaran[2], Daniel Silverman[3], Keith Vossel[1]
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Aims: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is an emerging neurogenerative disease affecting older populations that frequently coexists with Alzheimer's Disease (AD) and shares similar neuroanatomical networks. LATE is found in over 20% of autopsies in patients over 80, however, consensus on antemortem diagnosis is lacking, leaving LATE frequently missed in diagnosis. This study aims to characterize how neuroimaging influences physicians' diagnosis of LATE.
Methods: This study analyzed demographic, neuroimaging, and clinical data across a cohort of 26 patients (12 males; 14 females) averaging 80 years old (SD=6.6) from UCLA Health with suspected LATE or LATE with AD/other comorbidities. Sixty-two percent (n=16) were of white or European race and 84% responded as Non-Hispanic/Latino. We focused on the role of MRI and FDG-PET in diagnosis, and analyzed cognitive, behavioral, and motor symptoms.
Results: FDG-PET identified possible LATE in 69% of cases and was inconsistent with LATE in 23% of cases. MRI identified possible LATE in remaining 8% of cases. FDG-PET significantly influenced physicians' decisions to change diagnosis to include/exclude LATE (p=0.033, McNemar test). Major symptoms of LATE included short-term memory loss and language impairment, with notable absence of behavioral changes or motor deficits. Of the 18 collected MoCA assessments, the average score was 17.3/30 demonstrating mild-to-moderate cognitive impairment. Among 25 cases that were followed every 1-3 months for an average of 2 years or 24.5 months (SD=8.9), 9 progressed from MCI to dementia.
Conclusions: Neuroimaging with FDG-PET was critical in identifying early signs of LATE and should be considered in the clinical evaluation of patients with suspected LATE. Early detection of LATE is crucial to ensure optimal quality of life, aid in prognosis, and decrease morbidity.

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TDP-43 LOCALIZATION AND AGGREGATION IS INFLUENCED BY SUMOYLATION

Rachele Marino[1,2], Camilla Barchi[2], Rita Maccarone[1], Massimo Corbo[3], Marco Feligioni[2,3]
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Aims: TDP-43 is a nuclear RNA/DNA binding protein involved in RNA processing and linked to neurodegenerative disorders like Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease. In pathological conditions, TDP-43 forms toxic cytoplasmic aggregates in neurons. Recently, TDP-43 has been proposed as a target of SUMOylation, a post-translational modification. This study aims to further explore the role of SUMOylation in TDP-43 mis-localization and aggregation.
Methods: Immunofluorescence (IF), western blot (WB), and immunoprecipitation (IP) analyses were conducted to study TDP-43 and SUMO-1 localization and aggregation in neuroblastoma SH-SY5Y cell line. TDP-43 aggregation was induced by sodium arsenite (SA), while the global de-SUMOylation was triggered using Ginkgolic Acid (GA).
Results: Cells were treated with 50mM SA for 45 minutes to induce TDP-43 aggregation. IF images revealed that SUMO-1 aggregates in the nucleus and co-localizes with TDP-43. Nuclear/cytoplasmic fractionation showed decreased TDP-43 in the nucleus and increased TDP-43 in the cytoplasm of SA-treated cells, while global SUMOylation remained unchanged. IP of endogenous TDP-43 from both nucleus and cytoplasm revealed that TDP-43 decrease in the nucleus of SA treated cells compared to the control. In contrast, cytoplasmatic TDP-43 was increased in the cytoplasm of SA treated cells compared to the untreated. Moreover, the SUMO-1ylation of TDP-43 was found be more present in the cytoplasm of the SA treated cells. Furthermore, to better assesses that SUMOylation is involved in TDP-43 mis-localization and aggregation cells were treated with SA and GA and it was found that TDP-43 did not get out of the nucleus and SUMO-1 appeared to decrease when compared to untreated cells.
Conclusions: Our findings demonstrate that SUMOylation is involved in TDP-43 mis-localization and toxic cytoplasmic aggregation. SUMOylation could be a novel therapeutic target for neurodegenerative diseases.

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VASCULAR BURDEN IN PATIENTS WITH ALZHEIMER'S AND PARKINSON'S DISEASE

Jae-Hyeok Heo
Seoul Medical Center, Neurology, Seoul, Korea, Republic of

Aims: Alzheimer's dementia(AD) and Parkinson's disease(PD) are representative disorder of neurodegenerative disease. In previous studies, cerebral atherosclerosis was suggested as possible etiology for AD and PD. We performed brain MRI and MRA to evaluate association of neurodegenerative disease and cerebral atherosclerosis in patients who visited in neurologic clinic of a hospital.
Methods: The study recruited patients who visited the department of neurology in Seoul Medical Center. Among those, patients who had been diagnosed as AD or PD were included for analysis. In Brain MRI, the degree of white matter hyperintensities and presence of cerebral infarction were assessed. In brain MRA and Neck MRA, the degree of arterial stenosis and presence of aneurysm were confirmed.

Results: A total 159 patients were included, and 69 were men. The mean age was 76.3(±8.1) years. The AD group consisted of 101 patients and PD group consisted of 58 patients. In brain MRI, white matter hyperintensities were observed in 151 patients(95%) and cerebral infarction was present in 75 patients(47.2%). In brain brain MRA and Neck MRA, 116 patients (72.9%) confirmed that more than one stenotic lesions in intracranial vessel or extracranial vessel presents.
Conclusions: Our observational study confirmed the high incidence of white matter hyperintensities and cerebral artery stenosis in degenerative disease patients. We suggest that cerebral angiography including neck MRA should be confirmed with brain MRI.

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ASSOCIATION BETWEEN CEREBRAL MICROINFARCTS WITH CEREBRAL AMYLOID ANTIPATHY INCIDENTALLY DETECTED ON MRI AND COGNITIVE DECLINE IN MEMORY CLINIC PATIENTS.

Teruaki Kawasaki[1], Michio Ono[2], Yoshitomo Shirakashi[3], Ichiro Akiguchi[4]
[1]Kyoto Clinical and Translational Research Center for Neurocognitive Disorders, Neurology, Uji, Japan, [2]Takeda General Hospital, Neurology, Kyoto, Japan, [3]Uji Takeda Hospital, Uji, Japan, [4]Kyoto Clinical and Translational Research Center for Neurocognitive Disorders, Uji, Japan

Aims: Cerebral amyloid angiopathy (CAA) is known to be highly coexisted with Alzheimer's dementia (AD) pathology and has been related to the pathogenesis of small artery disease as well as microhemorrhage. In addition, it also causes vascular cognitive impairment (CAA-VCI; Greenberg SM, 2004). We investigated an association between cerebrovascular disorders and CAA that incidentally detected on MRI in the initial visit to a memory clinic and cognitive impairment.
Methods: We examined 53 patients (53% females, mean age 79.7±6.3) who showed abnormal findings on initial MRI (1.5T MRI-DWI, T2* and/or SWI), among 1,315 patients who visited to our memory clinic during 3 years. Clinical data including with or without incidental microinfarcts and microbleeds, vascular risk factors, neuropsychological tests and the degree in addition to the type of dementia were evaluated.
Results: Abnormal findings on initial MRI included 42 cases of cerebral infarction, 4 cases of cerebral hemorrhage, 6 cases of chronic subdural hematoma, and 1 case of brain tumor. Hypertension was found in 43 cases. Microbleeds were observed in 29 cases. CAA including cases with cortical superficial siderosis, was detected clearly and more extensively on 3T MRI-SWI. CAA-VCI was suspected in 19 cases (35.8%), including AD comorbidity with hippocampal/temporal lobe atrophy. Microbleeds were predominantly in the occipital lobe in CAA-VCI. Neuropsychological exams in CAA-VCI showed a tendency to decline of executive function and/or visuospatial ability.
Conclusions: It has been reported CAA is highly coexisted with AD pathology. It is necessary, however, to take a presence of VCI into consideration when we perform a clinical practice of elderly patients.

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LONGITUDINAL TRAJECTORIES OF VERBAL MEMORY AND HIPPOCAMPAL VOLUME IN SUBJECTIVE COGNITIVE DECLINE WITH UNDERLYING CEREBROVASCULAR DAMAGE

Jennifer Suárez[1], Roraima Perez-Yanez[2], Eric Westman[3], Daniel Ferreira[4], Jonas Olofsson[3], Jose Barroso[1], Nira Cedres[5]
[1]Fernando Pessoa University, Santa María de Guía, Spain, [2]La Laguna University, La Laguna, Spain, [3]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society (nvs), Huddinge, Sweden, [4]Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Division Of Clinical Geriatrics, Stockholm, Sweden, [5]Stockholm University, Stockholm, Sweden

Aims: Objective: In individuals with high underlying cerebrovascular pathology (V+), we aim to determine whether the presence of subjective cognitive decline (SCD) at baseline is associated with worse long-term trajectories of memory and hippocampal volume compared to those without SCD.
Methods: Method: Longitudinal cognitive and MRI assessments from 111 cognitively unimpaired individuals (mean age= 58.9; 48.65% female) with high underlying cerebrovascular pathology (V+SCD= 69, V+no-SCD= 42) from the GENIC database were used to quantify these changes. Verbal memory was assessed based on the Spain-Complutense Verbal Learning Test (TAVEC) for long-term recall. Cerebrovascular pathology was assessed using automatic segmentations of white matter lesions (WML) on MRI. Hippocampal volume was assessed using automatic subcortical volume segmentation on MRI. Individuals were categorized at baseline and followed-up after 60 months.

Results: SCD group showed significantly poorer cognitive performance (u= 1092, p= 0.027) and lower hippocampal volume (u= 1145, p=0.032) at baseline compared to no-SCD. Within-group baseline-to-follow-up comparisons showed significant decline in memory and hippocampal volume for both groups (t_{23}= 1.84, p= 0.039); (t_{21}= 2.48, p= 0.011). V+ SCD and no-SCD groups were comparable in memory performance and hippocampal volume at follow-up.

Conclusions: Conclusions: In individuals with high underlying cerebrovascular pathology, while the presence of SCD is associated with concomitant poorer memory performance (within the normal range) and reduced hippocampal volume compared to those without SCD, both groups declined similarly after 60-months follow-up. Our findings suggest that SCD individuals are sensitive to early changes. However, the presence of higher levels of cerebrovascular pathology results in similar long-term trajectories for both SCD and non-SCD individuals.

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Virtual EP - 118

Virtual E-Posters and Oral On-Demand
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GLIA-LIKE CELLS FROM HUMAN MESENCHYMAL STEM CELLS AMELIORATE COGNITIVE DEFICITS IN A MOUSE MODEL OF VASCULAR COGNITIVE IMPAIRMENT AND DEMENTIA

Yejin Ryu[1], Eun Ji Lee[1,2], Seon Ju Lee[1], Hyunhee Park[1], Jeong-Min Baek[1,2], Min-Ju Kim[1,2], Hyun-Jung Yu[3], Hyuk Sung Kwon[1], Seong-Ho Koh[1,2]
[1]Department of Neurology, Gyeonggi-do, Korea, Republic of, [2]Hanyang University, Seoul, Korea, Republic of, [3]Department of Neurology, Seongnam, Korea, Republic of

Aims: Vascular cognitive impairment and dementia (VCID) is the second most prevalent dementia type, occurring when the arteries supplying blood to the brain are obstructed. This leads to chronic reduced blood flow, brain tissue damage, and neuron loss in the hippocampus, presenting as cognitive dysfunction. The beneficial capability of glia-like cells derived from human mesenchymal stem cells (ghMSCs) for AD and ischemic stroke has been established. Therefore, this study aims to investigate the efficacy of ghMSCs in a mouse model of VCID.
Methods: We utilized bilateral common carotid artery stenosis (BCAS) surgery to mimic characteristics lesions of VCID in mice by inducing chronic cerebral hypoperfusion. They included those intracerebroventricularly administered hMSCs, ghMSCs (at varying concentrations), or neurobasal medium as a Vehicle group. Additionally, the CXCR2 antagonist SB225002 treatment group was intraperitoneally administered for 5 days. Cognitive function estimation was conducted using the Morris Water Maze (MWM) test to record the time taken to find a platform within a 60-s timeframe.
Results: During the MWM test, the escape latency of VCID mice treated with 2×10^5 cells ghMSCs was significantly decreased than other groups. However, this effect was decreased with the administration of a SB225002. Molecular analysis confirmed the presence of ghMSCs in the brain up to 5 weeks following administration. The expression levels of the markers associated with neuroregeneration, neuroplasticity, and the tight junction were higher in the ghMSC-treated group than in the other groups. Nonetheless, these expressions were inhibited by SB225002 administration.
Conclusions: These findings suggest that ghMSCs can enhance neuronal regeneration and tight junction restoration, thereby contributing to cognitive improvement in an animal model of VCID. Furthermore, we found that CXCR2 is crucial in the mechanism of action of ghMSCs.

Virtual EP - 119

Virtual E-Posters and Oral On-Demand
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SMALL ORGANISM, BIG HOPE: SECONDARY METABOLITES FROM DICTYOSTELIUM DISCOIDEUM AS INNOVATIVE INTERVENTIONS FOR ALZHEIMER'S DISEASE

Nil Patil
Parul University, Life Sciences, Vadodara, India

Aims: Small Organism, Big Hope: Secondary metabolites from Dictyostelium discoideum as innovative interventions for Alzheimer's disease
Methods: In our quest for therapeutic molecules, we embarked on pharmacokinetic screening of secondary metabolites derived from D. discoideum, specifically focusing on genes associated with AD. Following gene screening, the upregulated genes were characterized through AlzData. after describing the target we did molecular docking & simulation with target ligands. and also isolate & characterize through GC-MS & LC-MS.
Results: Molecular docking studies unveiled the robust binding affinity of the terpene compound PQA-11 to the neuroinflammatory receptor COX2, registering an impressive -8.0 Kcal/mol binding affinity. Subsequently, the docked complex (COX2-PQA11) underwent thorough scrutiny via Molecular Dynamics Simulation, displaying lower RMSD, minimal RMSF fluctuations, and a reduced total energy of -291.35 KJ/mol compared to the standard drug. Upon the successful completion of our in-silico approach, we conducted the isolation and characterization of these bioactive compounds from the fruiting body stage of D. discoideum. Using GC-MS, we identified Discodiol with a retention time of 12.93 and a mass-to-charge ratio (m/z) of 95. For non-volatile compounds like PQA11, identification was achieved through LC-MS/MS, where a retention time range of 11.32-11.82 and an intact mass of 233.25 m/z were observed.
Conclusions: Continued research on PQA-11 and Discodiol holds promise for advancing our understanding of their potential role in AD management, particularly through the modulation of neuroinflammatory mechanisms.

Virtual EP - 120

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INFLUENCE OF SOCIODEMOGRAPHIC VARIABLES ON PATIENT AND PRACTITIONER KNOWLEDGE OF PHARMACOLOGICAL MANAGEMENT FOR PARKINSON'S DISEASE

Paula Abola, Kristin Lefebvre
University of Jamestown, Fargo, United States of America

Aims: Our primary aim was to investigate the current knowledge of pharmacological management options in patients with PD and practitioners. Our secondary aim was to identify the influence of sociodemographic variables on patient and practitioner knowledge of pharmacological management for PD. Determining whether patients and practitioners are knowledgeable of the various options for the pharmacological management of PD may propose solutions that improve patient outcomes.
Methods: The Knowledge Attitude Practice (KAP) model was adapted to develop a questionnaire that assesses patient and practitioner knowledge of pharmacological management options for PD. The questionnaire consisted of 11 questions. Basic frequency, likelihood-ratio chi-squared, Spearman's correlation, univariate, and multivariate analyses were performed on the collected data.
Results: The most widely known pharmacological management by both populations was Levodopa-Carbidopa immediate-release tablets and the least-known pharmacological management by both populations was the anticholinergic drug Procyclidine. A higher education level is significantly related to higher knowledge of all Levodopa-Carbidopa forms of management (aOR range 1.23-1.83), with the largest effect size between education level and Levodopa-Carbidopa subcutaneous delivery system. Younger age is significantly related to higher knowledge of several PD management (aOR 0.42-0.58) including extended-release capsules, Levodopa-Carbidopa-Entacapone tablets, Rasagiline, Safinamide, Ropinirole, Pramipexole, Opicapone, Amantadine, and Trihexyphenidyl/Benzhexol.
Conclusions: Practitioners have a statistically significant advantage in identifying most pharmacological management for PD compared to patients. Future research should investigate the quality of communication between patients with PD and practitioners to identify what might be causing this knowledge gap.

Virtual EP - 121

Virtual E-Posters and Oral On-Demand
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CHOROID PLEXUS CHANGES AND COGNITIVE DECLINE: WHAT ADVANCED MRI TELLS US ABOUT AGING BRAINS

Zhaoyuan Gong, Jonghyun Bae, Noam Fox, Nathan Zhang, Alex Guo, John Laporte, Josephine Egan, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

Aims: The choroid plexus (CP) is essential for cerebrospinal fluid production and brain homeostasis, including regulation of neuroinflammation and clearance of harmful substances. Existing evidence links CP alterations to cognitive impairment in aging and neurodegenerative diseases like Alzheimer's and Parkinson's. However, the impact of CP microstructural integrity on cognition is not well understood. This study employs advanced MRI to assess CP macro/micro-structure and investigate their associations with cognitive changes in cognitively unimpaired individuals.
Methods: We analyzed 116 cognitively unimpaired participants who underwent advanced MRI to quantify CP volume and microstructural metrics (T_1, T_2, fractional anisotropy [FA], mean diffusivity [MD]). Cognitive assessments covering memory, attention, executive function, verbal fluency, and processing speed were conducted over 320 visits. Cross-sectional and longitudinal associations between CP metrics and cognition were evaluated using multiple linear regression and linear mixed-effects model respectively, adjusting for age, sex, education, and race. Structural equation modeling (SEM) explored the longitudinal relationship between overall cognitive decline and CP structural damage.
Results: Elevated T_1, T_2, and MD values and lower FA—indicating compromised CP microstructure—were significantly associated with lower processing speed; higher MD was also linked to lower verbal fluency. Larger CP volume and compromised microstructural integrity were associated with faster declines in multiple cognitive domains. SEM revealed that a greater overall macro- and microstructural damage strongly predicted faster cognitive decline.

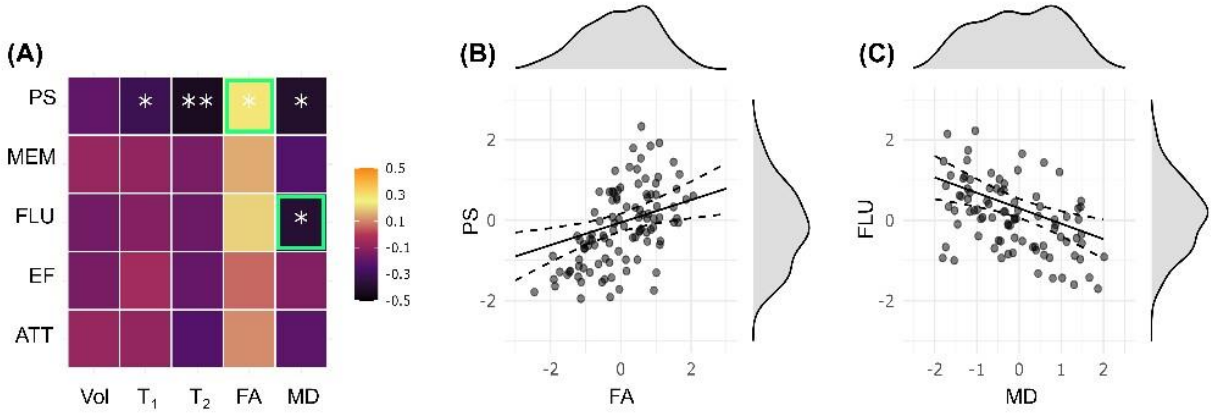


Figure 1. Panel A shows the regression coefficients for the MRI metric term. Statistically significant results are labeled with stars, with * indicating p < 0.05 and ** indicating p < 0.01. All p-values are FDR corrected using the BH procedure. Panel B shows an example analysis result where a higher level of fractional anisotropy is significantly correlated with higher processing speed. Panel C shows an example analysis result where a higher level of mean diffusivity is significantly correlated with lower verbal fluency.

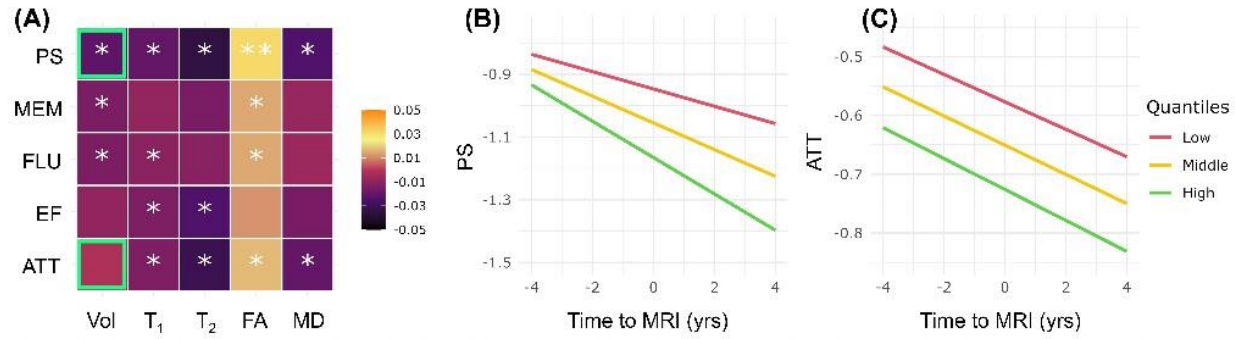


Figure 2. Panel A shows the regression coefficients for the MRI metric × Time interaction term. The same labeling method was applied using FDR corrected p-values. Panel B shows an example analysis result where a higher level of CP volume is significantly correlated with a faster longitudinal decline rate of processing speed. Panel C shows an example analysis result where a higher level of CP volume is not significantly correlated with the longitudinal decline rate of attention.

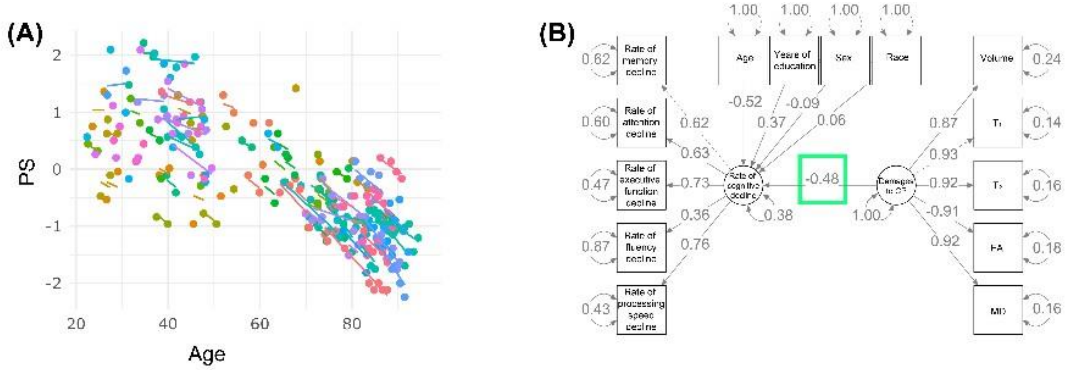
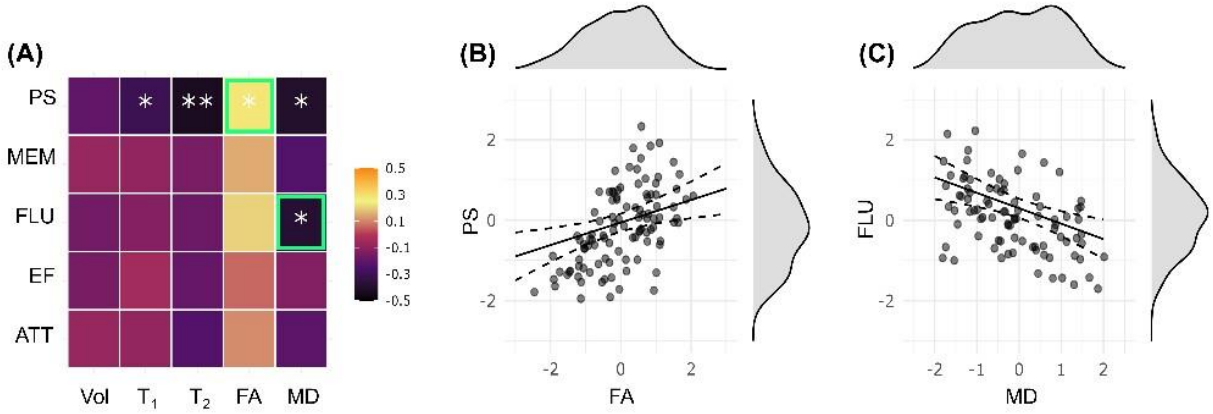


Figure 3. Panel A shows the example of estimated decline rates of processing speed per individual subject. Panel B illustrates the construction of latent variables, including the rate of cognitive decline and damages to the CP. The regression results indicate that greater overall CP damage is significantly associated with greater overall faster cognitive decline.



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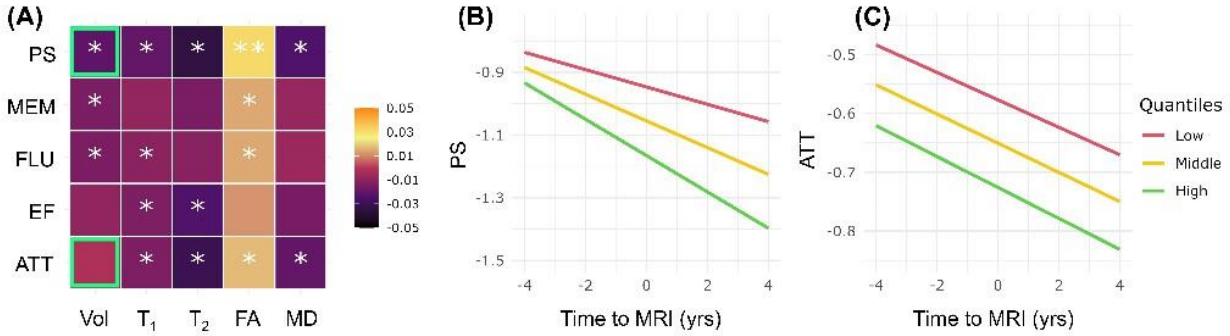

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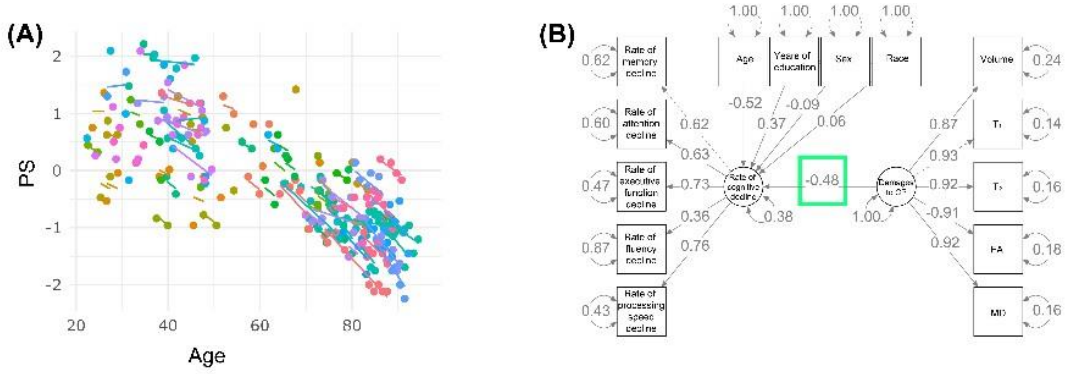

Figure 3. Panel A shows the example of estimated decline rates of processing speed per individual subject. Panel B illustrates the construction of latent variables, including the rate of cognitive decline and damages to the CP. The regression results indicate that greater overall CP damage is significantly associated with greater overall faster cognitive decline.

Conclusions: Our findings demonstrate that compromised CP structural integrity is significantly associated with cognitive decline in aging among cognitively unimpaired individuals. This underscores the importance of CP health in maintaining cognitive function and suggests that advanced CP imaging biomarkers could aid in early detection and intervention strategies for cognitive decline.

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Virtual EP - 122

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DECIPHERING MIR-802'S ROLE IN GLIAL CELLS: IMPLICATIONS FOR INSULIN SIGNALING AND NEURODEGENERATION IN DOWN SYNDROME

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Aims: Individuals with Down syndrome (DS) exhibit a variety of pathological phenotypes across tissues, with a marked predisposition toward accelerated aging and Alzheimer-like dementia within the central nervous system. A critical link between neurodegeneration and metabolic disorders is well-documented, with evidence suggesting that disruptions in insulin signaling (IS) may contribute to cognitive decline. MicroRNAs (miRNAs), particularly those encoded on chromosome 21, have emerged as key post-transcriptional regulators of metabolic pathways, influencing various aspects of IS. Among these, miR-802 has been highlighted due to its role in promoting insulin resistance (IR) in obesity and diabetes. Based on the "gene dosage hypothesis" of DS, **our study focuses on elucidating how miR-802 may contribute to altered IS and potentially accelerate dementia risk in DS.**
Methods: To assess the role of miR-802 in IS dysregulation, we evaluated miR-802 expression in brain tissues from Euploid (Eu) and Ts (DS model) mice. In parallel, we investigated miR-802's role in astrocytes isolated from Eu and Ts brains. Our experimental approach first evaluated the onset of IR in the astrocytes, after which we quantified miR-802 levels and examined its regulatory effects on target genes involved in IS, including PTEN and GSK-3β, identified through bioinformatic tools.
Results: Our findings indicate that IS alterations worsen at 9 months in Ts65Dn mice. Notably, these changes appear to be driven by miR-802 overexpression, which negatively regulates PTEN and GSK-3β in the brain of Ts65Dn mice. In astrocytes, we observed a marked increase in miR-802 levels associated with the onset of IR, particularly in Ts65Dn cells, suggesting that miR-802 may have a specific role in promoting IS dysregulation in DS astrocytes.
Conclusions: Our study provide a molecular framework for developing therapeutic strategies focused on miRNAs regulation.

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THE ASSOCIATION BETWEEN THE MEDITERRANEAN DIET AND MULTIPLE SCLEROSIS RISK : A META-ANALYSIS

Fatemeh Shakouri[1], Amirreza Naseri[1], Mahnaz Talebi[2], Sarvin Sanaie[2], Morteza Lotfi[1], Ali Rostami[1]
[1]Tabriz University of Medical Sciences, Student Research Committee, Tabriz, Iran, [2]Tabriz University of Medical Sciences, Neurosciences Research Center (nsrc), Tabriz, Iran

Aims: Multiple sclerosis is a chronic inflammatory demyelinating disease affecting the central nervous system. The Mediterranean diet has gained attention for its anti - inflammatory properties. This meta-analysis aims to evaluate the effect of the Mediterranean diet on Multiple Sclerosis risk.
Methods: A systematic search of databases was conducted up until March 2024 in order to find potentially relevant papers. Original observational or interventional studies which have investigated the relationship between the Mediterranean diet and MS risk were included. The selected studies were subjected to rigorous quality assessment and data extraction. Finally, three studies which categorized the results of the Mediterranean diet questionnaire into 3 groups were included in meta-analysis.
Results: There were two subgroups; intermediate vs low adherence (tertile 2 vs 1) and high vs low adherence (tertile 3 vs 1). Tertile 2 vs 1 didn't present a significant association with MS risk (OR = 0.690, 95% CI : 0.425 - 1.119, p- Value = 0.133, I2 = 74.8%), but Tertile 3 vs 1 revealed a significant association with the risk of MS (OR = 0.275, 95% CI : 0.106 – 0.716, p-Value = 0.008, I2 = 0%). So, high adherence to Mediterranean diet has an important role in decreasing risk of MS.
Conclusions: This meta-analysis provides strong evidence supporting the beneficial effect of the Mediterranean diet in reducing the incidence rate of MS. Adherence to the Mediterranean dietary pattern may serve as a potential preventive strategy for individuals at risk of developing MS. Further research, including prospective studies and randomized controlled trials, is warranted to validate these findings and explore the underlying mechanisms. The results of this meta-analysis have important implications for public health strategies aimed at reducing the burden of MS.

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APOE4 IMPAIRS MITOPHAGY BY INDUCING BAX-DEPENDENT LYSOSOMAL MEMBRANE PERMEABILIZATION IN NEURONAL CELLS

Boram Lee[1], Soo Hyun Kang[1], Ji Min Lee[1,2], Hye Eun Lee[1,3], Changjae Yoo[1,4], Eugene Bok[1], Sang Ryong Kim[2], Ji Young Mun[1], Jaekwang Kim[1]
[1]Korea Brain Research Institute (KBRI), Dementia Research Group, Daegu, Korea, Republic of, [2]Kyungpook National University, School Of Life Sciences, Daegu, Korea, Republic of, [3]Kyungpook National University, School Of Medicine, Daegu, Korea, Republic of, [4]Daegu Gyeongbuk Institute of Science and Technology, Daegu, Korea, Republic of

Aims: Mitochondrial dysfunction is a hallmark of Alzheimer's disease (AD). Mounting evidence suggests that clearance of damaged mitochondria, termed mitophagy, is dysregulated and thereby, damaged mitochondria are accumulated in AD brains. However, the underlying mechanisms for mitochondrial deficits are largely unknown. *Apolipoprotein E4 (APOE4)* genotype is the strongest genetic risk factor for AD. Although the pathophysiological role of glial ApoE4 have been under intense investigation, our understanding of neuronal APOE's role is still limited. In this study, we investigated the effects of *APOE* genotype on mitophagy in neuronal cells.
Methods: We developed a neuronal N2a cell line stably expressing mito-QC which enable us to assess mitophagy quantitatively. Using this cell line, we examined the effect of APOE genotypes on mitophagy in neuronal cells.
Results: We found that intracellular ApoE4 inhibits CCCP-induced mitophagy in N2a cells, while ApoE2 and ApoE3 do not affect mitophagy. However, extracellular ApoEs from astrocytes do not affect mitophagy in neuronal cells. We observed that ApoE4 does not influence mitophagy induction evidenced by no alteration of PINK1 stabilization and Parkin translocation to mitochondria. Interestingly, we found that intracellular ApoE4 induces Bax translocation to lysosome and thereby, lysosomal membrane permeabilization (LMP), leading to lysosomal deacidification. Furthermore, Bax channel blocker restores lysosomal pH and mitophagy in N2a cells expressing ApoE4. In addition, small molecules promoting lysosomal acidification, such as C381 and EN6 also restore lysosomal pH and mitophagy in N2a cells expressing ApoE4.
Conclusions: Taken together, we demonstrated that intracellular ApoE4 suppresses lysosomal degradation of damaged mitochondria in neuronal cells by inducing Bax-dependent LMP. Our data suggest that targeting lysosomal acidification may represent a novel therapeutic intervention for Alzheimer's disease associated with ApoE4.

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TRICYCLES AND THE RISK OF SUICIDAL IDEATION; ADVANCING STUDY

Raafat Mandour
Mansoura University, Mansoura, Egypt

Aims: Suicidal behavior could be an important public health problem. The main objective of study was too lightness utilization of various antidepressants, additionally, their explicit types to forestall or reduce the risk of suicidal attempts.
Methods: In total, 1348 patients of different ages were selected from different localities and alternative close regions and approved to participate in this study. Blood and urine samples obtained from everywhere the past few years from 2018 to 2021 once consent. Enzyme multiplying immunoassay technique (EMIT) is subject to the reference standard materials accustomed assess the precision and accuracy of the procedure. Gas chromatography-mass spectrum (GC – MS) used for confirmation of positive samples.
Results: A statistically highly significant association was found relating to Para suicide in relevancy age and gender of patients. A statistically significant distinction was found as regards Para suicide in association with type of drug overdose. Findings from this review should be considered in light of potential limitations, such as the lack of comparative information concerning several antidepressants. Para suicide risks for selective serotonin reuptake inhibitor were significantly low than those of tricycles' antidepressants,
Conclusions: A substantial difference between different types of antidepressants was found, so in suicide prevention, risks and benefits of antidepressant should be taken into account when choosing treatment for depressive patients. Depressed patients should be under close psychiatric assessment in order to prevent such possible suicidal attempts

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RECENT ADVANCES IN PHARMACOLOGICAL TREATMENT OF LATE-LIFE DEPRESSION

In Hee Shim[1], Dong Sik Bae[2]
[1]Dongnam Institute of Radiological & Medical Sciences, Busan, Korea, Republic of, [2]Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea, Republic of

Aims: Elderly patients with depression are more likely to have poor treatment response due to clinical characteristics such as comorbid physical illnesses, severe depressive and anxiety symptoms, frequent relapses, and cognitive decline. Therefore, applying appropriate treatments to patients with depression in late life is clinically crucial. In this study, we will explore the latest insights into the pharmacological treatment of late-life depression, focusing on clinical trials.
Methods: We searched PubMed from January 2008 to October 2024 using the following keyword combinations linked with the word OR: (a) geriatric, elderly, old age; (b) depressive, major depressive, MDE, MDD; and (c) antidepressant, antipsychotic, mood stabilizer, anticonvulsant, treatment, medication, algorithm, guideline, pharmacological. The search was limited to randomized controlled trials.
Results: In late-life major depressive disorder, antidepressants with relatively good tolerability, such as SSRIs and SNRIs, can be considered as first-line treatments. If there is insufficient treatment response, switching antidepressants, combination therapy, or adjunctive therapy with antipsychotic medications like aripiprazole or quetiapine may be considered (Table1).
Conclusions: In the pharmacological treatment of late-life depression, studies have primarily focused on confirming the efficacy and safety of antidepressants in monotherapy or adjunctive therapy, as well as examining the effects of adjunctive therapies with antipsychotics and other medications. However, there is a lack of evidence from randomized placebo-controlled clinical trials on pharmacological treatment for depression in late life, highlighting the need for further research.

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FUNCTIONAL CONNECTIVITY CHANGES IN ALZHEIMER'S DISEASE WITH APATHY

Wangyoun Won
The Catholic University of Korea, Incheon, Korea, Republic of

Aims: The aim of this study was to investigate default mode network (DMN) changes in Alzheimer's disease (AD) patients with apathy and to observe the relationships with the severity of apathy.

Methods: Thirty AD patients with apathy and 30 healthy controls took part in this study. DMN data was compared with seed based analysis. Correlation analysis was also conducted using FDR correction.

Results: In group comparison of DMN functional connectivity, the AD group showed less DMN functional connectivity in right PCC, left superior frontal gyrus, right precuneus, and left subcallosal cortex compared to HC. The Apathy Inventory scores showed positive correlation with functional connectivity of DMN in the left anterior cingulate cortex (ACC) in the AD group.

Conclusions: This study was to explore the impact of apathy severity on DMN alterations. These findings might suggest that ACC may be one of core structures understanding neurobiological mechanism and clinical significances of apathy in AD.

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DEVELOPMENT OF DEMENTIA AND OPIOID EXPOSURE FOR NON-CANCER PAIN CONTROL: A POPULATION-BASED COHORT STUDY

Areum Moon, Tak Youn
Dongguk University International Hospital, Psychiatry, Goyang, Korea, Republic of

Aims: Opioid medications is neurotoxic and could induce the development of dementia. Therefore, opioid exposure can influence the development of dementia.. We investigated the association between opioid exposure for non cancer pain control and the development of dementia in patients with chronic non cancer pain without any psychiatric mediation or previous psychiatric diagnosis in South Korea.
Methods: This study is a population based cohort study using big data from the NHIS database in South Korea. From 2017 to 2019. Patients diagnosed with musculoskeletal diseases and chronic non cancer pain for control group. Patients with a cancer diagnosis who received surgery or those with psychiatric disorders or medicated psychiatirc medicines were excluded from the analysis. Patients who had been regularly and continuously prescribed opioids (morphine, hydromorphone etc...) for ≥ 90 days were classified as opioid group. The patients who were diagnosed with dementia from 2020 to 2022 were included for analysis.
Results: A total of 850,734 patients with chronic non-cancer pain for control group. 13,867 (1.63% of the control group, 13,867/850,734) were opioid users. A total of 23,140(2.72%) patients with chronic non-cancer pain were newly diagnosed with dementia from 2020 to 2022. The proportions of dementia were AD 1.9%, VD 0.5%, and unspecified dementia 0.7%. The opioid group showed a 16% increased likelihood of developing Alzheimer's dementia and unspecified dementia of compared to opioid-naïve patients. In the over 60-years-old group, the opioid group showed a 21% higher risk of developing dementia compared to the control group.
Conclusions: Our results suggest that elderly individuals who were prescribed opioids may be at a higher risk for developing dementia. Early intervention for detecting cognitive declines and diagnosing dementia in opioid users is needed for the public health system.

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MATERNAL TRANSMISSION OF IMMUNE RESPONSES IN OFFSPRING

Kim Young Jin, Seung Pil Yun
Department of Pharmacology, Gyeongsang National University School of Medicine, Room No. 422, Jinju, Gyeongsangnamdo, Korea, Republic of

Aims: This study aims to explore whether immune responses triggered in pregnant mice can be passed on to their offspring, potentially offering them early immune protection and enhancing our understanding of the role of maternal immunity in early development.
Methods: Pregnant mice were immunized with a specific antigen to induce an immune response. Their pups were tested for immune markers such as TNF-α, IL-6, IL-17A, and inflammatory immune cell activity on spleen and lymph node tissue samples. These findings were compared with those from a control group of non-immunized pregnant mice and their offspring to determine any transmission of immune traits.
Results: These results indicate that the pups of immunized pregnant mice have higher levels of specific antibodies and greater immune cell activity, mirroring the immune responses of their mothers. Also, inflammatory cytokines were either absent or significantly lower in the control group, suggesting that some aspects of the maternal immune response may be transmitted to the offspring.
Conclusions: The study suggests that immune responses from pregnant mice can be partially transmitted to their offspring, potentially strengthening their early immunity. These results offer valuable insights into how maternal immunity affects fetal health.

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PIONEER STUDY OF MILD COGNITIVE IMPAIRMENT IN PARKINSON'S IN NORTHERN NIGERIA

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Aims: To determine the prevelance, severity and predictors of mild cognitive impairment among patients with parkinson's disease in northern Nigeria, a puooner study
Methods: A cross sectional study of 153 volunteers including 109 Parkinson's patients and 53 healthy cobtrols attending the department of neurology, Aminu Kano Teaching Hospital, Nigeria.
69% were males and 31% were females. 70% of PD patients were on active treatment and 30% were treatment naive. All subjects were assesed for cognitive status using the Montreal Cognitive Assesment Tool (MOCA) after piloting and validation in 30 subjects. Median age of subjects was 64 years. 24% of Parkinson's disease patients (PD) were found to have a low MOCA score/Mild Cognitive Impairement (MCI) compared to control with a p value of 0.001/adjusted odd ratioo of 6.8. The only independent oredictiors of PD MCI based on the MOCA was less than 12 years of formal education with a p value of 0.002 on multiple regression analysis.
Results: 255% of PD patients had MCI based on a low MOCA with a p value of 0.01 and an adjusted OR of 6.8. Mean age of subjects was 69 years, 70% makes and 30% females. On multiple regression analysis lack of firmal education ie less than 12 years of formal education was the sole independant predictor iof MCI in PD bssef on the MOCA scores.
Conclusions: MCI is common in PD patients and is associated with less than 12 years if formal education. Lack of screening for MCI can wirsen the outcomes and wuality if lives of OD patients and thier familues and care givers and even general practioners/non neurologist. Screening of PD MCI is thus an importsnt strategy in the continum of care of PD.

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WHICH FACTORS ARE ASSOCIATED WITH DEPRESSION AND ANXIETY IN OCCUPATIONAL CAREGIVERS FOR DEMENTED PATIENTS

Oh Dae Kwon
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Aims: The aging of the population has rapidly progressed in recent years in Korea, and the number of demented patients is increasing these days. Many studies have found that caregiving is highly stressful and results in adverse physiologic and psychologic outcomes, not only for caregivers themselves but also for recipients. This study investigated the factors associated with the depression and anxiety of caregivers. Furthermore, we aimed to arouse attention to the psychiatric burden of caregivers.
Methods: Caregivers for demented patients were recruited from 9 medical care centers in the metropolitan city of Daegu and Gyeongsanbuk-do province. 220 participants were included, and they were all non-family groups. During face-to-face interviews with a psychologist, they completed the Burden Interview, Beck Depression Inventory(BDI), Beck Anxiety Inventory(BAI), their health status, the severity of dementia in their patients, and the length of care time were evaluated. The depression and anxiety experienced by care workers and the factors affecting it were assessed using statistical analyses.
Results: The caregivers were mainly women, with a mean age of 46. The mean caregiver's BDI was 8.68 and BAI 7.33. The level of the caregiver's depression was affected by health status(p=0.009) and residing form(p=0.004). The level of caregiver's anxiety was associated with age(p=0.000), total time for care(p=0.003), BMI (p=0.000), educational status(p=0.000), health status(p=0.000), and residing form(p=0.013).
Conclusions: Our study investigated factors affecting caregivers' depression and anxiety in Korea. The health status was most closely related to depression. For the anxiety of the caregiver, the total time for care was the most closely related.

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EVALUATING THE ROLE OF THE CARE PARTNER IN UNDERSTANDING ALZHEIMER'S PATIENT CAPABILITIES

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GSK, London, United Kingdom

Aims: The aim of the Alzheimer's Disease (AD) Patient Capabilities research is to investigate physiological and psychological patient capabilities from a care-partner perspective in the USA and UK.
Methods: The market research involved the deployment of a user capabilities tool and interviews. The user capabilities tool is a bespoke survey with six areas of investigation: Thinking, Feeling, Moving, Sense, Diet and Living. The sample includes care partners and patients diagnosed with mild cognitive impairment (MCI) and AD (mild, moderate or severe). Overall, 101 completed the survey only and 40 completed interviews (individual/dyad) and the survey.
Results: In total, 141 participants (98 care partners and 43 patients) were included in this research. The mean patient age was 73.5 years with reported stage of disease as 26% MCI, 34% mild dementia due to AD, and 40% moderate or severe dementia due to AD. The results highlight capability deterioration in all areas as AD progressed except for diet (stomach and thirst). Significant capability loss was reported at all disease stages in: (1) Thinking (memory, concentration); (2) Moving (strength/dexterity, mobility); (3) Feelings (confidence); and (4) Living (day-to-day household activities). Perception of capabilities differed at the early stages between care partners and patients with mild dementia due to AD and MCI in the Living, Feelings and Moving areas.
Conclusions: The findings indicate that care partners supporting patients at the MCI and mild dementia stages very quickly become involved in all aspects of the patient's life and evolve into key decision makers in areas where there is capability loss. Care-partner perspectives must be considered alongside patients from the earliest stages to develop a clinical care pathway that is optimised to the capabilities and experiences of patients.

Funding: This market research was funded by GSK.

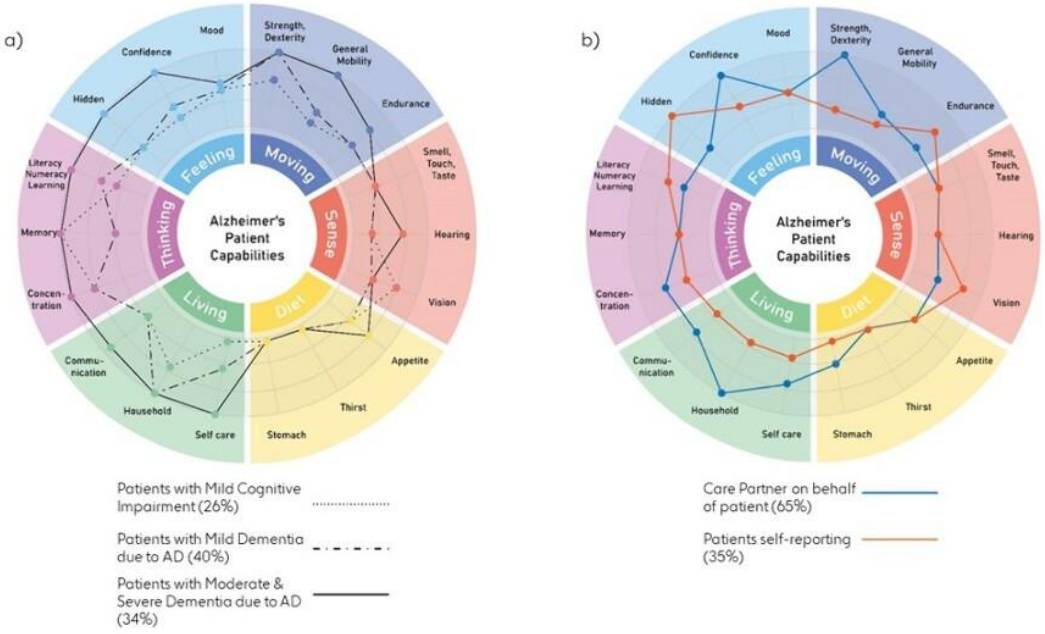

Figure 1. GSK user capabilities toll: 2024 Alzheimer's disease capability profile of patients and care partners. (a) Patients diagnosed with MCI and any AD stage (mild, moderate or severe), and their care partners (N=141) **(b)** Patients with mild dementia due to MCI and AD, and their care partners (n=141).

AD, Alzheimer's Disease; MCI, mild cognitive impairment.

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COMPARISON OF THE CEDARS-6 ASSESSMENT TOOL TO THE CLINICAL DEMENTIA RATING SCALE IN A DEMENTIA CARE MANAGEMENT PROGRAM

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Aims: To improve identification of clinical care needs and match appropriate resources for people living with dementia (PLwD) and their caregivers, the Cedars-Sinai C.A.R.E.S. Program developed the novel CEDARS-6 assessment tool which scores patients across 6 domains of care needs and classifies patients by risk. We sought to determine: 1) whether the CEDARS-6 risk classification is associated with healthcare utilization and patient and caregiver outcomes and 2) whether the CEDARS-6 risk classification aligns with the dementia staging tool Clinical Dementia Rating (CDR) scale.
Methods: We utilized a comparative analysis approach to compare the CEDARS-6 assessment to the CDR. The primary outcomes were healthcare utilization for one-year post-enrollment. Secondary outcomes were patient behavioral and psychological symptoms of dementia (BPSD) and caregiver distress (NPI-Q), caregiver strain (MCSI), and caregiver depression (PHQ-9). We used bivariate and multivariate approaches to assess differences by risk category.
Results: There were 386 patients with dementia enrolled in the CARES program. Mean age was 81.3 years old. 63% were female, 61% White, 68% lived at home with someone. Twenty-nine patients were classified as high risk and were distributed across CDR scores 0.5 to 3. We found significant differences between CEDARS-6 groups for NPI distress ($b=5.80$, $p<.003$) and MCSI scores ($b=3.92$, $p<.005$). We found significant differences by CDR groups for NPI severity ($b=2.06$, $p=0.015$), NPI distress ($b=2.48$, $p<0.040$), and MCSI scores ($b=2.01$, $p<0.019$). We found no statistical differences for utilization after enrollment.
Conclusions: The study suggests that the CEDARS-6 assessment tool is associated with patient BPSD, and caregiver distress/strain/depression and is comparable to differences seen with the CDR scale. The CEDARS-6 tool is consistent with the CDR and additionally identifies important clinical information for matching patient and caregiver needs.

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EFFECTIVENESS OF DIGITAL TOOLS IN COGNITIVE AND COMMUNICATIVE REHABILITATION FOR VASCULAR DEMENTIA: A CLINICAL CASE STUDY

Hemaraja Nayaka.S
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Aims: This clinical case study explores the effectiveness of digital cognitive and communicative training tools in a 79-year-old female with vascular dementia. The study specifically evaluates how innovative neuro-cognitive applications contribute to rehabilitating cognitive and language deficits following stroke and during the progression of vascular dementia.
Methods: The patient was assessed using the Neuro-Cognitive Toolbox (NCTB) from ICMR-India and the Montreal Cognitive Assessment (MOCA). The therapeutic regimen included both conventional methods and digital interventions such as Tactus Therapy, Lingraphica, and Constant Therapy. Over 18 months, the patient attended 240 therapy sessions, complemented by physiotherapy and occupational therapy.
Results: Despite ongoing therapy, the patient experienced notable cognitive decline, with scores worsening from Level 4 (moderate decline) to Level 6 (severe decline) on the Global Deterioration Scale. Although some improvements were observed in specific language tasks initially, overall speech fluency and output declined further, exacerbated by a COVID-19 infection.
Conclusions: This case underscores the advantages and limitations of using digital tools for cognitive and communicative therapy in vascular dementia. Although applications like Tactus Therapy and Lingraphica provided temporary benefits, they could not halt the progressive cognitive decline. This case highlights the need for tailored treatment strategies and ethical considerations in managing advanced stages of cognitive impairment.

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EXPLORING THE FEASIBILITY OF USING ZUMBA AND COGNITIVE STIMULATION EXERGAME IN PERSONS WITH DEMENTIA AND LATE-LIFE DEPRESSED INDIVIDUALS: A PILOT STUDY

Sarah Pistritto
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Aims: There is a need for the development of feasible interventions aimed at improving cognitive decline for people with dementia (PWD) and individuals with late-life depression (LLD) symptoms.
Methods: This thesis explores the design considerations to create a feasible ZUMBA and cognitive stimulation exergame and explores its implications on the physical, cognitive, and psychosocial health outcomes of participants. The second objective is to explore the feasibility and reliability of collecting saliva samples in older adults and analysis through a digital PCR environment for the exploration of neuroplastic BDNF and its impact on learning.
Results: indicated the exergame and collection of saliva was feasible and found evidence to suggest that exergaming can provide positive benefits to PWD and LLD individuals.
Conclusions: Future research should investigate the clinical effectiveness in larger samples and examine the expression of BDNF and its potential application as a screening/preventative assessment tool to identify risk of cognitive decline and depression.

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EFFECTS OF MULTIFACTORIAL INTERVENTIONS ON SUPPRESSING COGNITIVE DECLINE IN OLDER ADULTS: A RANDOMIZED CONTROLLED STUDY FOCUSING ON THE RELATIONSHIP BETWEEN EXERCISE INTERVENTIONS AND SLEEP QUALITY

Yuhei Chiba[1], Keiko Ide[1], Shoko Suzuki[2], Masataka Taguri[3], Hiroko Suzuki[4], Kie Abe[1], Asuka Yoshimi[1], Tadahisa Okuda[3], Kyoko Saito[5], Shunsaku Mizushima[6], Taro Yamanaka[7], Takashi Sakurai[8], Hidenori Arai[8], Toshinari Odawara[1]
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Aims: Sleep pattern change in the elderly is thought to be a risk for dementia. This study was part of "the Japan-Multimodal Intervention Trial for the Prevention of Dementia (J-MINT)". We focused on assessing the impact of physical activity on sleep quality in the elderly.
Methods: This study was an open-label, randomized controlled trial conducted in Kanagawa Prefecture on 198 people aged 65 and older at risk for lifestyle-related diseases. Subjects were randomly assigned to an exercise intervention group or a non-intervention group. Using the wrist-worn device (Fitbit® Inspire HR activity monitor, Google LLC, CA, USA), we measured daily steps, activity level, and sleep characters (percentages of deep NREM sleep, light NREM sleep, and REM sleep) at six months, 12 months, and 18 months. We compared the results between groups and over time. The study was approved by the Ethics Committee of the National Center for Geriatrics and Gerontology and Yokohama City University School of Medicine, and all participants provided fully informed written consent.
Results: In comparison between groups, the number of daily steps and the amount of activity increased significantly in the intervention group compared to the non-intervention group. However, no significant difference in sleep patterns was found between the intervention and non-intervention groups. Multiple regression analysis for all cases showed that an increase in the number of daily steps was significantly associated with an increase in deep NREM sleep and an increase in activity was positively associated with sleep duration.
Conclusions: It was shown that increasing physical activity may improve sleep quality in older people at risk for lifestyle-related diseases. Further large-scale trials are needed.

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OLD-AGE MENTAL TELEHEALTH IN REMOTE GREEK REGIONS: INSIGHTS FROM THE INTRINSIC NETWORK

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Aims: The INTegRated InterveNtion of pSychogerIatric Care (INTRINSIC) network embodies a model of digitally interconnected tertiary old age mental healthcare services and primary healthcare services for seniors in remote areas in Greece yielding promising outcomes, improving quality of healthcare. This study presents the healthcare professionals' experiences and perspectives on the INTRINSIC network's implementation.
Methods: A total of 24 healthcare professionals, comprising 13 medical and 11 non-medical staff from 11 healthcare units across urban, rural, and insular areas of Greece, participated in a questionnaire survey. The survey focused on their perceptions of the INTRINSIC network. Thematic analysis was applied to evaluate the responses and to identify key insights.
Results: The questionnaire assessed eight main aspects of the INTRINSIC program. The findings indicated high usability of the digital platform (79.2%), timely care delivery and cost-effectiveness, including reduced transportation costs and lower hospital strain. The holistic approach of the network was positively rated (79.2%). Additionally, 70.8% of respondents expressed high satisfaction with the model, citing its specialization in psychogeriatric healthcare, improved access to care (45.8%), and enhanced collaboration. Nevertheless, challenges were also identified, including increased workload (16.7%), technical difficulties (20.8%), mistrust from beneficiaries (29.2%), and difficulty in managing complex cases.
Conclusions: The INTRINSIC model offers a pragmatic opportunity to provide high quality old age healthcare services to seniors living in remote communities. The overall positive feedback from healthcare

professionals emphasizes the model's potential to effectively address the needs of the elderly population in these areas while acknowledging the need to address specific challenges.

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A 180-DEGREE TURN WHILE WALKING AMONG PEOPLE WITH MILD COGNITIVE IMPAIRMENT - COMPARING THOSE WITH AND WITHOUT ABNORMAL AMYLOID-B LEVELS

Magnus Lindh-Rengifo[1], Sofie Fors[1,2], Niklas Mattsson-Carlgren[3,4,5], Sebastian Palmqvist[1,3], Erik Stomrud[1,3], Oskar Hansson[1,3], Maria Nilsson[1,2,3]
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Aims: The aim was to investigate whether a 180 degree turn while walking (i.e., as a single task and while dual tasking) differentiates between people with mild cognitive impairment (MCI) who are amyloid-β (Aβ)-positive versus Aβ-negative.
Methods: This cross-sectional study included 209 patients with MCI (mean age 74.3 ± 7.1 years; 41.6% women); 163 had abnormal cerebrospinal fluid (CSF) Aβ levels (ratio Aβ42/40 <0.08). Patients performed the Timed up and Go (TUG) test in comfortable gait speed, i.e., as a single task and while dual tasking (serial subtractions by 3, start:100). The first turn of TUG was evaluated by addressing two parameters: turn duration (s) and peak velocity (degrees/s). The data was extracted from a wearable sensor (placed: lumbar) by using Mobility Lab, Clario®. Independent samples t-tests were performed to compare the two groups: amyloid-β (Aβ)-positive versus Aβ-negative.
Results: Turning as a single task showed a statistically significant difference between the two groups (Aβ+ vs. Aβ-), which applied for both turn peak velocity (mean 144.8 vs 129.7 degrees/s, p=0.023) and turn duration (mean 2.95 vs. 3.33 s, p=0.011). While dual tasking, there was a statistically significant difference in turn peak velocity (114.2 vs. 102.1 degrees/s, p= 0.037), but not in turn duration (3.33 s vs. 3.52 s, p=0.139). There were no significant differences regarding age, sex, education or white matter hyperintensities between the two groups (p≥ 0.110).
Conclusions: Our findings suggest that digital measures of a 180-degree turn while walking can differentiate between those with MCI who are Aβ-positive versus Aβ-negative. Moreover, our findings indicate that those who were Aβ-positive performed the turn faster and had a higher peak velocity than those who were negative.

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DIGITAL TURNING (360°) MEASURES AMONG PEOPLE WITH MILD COGNITIVE IMPAIRMENT - COMPARING THOSE WITH AND WITHOUT ABNORMAL AMYLOID-B LEVELS

Magnus Lindh-Rengifo[1], Sofie Fors[1,2], Niklas Mattsson-Carlgren[3,4,5], Sebastian Palmqvist[1,3], Erik Stomrud[1,3], Oskar Hansson[1,3], Maria Nilsson[1,2,3]
[1]Skåne University Hospital, Memory Clinic, Malmö, Malmö, Sweden, [2]Lund University: Lunds Universitet, Department Of Health Sciences, Lund, Sweden, [3]Clinical Memory Research Unit, Lund University, Department Of Clinical Sciences Malmo,, Lund, Sweden, [4]Skåne University Hospital, Department Of Neurology, Lund, Sweden, [5]Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden

Aims: The aim was to investigate whether turn duration and peak angular velocity (360° turn test, assessed as a single task and while dual tasking) differ between people with mild cognitive impairment (MCI) who are amyloid-β (Aβ) positive versus negative.
Methods: This cross-sectional study included 201 MCI patients: mean (SD) 74.2 years (±7.0), 42.3% women. Of those, 157 were Aβ+ (ratio Aβ42/40 <0.08). The participants performed two 360° turns in standing (i.e., one in each direction) both as a single task and while dual tasking (i.e., serial subtractions by 3, start: 99). Turning data (mean turn duration [s] and peak angular velocity [degrees/s]) was collected by using a wearable sensor (placed: lumbar, Mobility Lab, Clario®). The independent samples t-test was used to investigate potential group differences, i.e., Aβ+ versus Aβ-.
Results: Regarding mean turn duration, there was no statistical difference between the two groups (Aβ+ versus Aβ-) when assessed as a single task: 3.5s (±0.8) versus 3.7s (±0.8), p=0.376. This applied also while dual tasking: 4.4s (±1.2) versus 4.5s (±1.2), p=0.597. Peak angular velocity showed similar patterns when turning was assessed as a single task (197 versus 185 degrees/s, p= 0.124) and while dual tasking (161 versus 147 degrees/s, p=0.051). No statistically significant differences between the groups were observed regarding age, sex, educational level, Mini-Mental State Examination total score or white matter lesion load, p≥0.110
Conclusions: While those with MCI who were Aβ- had a tendency to perform worse on the 360-degree turn test (e.g., lower peak velocity), no statistically significant differences were detected between the two groups. These findings need to be verified in other samples.

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A RELATIVELY ACCURATE PREDICTION MODEL FOR THE RISK OF DEVELOPING MILD COGNITIVE IMPAIRMENT IN PATIENTS WITH SARCOPENIA

Xinyue Liu, Chenbo Ji
Nanjing Women and Children's Healthcare Hospital, NanJing, China

Aims: **肌肉减少症**显着增加了老年人认知障碍的风险。肌肉减少症患者轻度认知障碍 （MCI） **的早期**预警对于及时干预至关重要。

Methods: Our approach was comprehensive, combining machine learning (ML) with deep learning (DL) and utilizing physical measurement and cognitive data of 597 sarcopenia patients from the China Health and Retirement Longitudinal Study (CHARLS). We developed and validated an MCI incidence probability prediction model, ensuring its reliability and accuracy. We further calculated the risk of morbidity for each individual to identify those at high risk for MCI in the next 4 years, leaving no stone unturned in our quest for precision.

Results: The model was constructed using CHARLS data from 2011-2015 and included seven validated variables. It performed superior to logistic regression, achieving an Area Under the Curve (AUC) of 0.808 (95% CI: 0.704-0.899) for the test set and accurately classifying patients' risk in the training set. The deep learning model demonstrated a low false-positive rate of 1.63% for MCI in higher-risk groups. Independent validation using 2015-2018 CHARLS data confirmed the model's efficacy, with an AUC of 0.76 (95% CI: 0.67-0.83). A convenient online tool to implement the model was developed at http://47.115.214.16:5000/.

Conclusions: 这种深度学习模型可有效预测肌肉减少症患者的 MCI 风险，支持早期干预。它的准确性有助于识别高危个体，从而可能改善患者护理。

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BEHAVIORAL AND PSYCHIATRIC SYMPTOMS IN COMMUNITY-DWELLING OLDER ADULTS WITH DEMENTIA IN TAIWAN

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Aims: Behavioral and psychiatric symptoms of dementia (BPSD) are implicated in a cycle of negative events, including increased caregiver burden, institutionalization, and risk of death in people with dementia. We aimed to investigate BPSD in community-dwelling older adults with dementia in Taiwan.
Methods: Using the stratified multi-stage cluster sampling method, we conducted a two-stage survey on adults aged 65 years and older in 2020-2022 from 22 cities/counties across the country. The first stage was conducted by well-trained interviewers to collect information about each participant's demographic profiles, Mini-Mental State Examination (MMSE), activity of daily living (ADL), instrumental activities of daily living (IADL), presence of BPSD, and other comorbidities. The second stage was conducted by neurologists or psychiatrics with dementia care experience to assess the Clinical Dementia Rating for participants with abnormal findings on MMSE test or a history of dementia noted in the first stage.
Results: A total of 10,831 community-dwelling older adults were recruited and analyzed in our study. The weighted prevalence of dementia was 7.99%. Among people with dementia, 66.01% had presented BPSD in the past 3 months. The three most common types of BPSD were depression (33.37%), nighttime behavior (32.94%) and anxiety (27.75%). Old age, female gender, and lower MMSE scores were associated with BPSD. Moderate dementia and mild ADL dependence increased the risks of BPSD. Reviews of past medical history showed that orthopedic disease, eye disease, genitourinary disease, dementia, psychiatric disorder, and intellectual disability were associated with increased risks of BPSD.
Conclusions: We concluded that moderate dementia and mild ADL dependence increased the risks of BPSD in community-dwelling older people with dementia. This research will provide a better understanding of BPSD when caring for older people with dementia living at home.

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EVALUATION OF THE EFFECTIVENESS OF BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD) APP IN SUPPORTING MEDICAL OFFICERS IN MANAGING PATIENTS ON THE WARD

Mei Min Soong
Wyong Hospital, Hamlyn Terrace, Australia

Aims: A behavioural and psychological symptom App was developed as previous quantitative audits at Wyong Hospital, a 300 bed regional and teaching hospital showed that the majority of clinical aggression response team (CART) calls occured in the elderly. Results of the audits showed that often BPSD guidelines which were on the Central Coast Local Health District (CCLDH) Guidelines were not adhered to and medical officers were unsure of how to manage CART calls. A survey was then conducted a year later to evaluate junior medical officer's opinion on the usability, effectiveness, barriers and facilitators in managing BPSD on the ward using the App.
Methods: All junior medical officers working at Wyong hospital were invited to participate in a survey evaluating the effectiveness of the BPSD App in supporting doctors in their role in managing patients with symptoms of BPSD on the ward via their work email. The survey has been developed using the Clinical Excellence Commision quality audit reporting system (QARS) platform. Ethic approval was obtained
Results: There were 21 respondents. 80% of participants were likely to recommend the App 95% found the App concise and easy to use 1/3 used the App weekly, 1/3 monthly and 1/3 less frequently 72% were satisfied that the App was able to assist them Barriers The App required a login using work email and password prior to download of the App Knowledge of the App was poor
Conclusions: The BPSD App was easy to use and navigate. We aim to improve knowlegdhe of the App by introducing the App to all doctors during their orientation days and print information about the App in their orientation book.

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ANALYSIS OF STROKE MIMICS IN SUSPECTED STROKE PATIENTS TRANSPORTED BY EMERGENCY MEDICAL SERVICES

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Aims: Early and correct identification of symptoms of unexpected change in clinical condition in patients influences the provision of appropriate care (teimely and quality care). Increasing life expectancy has a major impact on the increased need for long-term nursing care and social service facilities for patients at the national level in the Czech Republic. There is a shortage of non-medical health care staff in long-term care facilities and in social service facilities, nurses do not have sufficient differential diagnostic skills and may misidentify sudden deterioration in a patient's clinical condition, triage and provide appropriate care based on proper refferal.
Methods: Retrospective analysis of the emergency services (ambulance) records of the South Moravian Region Emergency Medical Service in patients with suspected stroke (ICD-10, dg. I64 and I63.1) transported to St. Anne's University Hospital in Brno with subsequent data analysis from the hospital information system. Study over 24 months (period 2022-2023) in a group of patients with suspected stroke transported from long-term nursing care and social services facilities.
Results: A total of 138 cases were identified transported from long-term nursing care and social services facilities and analysed in detail. Acute stroke was ruled out in 33 patients and was an exacerbation of the main diagnosis of Parkinson's disease (n=28) and Alzheimer's dementia (n=5) in combination with infection and dehydration. Acutely intrusive motor symptoms and speech impairment were described by the attending staff and they were assessed as FAST+ by the emergency ambulance service.
Conclusions: Data analysis allowed the evaluation of acute changes in clinical symptoms and the resulting diagnosis in patients with suspected stroke. Recommendations and algorithms of care for non-medical staff working outside inpatient health service facilities will be developed.

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ASSOCIATION BETWEEN OSTEOPOROSIS AND RISK OF DEMENTIA: A KOREAN WOMEN NATIONWIDE POPULATION-BASED COHORT STUDY

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Aims: Dementia and osteoporosis share common risk factors and are increasing in prevalence among the aging population. This study aimed to investigate the impact of osteoporosis on the development of dementia and its subtypes in older women using data from a population-based, health-screening cohort over a follow-up period exceeding 10 years.
Methods: This retrospective cohort study included 66-year-old Korean women who participated in the "National Screening Program for Transitional Ages." Participants were categorized into three groups based on spine bone mineral density T-scores: normal (T-score ≥ −1.0 standard deviation [SD]; 18.7%), osteopenia (−2.5 SD < T-score < −1.0 SD; 42.5%), and osteoporosis (T-score ≤ −2.5 SD; 38.8%). The primary outcome, incident dementia cases, was assessed using national healthcare claims databases. Cox proportional hazard regression models were used to assess the risks of all-cause dementia, Alzheimer's disease (AD) dementia, and vascular dementia (VaD).
Results: Among 131,865 dementia-free women, 9,711 individuals developed all-cause dementia (7.4 %) over an average follow-up of 10.43 ± 1.81 years. Osteoporosis (T-score ≤ −2.5 SD) was associated with increased risks for all-cause dementia (adjusted hazard ratio [aHR] 1.16; $p < 0.001$), AD dementia (aHR 1.19; $p < 0.001$), and VaD (aHR 1.33; $p = 0.005$), compared to normal (T-score ≥ −1.0 SD).
Conclusions: Our findings highlight a significant association between osteoporosis and increased risks of developing all-cause dementia, AD dementia and VaD. Further study is needed on the relationship and potential effects of early identification and treatment of osteoporosis with regards to the development of dementia.

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FUNCTIONAL ACTIVATION ASSOCIATED WITH VERBAL-NONVERBAL TASKS AND THE EFFECT OF COGNITIVE RESERVE: A SYSTEMATIC REVIEW.

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Aims: Aging is a process characterized primarily by cognitive and cerebral changes. In these lines, cognitive reserve (CR) may explain individual differences in age-related cognitive or functional decline, allowing for better performance than expected given the degree of age-related brain changes. Previous research has studied brain markers associated with CR; however, the neural substrate of individuals with high and low CR during the performance of cognitive tasks is not entirely clear.The present systematic review aimed to study the effect of CR on functional brain activity during task performance.
Methods: This systematic review was carried out following the recommendations of the PRISMA declaration. Two researchers screened the studies independently. After applying methodological quality criteria, 8 studies with high methodological quality were included in the review.
Results: There is evidence linking CR and functional activity in fronto-parietal networks, the default mode network, the fronto-striatal network, and more specific regions such as posterior areas including the cerebellum, and subcortical structures. Likewise, it was observed that individuals with higher CR showed greater intra-hemispheric connectivity, while those with lower CR showed more inter-hemispheric connectivity.
Conclusions: Evidence suggests CR is linked to task-invariant networks supporting cognitive function, with higher CR showing lower fronto-parietal activity (efficiency) and increased activation under higher demands (capacity). Higher CR also correlates with greater intra-hemispheric connectivity, while lower CR shows more bilateralization. These findings may have important implications for improving the early detection of neurodegenerative markers and developing interventions aimed at enhancing individuals' CR throughout their lives.

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TRENDS IN ANTIDEPRESSANT USE AMONG ETHNIC-RACIAL GROUPS IN HAWAI'I: FOCUS ON NATIVE HAWAIIAN AND OTHER PACIFIC ISLANDERS

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Aims: In Hawaii, approximately 31,000 individuals aged 65 and older are affected by Alzheimer's disease (AD). Racial disparities exist in AD diagnosis and treatment of AD, but there is limited data on Native Hawaii and Pacific Islander (NHPI) populations. This study explores patterns of antidepressant use among NHPI AD patients compared to other ethnic-racial groups.
Methods: A retrospective chart review was conducted on 243 patients diagnosed with AD at Hawaii Pacific Neuroscience, using patient data collected from 5/1/2015 to 5/1/2023. Data collection included demographics, relevant comorbidities, Mini-Mental State Evaluation (MMSE) scores, and antidepressant medications, across ethnic-racial groups. Statistical analysis included Fisher's Exact Test and Kruskal-Walli's rank sum test.
Results: The study analyzed patients averaging 77.6 years old (80 males and 163 females). Antidepressant use was more common among Asian (N = 89) and White (N = 56) patients, primarily selective serotonin reuptake inhibitors (SSRI), while NHPI patients had lower antidepressant use (33/46). Patients with moderate cognitive impairment) had the highest usage of antidepressants, followed by those with mild impairment. Hypertension was the most common comorbidity (57/84) among those on antidepressants. Significant differences in MMSE scores ($p<0.001$) were found across racial groups, with moderate impairment most common among Asian (20/39) and NHPI patients (16/39). NHPI patients exhibited lower rates of anxiety despite the moderate degree of cognitive impairment.
Conclusions: Antidepressant use was found higher among Asian and White ethnic-racial groups, particularly SSRIs, and lowest among NHPI. While acknowledging the limitations associated with a retrospective study based in a single center, these are interesting findings on the NHPI population afflicted with AD with merit further exploration.

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PAUSE CHARACTERISTICS BY UTTERANCE POSITION AND WORD-CLASS IN PRIMARY PROGRESSIVE APHASIA

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Aims: Primary progressive aphasia (PPA) is a neurodegenerative disease characterized by prominent language impairments within the first two years of onset. PPA is clinically categorized into three subtypes: semantic variant (svPPA), logopenic variant (lvPPA), and non-fluent/agrammatic variant (nfvPPA). Pauses that occur during speech production are emphasized as simple and reliable biomarkers for classifying and diagnosing subtypes of PPA. Additionally, pauses which reflect issues such as semantic knowledge impairment, word retrieval difficulties, and syntactic problems can be distinguished by parts of speech. The patterns of pauses corresponding to different parts of speech may serve as useful speech indicators for differentiating PPA subtypes. In this study, we aimed to examine the characteristics of pauses in PPA subtypes based on the location of pauses and the parts of speech produced during a picture description task.
Methods: The study included 60 participants: 9 with svPPA, 19 with lvPPA, 11 with nfvPPA, and 21 healthy controls. After transcription, the length and proportion of pauses were measured using Praat, and parts of speech were tagged using UTagger. Pauses were categorized as inter-utterance, intra-utterance, inter-word, and intra-word pauses, and were analyzed before nouns, verbs, adjectives, and adverbs.
Results: The study found longer pauses between utterances in nfvPPA, especially before nouns and adverbs, due to speech and motor issues. lvPPA also paused for word retrieval, but less than nfvPPA. In lvPPA, longer inter-word pauses showed compensation for word retrieval issues, while svPPA used shorter pauses with strategies like circumlocution. All groups had longer pauses before nouns, aligning with Korean sentence structure.
Conclusions: This study provides important data on pause characteristics in svPPA, lvPPA, nfvPPA, and control groups through acoustic analysis. It is the first to examine these traits with Korean parts of speech.

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IDENTIFICATION OF RELEVANT CLINICAL VARIABLES PREDICTING OVERALL COGNITION IN A 5-YEAR FOLLOW-UP STUDY

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Aims: Patients complaining of cognitive decline are diagnosed with SCD, MCI, and dementia through cognitive examination, but the speed and pattern of deterioration may vary from person to person. To identify associated variables across processes, we examined changes in several cognitive domains and mood based on initial diagnosis.
Methods: Among patients who visited for cognitive complaints, subjects who underwent K-MMSE and comprehensive neuropsychological tests (SNSB) at least three times in the past five years were included. Among 91 subjects, 11 subjects were excluded for very severe degree of dementia. For statistical analysis, frequency analysis were used for comparative analysis. And repeated measures 2-Way ANOVA and linear mixed models were used for examining cognitive progress over time.
Results: Cognitive decline over 5 years in the SCD, MCD, and dementia groups was significant, and independence between groups was secured. Examining by diagnostic subgroups, high inital score in Frontal/Executive domain was related to an increase in SNSB-D scores ($P<.05$) in the dementia group. High initial scores in visuospatial, memory, and Frontal/Executive domains as well as K-MMSE were predictors of increased SNSB-D scores ($P<.05$) in MCI group. Notably, in the MCI group, drinking alcohol had a detrimental effect on SNSB-D score ($P<.05$). Drinking alchol had a particularly large effect on the change in the SNSB-D score. Depression scores, which were thought to have a meaningful impact on cognitive function, did not significantly correlate with changes in cognitive function over time.
Conclusions: High initial scores in the Frontal/Executive function can predict good prognosis in MCI and dementia groups. MMSE score did not predict change in the dementia group, but were a predictor in the MCI group. Alcohol consumption was associated with long-term cognitive changes, but not depression.

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TURNING 360 DEGREES IN STANDING- DO CLINICAL TURNING PARAMETERS DIFFER BETWEEN THOSE WITH AMNESTIC AND NON-AMNESTIC MILD COGNITIVE IMPAIRMENT (MCI)?

Sofie Fors[1,2], Magnus Lindh-Rengifo[2], Niklas Mattsson-Carlgren[3,4,5], Sebastian Palmqvist[2,3], Erik Stomrud[2,3], Oskar Hansson[2,3], Maria Nilsson[1,2,3]
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Aims: The aim was to compare turning (360˚) parameters (single and dual tasking) among people with amnestic and non-amnestic mild cognitive impairment (MCI).
Methods: The sample included 272 participants; 215 had amnestic MCI (Mean [SD] age 74.3 [7.0] years, 41.0% women) and 57 non-amnestic MCI (72.0 [8.0] years, 52.6% women). Turning 360˚ in standing (i.e., two 360˚ turns, one in each direction) was assessed as a single task and while dual tasking (subtraction task, -3). Included turning parameters: the total time (s) by using a digital stopwatch, and a clinical rating of instability: scored from 0-4 (higher=better). Those who scored from 0 to 3 were classified as unstable; those scoring 4 were classified as stable. Mann-Whitney U and Chi^2 tests were used for group comparisons.
Results: The median (q1, q3) total time to perform the 360° turn test (single task) was 7.35s (6.25, 8.93) in the amnestic group versus 7.66s (6.19, 8.33) in the non-amnestic group, p=0.775. Corresponding values while dual tasking were 10.99s (8.74, 13.77) and 10.37s (8.87, 13.82), p=0.943. Several did not manage the test while dual tasking: 29 (13.9%) in the amnestic group, and 7 (12.5%) in the non-amnestic group, p=0.832. During single task, 104/214 (48.6%: amnestic) and 22/57 (38.6%: non-amnestic) were unstable, p=0.183. While dual tasking, the percentages were 50.0% (amnestic) versus 32.7%, p=0.036.
Conclusions: We found no significant differences between those with amnestic and non-amnestic MCI in single task turning, but dual tasking seems to increase the number who are unstable in the amnestic group. Further and longitudinal studies are needed that address a 360˚ turn, and future studies should also include digital measures.

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PREVALENCE AND SUBTYPES OF DEMENTIA IN TAIWAN: A COMMUNITY SURVEY OF 11,298 INDIVIDUALS

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Aims: The rapid growth of the older adult population requires a greater epidemiological characterization of dementia, which is crucial for estimating the disease burden and planning healthcare. This study developed national prevalence estimates of dementia and the relative frequencies of its subtypes in Taiwan.
Methods: Using the stratified multi-stage cluster sampling method, we conducted a two-phase screening design to ascertain dementia among 11,298 adults aged 65 years and older from 22 cities/counties across the country. In the first stage, well-trained interviewers conducted face-to-face home interviews to collect information about the older adults' demographic profiles and dementia-related scales, including Ascertain Dementia 8 questionnaire and Mini-Mental State Examination. Based on the results derived from the first-stage survey, 2,403 people suspected of cognitive impairment were identified to receive face-to-face home interviews by well-trained physicians for clinical ascertainment of dementia through the diagnosis principles of NINCDS-ADRDA.
Results: The weighted prevalence of dementia in Taiwan is 7.99%. Dementia prevalence among women (9.36%) was higher than men (6.35%). Dementia was more prevalent among illiterate individuals (15.93%). Dementia prevalence increased with age, from 2.40% of those aged 65–69 years to 29.45% of those aged 90 and older. The most common subtype was Alzheimer's disease (56.88%), followed by vascular dementia (22.91%), Parkinson's disease dementia (7.12%), dementia with Lewy body (2.63%), and frontotemporal dementia (0.99%). The remaining 69 patients had other diagnoses, including combinations of dementia disorders other than combined Alzheimer's and vascular pathology.
Conclusions: Consistent with common findings from other parts of the world, a high rate of dementia was associated with female gender, older age, and illiteracy. Alzheimer's disease was the most common cause. The findings of this study can help prioritize dementia research, clinical services, and care resources in Taiwan.

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THE EFFECTIVENESS OF HOME-BASED REABLEMENT PROGRAMS FOR COMMUNITY-DWELLING OLDER PEOPLE LIVING WITH DEMENTIA IN TAIWAN

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Aims: There is a major knowledge gap in providing reablement for people with dementia living at home. In 2018, Taiwan's National 10-Year Long-Term Care 2.0 (LTC 2.0) Plan launched a policy of strengthening home-based services with a focus on person-centered interdisciplinary reablement programs, which are delivered by an occupational therapist, registered nurse, psychologist, and other allied health professionals. This study aimed to test the effectiveness of home-based reablement interventions for community-dwelling older people with dementia in Taiwan.
Methods: We analyzed the LTC 2.0 and National Health Insurance databases from 2018 to 2023. The study population consisted of people with dementia who applied for and used LTC 2.0 services. Outcome variables were measured by change scores between successive assessments of activities of daily living (ADL), instrumental activities of daily living (IADL), occurrences of behavioral and psychiatric symptoms of dementia (BPSD), LTC and medical care costs, and caregiver burden. In order to determine whether the change in outcome was due to the natural evolution of the person's condition or to the intervention, we used a pretest-posttest control group design with propensity score matching and generalized estimating equations models to evaluate changes in physical and mental health outcomes of users and caregiver burden.
Results: Our preliminary findings showed that home-based reablement interventions could improve users' ADL and IADL. Reablement interventions could also significantly reduce BPSD occurrences, the growth of medical and LTC costs, and caregiver burden.
Conclusions: Future directions and strategies for reablement approaches to care for community-dwelling people living with dementia, will be developed. This study will provide evidence to inform key stakeholders in their decision making and the use/delivery of the LTC 2.0 program, as well as influence future systems-thinking and changes for dementia care.

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PRIMARY PROGRESSIVE APHASIA WITH COMORBID ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA: A MULTIMODAL MANAGEMENT APPROACH: CASE REPORT

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Aims: This case report aims to describe the clinical presentation and management of a 64-year-old male, Mr. Bha. Ach., diagnosed with Primary Progressive Aphasia (PPA) alongside comorbid Alzheimer's disease (AD) and vascular dementia. It focuses on the progression of cognitive and language impairments, as well as the multimodal therapeutic approach used to address the patient's declining communicative abilities.
Methods: The patient underwent a series of neurocognitive assessments, including the ACE III and Montreal Cognitive Assessment (MoCA). Cognitive and communicative therapy was initiated, targeting speech clarity, naming, fluency, and working memory. Speech-language therapy employed activities such as block recall, digit recall, and verbal fluency tasks. Technological interventions, including Lingraphica SmallTalk and Tactus therapy, were integrated into the treatment plan to enhance language function. Therapy sessions were conducted regularly, with 6–8 sessions per month over a six-month period.
Results: The patient demonstrated progressive cognitive and communicative decline, consistent with the semantic variant of PPA, characterized by impaired object naming and comprehension. Behavioral symptoms, including obsessive-compulsive behaviors, hypomania, and serotonin syndrome, were also observed. Speech therapy interventions led to some improvements in naming and verbal fluency, although the patient's overall condition continued to deteriorate.
Conclusions: This case higlights the challenges of managing PPA with comorbid AD and vascular dementia. A multimodal therapeutic approach, combining cognitive-communicative training and technological aids, can offer limited but valuable improvements in communicative function. The importance of individualized therapeutic strategies in addressing the specific cognitive-linguistic deficits associated with PPA variants is noted from the present case.

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HEALTH REFORM AS A PREDICTOR OF THE DIAGNOSTIC EXPERIENCE OF PEOPLE WITH FRONTOTEMPORAL DEMENTIA (FTD): A UNITED STATES CASE STUDY.

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Aims: The impact of health reform on the diagnostic experience of individuals with Frontotemporal Dementia (FTD) remains understudied. This research examined the relationship between Medicaid expansion and the diagnostic experience of individuals with FTD.
Methods: Retrospective data analysis of the Association for Frontotemporal Degeneration (AFTD) Insights Survey used self-reported information from 1049 caregivers on "misdiagnosis," defined as patients receiving one or more incorrect diagnoses before FTD diagnosis, demographic characteristics of patients, and their FTD symptoms. Patients were grouped by the Medicaid expansion status of their state at the date of diagnosis (expanded, not expanded, or inconclusive status). We used multivariate logistic regression to explore the association between misdiagnosis and Medicaid expansion. Sensitivity analyses were conducted (1) excluding the inconclusive group and (2) including it as part of the Medicaid expanded group.
Results: A total of 527 (50.2%) individuals experienced misdiagnosis prior to correct FTD diagnosis. Of these, 40 (7.6%) lived in states with Medicaid expansion at the time of diagnosis, and 220 (41.7%) lived in states without Medicaid expansion. Out of the 522 individuals who did not experience misdiagnosis, 48 (9.2%) were in states with Medicaid expansion, and 220 (41.7%) were not. After adjusting for race/ethnicity, marital status, and FTD symptoms, multivariate logistic regression showed that individuals in Medicaid-expanded states were less likely to experience misdiagnosis (odds ratio [OR] 0.55; 95% confidence interval [CI] 0.33–0.91) compared to those in states without Medicaid expansion. Sensitivity analyses supported these findings.
Conclusions: Medicaid expansion under United States health reform was associated with a lower likelihood of misdiagnosis among individuals with FTD. These results highlight the need for future research to guide health policies aimed at improving the FTD diagnostic experience.

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DOES VASCULAR DEMENTIA EXIST? REPORT OF TWO CASES PREVIOUSLY DIAGNOSED WITH VASCULAR DEMENTIA TREATED BY MEANS OF VENTRICULO-ATRIAL SHUNTS

Kiyoshi Takagi[1], Ryosuke Takagi[2], Hari Garachetla[3], Masamichi Atsuchi[4], Yoko Kato[5]
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Aims: Almost all epidemiological studies on dementia have listed vascular dementia (VaD) as the second common cause of dementia after Alzheimer's disease (AD). Yet new prom1ssing treatment agents have been developed for AD, no effective treatment is available for VaD up to now. We experienced two cases with VaD who recovered their cognitive function to normal levels after Ventriculo-atrial shunt (VA shunt).
Methods: Both cases complained cognitive impairment shortly after cerebral infarctions. Their brain images showed ventricular dilatation without the findings of disproportionately enlarged subarachnoid space hydrocephalus (DESH) which is regarded as characteristic for idiopathic normal pressure hydrocephalus (iNPH).
Results: Both cases were initially diagnosed as VaD by board neurosurgeons. However, since they showed positive response to lumbar tap test, VA shunts were performed. Both cases recovered their cognitive function to normal level.
Conclusions: These two cases indicate that lumbar tap test will disclose that many cases diagnosed as VaD would be candidates for cerebrospinal fluid shunt surgery for the treat ment of dementia. As a recent study of AD using biomarkers disclosed that about 40% of clinically diagnosed AD have been misdiagnosed, iNPH patients with lacunar infarcts may possibly be misdiagnosed as VaD.

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CAREGIVING APPRAISAL OF CAREGIVERS WITH PARKINSON'S DISEASE PATIENT: A LONGITUDINAL STUDY

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Aims: Caregivers with Parkinson's disease (PD) experience a significant burden, and caregiving appraisals are essential as they impact their well-being and outcomes. According to PD increased dependence over time, duration of the disease is a vital factor affecting caregiving appraisals. This study aims to explore what effects caregiving appraisal to PD caregivers based on the duration of the disease through a longitudinal approach.
Methods: Participants were recruited from the neurology outpatient clinics of two tertiary hospitals in Korea. Caregiving appraisal was surveyed using a structured questionnaire. The SPSS 26.0 program was used for analysis.
Results: A total of 85 PD caregivers were included in the study and 62 (72.94%) were spouses, 16 (18.82%) were adult children, and 7 (8.24%) were others. Most of the caregivers were female (n=54, 63.5%) and married (n=81, 92.3%), with a mean age of 60.87 years. Regardless of disease duration, the caregiver's gender, relationship with the patient, age, and self-efficacy did not affect caregiving appraisal. Among caregivers of PD with a disease duration of ≤60 months, family support showed a correlation over time with caregiving burden ($r = 0.423$, $p = 0.04$), satisfaction ($r = 0.517$, $p < 0.01$), demand ($r = 0.302$, $p = 0.05$), and impact ($r = 0.442$, $p < 0.03$). Among caregivers of PD with a disease duration >60 months, family support was correlated with caregiving satisfaction ($r = 0.447$, $p = 0.03$) and mastery ($r = 0.511$, $p < 0.01$).
Conclusions: Regardless of disease duration, family support was the main factor influencing caregiving appraisal. The caregiving appraisals of PD caregivers can define the patient's well-being. These results suggest the value of interventions to expand family support for PD caregivers.

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KNOWLEDGE, EXERCISE-EFFICACY AND PARTICIPATION (KEEP) INTERVENTION: CO-DESIGNING A PHYSICAL ACTIVITY AND EXERCISE PROMOTION INTERVENTION FOR PEOPLE WITH PARKINSON'S DISEASE

Ledia Agley, Louise Lafortune
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Aims: To co-design a digital intervention that promotes physical activity and exercise in people newly diagnosed with Parkinson's Disease.
Methods: The co-design was informed by three phases: a) the preparatory phase which included the use of convergent mixed-method design to leverage the strengths of the in-depth qualitative data and large-scale surveys completed by people with Parkisnon's (PwP) and healthcare professionals (HCPs). The second phase was the co-design phase, informed by the experience-based co-design approach. Phase three encompasses the development of the online modules and their validation which was completed by PwP who had not previously been involved in the study.
Results: The key themes from the qualitative and quantitative finding integration include: physical activity promotion at the time of diagnosis: current practice and need; motivators and barriers in exercise participation effective content of an intervention that aims to promote physical activity and exercise; practical considerations in delivering a physical activity and exercise intervention. Utilising an innovative blended learning format, the KEEP intervention included 6 self-directed online modules and 4 live online group discussions occurring every two weeks for 60 minutes. The group discussions were facilitated by a physiotherapist.
Conclusions: The co-design process for the KEEP intervention demonstrated the importance of involving both PwP and HCPs and represents a significant effort to fill the gap in physical activity promotion for PwP. The mixed-method study provided a deeper understanding on the needs and priorities of PwP regarding physical activity promotion, surpassing the insights from the literature. The co-design approach translated these findings into the design of key features for the interventions, which centred on providing trusted and personalised information. This process was chosen to aid the development of an acceptable, accessible, and usable intervention for real-life clinical practice.

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MOTOR LEARNING-BASED CLINICAL PILATES TRAINING FOR THE PARKINSON'S DISEASE REHABILITATION @PARKINSONPILATES: A PARALLEL-GROUP, RANDOMISED CONTROLLED TRIAL WITH 3-MONTH FOLLOW-UP

Beliz Belgen Kaygisiz, Fahriye Coban
European University of Lefke, Lefke, Cyprus

Aims: Objectives: "Parkinsonpilates" is a clinical pilates training designed to improve motor learning, postural stability, and gait for individuals with Parkinson's disease (iwPD). This randomized controlled trial (RCT) aims to provide evidence for the acceptability of the "Parkinsonpilates" as a new approach and to investigate the clinical outcomes.
Methods: 32 iwPD with Hoehn&Yahr stages 2-3 were randomly assigned to the Parkinsonpilates Group (PP) and the Conventional Physiotherapy (CP) Group. Outcomes were convened 4 times for both groups: at baseline, 6. weeks, 12. weeks(end), and 12 weeks after treatment. The Timed Up and Go Test (TUG) was used to assess functional mobility, the Functional Reach Test (FRT) to assess dynamic balance, and the Berg Balance Scale (BBS) to assess postural control and fall risk. The Gait and Balance Scale (GABS) was used to evaluate patients' gait and balance abnormalities and foot reaction time was measured using the Nelson Foot Reaction Test (NFRT).
Results: A significant difference between groups was observed for FRT measurements (F=4.581; p=.005), BBS scores(F=2.780; p=.046), and GABS total score(F=3.768; p=.013), with the PP group showing a greater increase compared to the CP group. There was no statistically significant difference between groups for TUG scores(F=0.371; p=.371) and NFRT scores(left; F=0.879; p=.455, right; F=2.164; p=.098) with the changes in TUG and NFRT scores were similar in both groups.
Conclusions: Our results showed that PP was as effective as CP, with better dynamic/static balance and gait results, and could be used in rehabilitation for patients with Parkinson's disease. Further studies are needed to clarify the effects of the program we developed for PD. It should not be forgotten that our protocol can be further improved according to the suggestions of future studies.

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PREDICTION OF PROBABILITY OF PARKINSON'S DISEASE THROUGH ARTIFICIAL NEURAL NETWORK (ANN) FROM GAIT ANALYSIS AND PRE-SCREENING SURVEY-BASED DATA

Anilendu Pramanik
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Aims: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms, difficulty with balance and coordination, and gait disturbances, chiefly affecting middle-aged and elderly people. PD is difficult to diagnose, particularly in its early stages, because the symptoms of other neurologic disorders can be like those found in PD, and we mostly ignore those symptoms as normal aging. To address these difficulties, ANN-based predictions are warranted. Therefore, the purpose of the current study is to develop an artificial neural network (ANN) model for predicting PD using gait analysis and pre-screening survey-based data.
Methods: This study collected data from available datasets of PD as well as healthy participants. Gait data were collected with temporal spatial and kinematic kinetic variables using 3D motion capture, and survey data was collected using the Unified Parkinson's Disease Rating Scale (UPDRS) and Montreal Cognitive Assessment (MoCA). An ANN model was trained using 70% of the data and tested on the remaining 30%. Features extracted from gait analysis and survey data were used as inputs.
Results: The ANN model demonstrated high accuracy in predicting PD. Sensitivity and specificity were proportionately high for both those parameters. Gait parameters, such as stride length and cadence, speed, vGRF and survey-based features, such as tremor and bradykinesia scores, were significant predictors.
Conclusions: This study demonstrates the potential of ANN-based prediction of PD using gait analysis and pre-screening survey data. Early detection and intervention can improve quality of life for PD patients.

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UTILIZING TAI CHI AND GROUNDING TECHNIQUES TO REDUCE FALLS IN INDIVIDUALS WITH PARKINSON'S DISEASE: AN OT PERSPECTIVE

Jane Tiller
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Aims: Current symptom management of Parkinson's disease focuses on pharmacological treatment and strength training as primary interventions. While this approach may yield positive outcomes, many individuals suffering from this chronic condition still report recurring symptoms and are at an increased risk for falls. Additionally, therapeutic intervention for Parkinson's is not addressing sensory components and internal cueing. The purpose of this study is to analyze the effects of Tai Chi and grounding on prospective falls and overall symptomology in individuals with Parkinson's disease.
Methods: Participants were recruited from Greenville Area Parkinson's Society and Magnolia Memory's Minds Matter program. 9 individuals diagnosed with idiopathic Parkinson's disease were enrolled in the study on a voluntary basis. This study utilized a pretest/posttest design to examine changes in symptomology and performance skills associated with falls in individuals with Parkinson's disease. Group Tai Chi classes were taught using moves learned from The Tai Chi Fundamentals® Programs (Adapted). Along with personalized tai chi sequences, guided meditations and warm up exercises were also incorporated to target each of the these component skills. Grounding techniques were integrated through completion of tai chi exercises with bare feet outdoors or through the utilization of grounding mats.
Results: Average scores on the self reported Fall Efficacy Scale (FES-1) revealed no significant change in overall fear of falling before and after program implementation ($p=0.382$). Additionally, performance scores on the Modified Romberg revealed no significant impact on static or dynamic balance. Contrarily, performance times during the Timed Up and Go (TUG) significantly decreased following tai chi intervention ($p=0.45$) demonstrating improved functional mobility among participants.
Conclusions: Results support findings from previous studies, demonstrating the efficacy of tai chi as an intervention for fall prevention.

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EFFECTIVENESS OF LSVT-BIG THERAPY ON THE SLEEP QUALITY IN INDIVIDUALS WITH PARKINSON DISEASE: CASE SERIES

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Aims: Parkinson's disease (PD typically has both motor and non-motor dysfunctions. Sleep disorders are disabling and highly prevalent in Parkinson's disease (PD).. This study's objective was to verify the effectiveness of LSVT-BIG Therapy in sleep quality, objectively and subjectively assessing it among individuals with PD at short- term follow-up in south east of Iran.
Methods: Persons with PD (Hoehn & Yahr stage 2-3; age ≥40; not in a regular exercise program) were assessed before and after LSVT-BIG Therapy (supervised 3x/week for 16 weeks) and three months later (follow-up). The following tools were used: Pittsburgh Sleep Quality Index (PSQI); Epworth Sleepiness Scale (ESS); Parkinson's disease Sleep Scale (PDSS). Participants underwent autography at baseline and post-intervention as well as 3-month follow-up to verify sleep quality objectively. Change in sleep efficiency was the primary outcome, measured from baseline to post-intervention. The effects of the intervention were evaluated with general linear model.
Results: 44 individuals aged 65.3 years old years (range 40–90) took part in the study. The mean Hoehn and Yahr stage was 2.11 (SD 0.8), and the mean UPDRS part III was 22.3 (SD 12.6). The experimental group showed significant improvement in sleep efficiency after the intervention. Other parameters of sleep architecture also improved ($p<0.01$)., including total sleep time and slow wave sleep. No differences were found in any of the variables measured with the ESS. Improvement was found from pre- to post-intervention in terms of nocturnal movements and total score, obtained on the PDSS($p<0.05$).
Conclusions: The results suggest that the training used is feasible and practical. The LSVT-BIG improves objective and subjective sleep outcomes in PD. More research is needed to further elucidate the impact of this therapy on sleep in patients with PD.

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FAMILIAL AGGREGATION OF RESTLESS LEGS SYNDROME/WILLIS EKBOM DISEASE IN THE POPULATION OF SWEDEN

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Aims: Restless legs syndrome (RLS) has a familial component but detailed data on the modification of familial risks are lacking. The aim of the study was to determine detailed familial risks for medically diagnosed RLS based on nationwide hospital and population records.
Methods: Subjects were obtained from the Multigeneration Register, contains the Swedish population in families, and RLS patients were identified from the Hospital Discharge Register and the Primary Health Care Register. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases.
Results: The overall familial risk was 2.59 (95% CI 2.52-2.66), risks were highest in persons diagnosed with RLS in younger age, males and females shown similar risk (2.64 and 2.57). The SIR was 2.76 (95% CI. 2.66-2.88) when parents diagnosed with RLS and 2.48 (95% CI. 2.40-2.58) for a sibling diagnosed with RLS. Very high familial risks were observed if two or more relatives were affected, for example, the high-risk group of multiple affected siblings with an SIR >65. The spouse risk was modestly increased 1.41.
Conclusions: Our results confirm and extend the existing body of knowledge that suggests RLS has a hereditary component. The strong association between family history and RLS indicates that genetic factors play a critical role in the etiology of this disorder, this finding has significant implications for both clinical practice and our understanding of the genetic underpinnings of RLS. Our data emphasize the contribution of familial factors to the RLS.

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_QUALITY OF LIFE IN PATIENTS WITH PARKINSON'S DISEASE: THE ROLE OF PATIENTS' AND CAREGIVERS ILLNESS PERCEPTIONS

Ines Martin Villalba
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Aims: Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that affects motor, emotional, cognitive, and social functioning. The gradual decline in motor abilities, cognitive impairment, and non-motor symptoms such as depression and sleep disturbances can significantly impact the quality of life for both patients and their caregivers. Furthermore, research indicates that there are often differences in how patients with chronic illnesses and their caregivers perceive the illness, which can negatively affect the patients' quality of life (QoL). The aim of this study is to describe the health-related quality of life in patients with Parkinson's disease and their caregivers, and to assess whether the illness perceptions of patients with Parkinson's disease differ from those of their caregivers and influence their quality of life.
Methods: This descriptive cross-sectional study included a comparison group of 19 Parkinson's patients with confirmed diagnosis and their primary caregivers. The WHOQOL-BREF scale was used to assess quality of life, evaluating four areas: physical health, psychological health, social relationships, and environment.
Results: Statistically significant differences were found in the perception of quality of life and satisfaction with health between the group of patients with Parkinson's disease and the group of caregivers. The areas of quality of life most affected in patients were physical health and psychological well-being. In addition, differences in the perception of the illness between patients and caregivers were observed, which had a negative impact on patients' quality of life.
Conclusions: Due to the complexity of Parkinson's disease symptoms, studying quality of life offers a comprehensive and valid assessment of the health and well-being of patients and their caregivers.

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QUALITY OF LIFE IN MULTIPLE SCLEROSIS PATIENTS WITH URINARY INCONTINENCE

Zvonimir Uzarevic[1], Anamarija Soldo Koruga[2,3], Ivana Kampic[2,4], Zeljka Popijac[2,4], Silva Butkovic Soldo[1,4,5]
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Aims: Multiple sclerosis (MS) is a progressive, inflammatory, chronic and neurodegenerative disease that results in a wide range of clinical manifestations. One of the most common symptoms of MS-patients is urinary incontinence (UI) with high rates of up to 90% which impacts their quality of life (QoL). The aim of this study was to determine the QoL in MS-patients with UI.
Methods: In this research was analysed data on 40 MS-patients, which included 21 women and 19 man (average 47.3±11.8 years) which underwent neurological care at Clinical Hospital Centre Osijek, Croatia. Our research problem was examined using the Croatian version of the King's health questionnaire (KHQ) which includes eight domains: general health perception (GHP), lower urinary tract symptoms impact (LUTSI), role limitations (RL), physical limitations (PL), social limitations (SL), personal relationships (PR), emotional problems (EP) and sleep/energy disturbances (SED). The data was descriptively analysed and internal consistency was assessed by Cronbach's alpha. Pearson correlations were performed on the eight domains of the KHQ. The level of significance was set to $p<0.05$.
Results: The more common lower urinary tract symptoms (LUTS) in MS-patients were related to the following domains: LUTSI (44.17), GHP (41.88), PR (37.08), SL (35.56) and PL (35.42). Less common LUTS were related to the following domains: RL (32.50), SED (27.08) and EP (26.39). Cronbach's alpha for the KHQ total score was 0.96 (range for domains: 0.80-0.98), indicating high internal consistency. All of the KHQ domains were highly correlated (Pearson correlation range: 0.35-0.91).
Conclusions: These results show that the KHQ domains have a desirable pattern of correlations and internal consistency. This results suggests that Croatian version of KHQ can be considered a comprehensive and reliable measure for LUTS in Croatian-speaking MS-patients.

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PARKINSON DISEASE AND LEGAL CAPACITY

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Aims: One recent area of study in Parkinson Disease (PD) concerns financial capacity (FC) and medical decision-making capacity. Patients frequently make ongoing treatment and clinical trial research participation decisions and obtaining informed consent to treatment is an important medical-legal and clinical aspect of neurological practice. There are limited studies in this field.
Methods: Pubmed database has been used.
Results: Regarding treatment decisions, PD patients with dementia (PDD) have been found impaired on the three clinical standards of understanding, reasoning and appreciation. They showed better understanding of the treatment situation relative to mild Alzheimer disease patients, but more difficulty for simple decisional choices. Financial incapacity was also found in PDD. Due to executive dysfunction, which constitutes a major neurocognitive factor for incompetency in PD, even patients with cognitive impairment without dementia show impaired ability to make treatment choices, through deficits in encoding and organization of new medical information, as well as not reasoning with or personally appreciating that information. Furthermore, depression, which affects cognitive functions, is common in PD and this further complicates the assessment of capacities. In fact, PD patients' cognitive functioning and financial capacity can be negatively influenced by apathy more than depression.
Conclusions: There are limited studies regarding legal capacity assessment in PD, since deficits in capacities are often related to progressive motor dysfunction. There is need for studies regarding the relationship of specific brain areas linked to apathy and components of legal capacities in PD. Inquiries about the patient's wishes early in the course of PD, before cognitive impairment arises, are also recommended. Finally, clinicians and researchers should carefully assess decisional capacity in PD patients with cognitive impairment.

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SPATIO-TEMPORAL, CLINICAL PHENOTYPES AND SOCIO DEMOGRAPHIC PATTERNS OF PRESENTATIONS OF PARKINSON'S DISEASE IN KANO, NORTHERN NIGERIA

Zakari Aliyu[1], Nuhu Abubakar[2], Yahya Aliyu[1], Aliyu Ibrahim[3], Lukman Owolabi[2]
[1]Emani American Clinical Specialists, LLC, Neurology, Catonsville, United States of America, [2]Aminu Kano Teaching Hospital, Neurology, Catonsville, United States of America, [3]Aminu Kano University Hospital, Neurology, Kano, Nigeria

Aims: To identify and elucidate the patterns of parkinson disease phenotypes, clinical presentaions and severity and sociodecmographic characteristics of PD in Northern Nigeria. The pattern of clinical care and socital stgma associated with such neurodegenerative disease will also be evaluated.
Methods: A large reference teachng hospital with diverse population groups cohort study. Subjects were patents attending the neurology clinic at AKTH Kano, Nigeria. Ethical review board approval was obtained from the management of the Hospital. Patients provided signed informed consents or IRB waiver as necessary for data sets/observations in this study.
Results: The age of PD onset, age at diagnosis, and PD duration were 59.05 ± 10.35, 60.68 ± 10.15, and 30.80 ± 31.77 (2.50 ± 2.50) years respectively. BMI: The mean BMI for all study participants was 20.49 ± 4.10/ PD Severity staging: The mean Hoehn and Yahr PD severity stage was 1.76. ± 0.99. Pulse rate: The majority of the study participants (90.6%) had a normal pulse rate of 60-100 beats per minute while the remaining 8.5% had above 100. Co-morbidities: One-third (33%) of the study participants had a history of hypertension while only 4.7% had diabetes. PD type: The majority of the study participants had a tremor-dominant PD phenotype (89%). 67 percent of participants were on Levo/Carbidopa with good adherence (96.2%). More than half (57.5%) of the participants were on Artane, while only 5.7% were on Selegiline (MAO-B Inhibitor).
Conclusions: Sociodemographic, clinical severity and management standards of PD in Nigeria were defined. Age of onset was 62. The seveity index trends towards severe ds and tremor predominat phentype is most prevalent. CI was 25% at all stages of the diesease. Physical impairements/disabilities, anxiety and depression were common. Cognitive imoairemen was 26%.

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HYPERKINETIC MOVEMENT DISORDERS: EPIDEMIOLOGICAL AND CLINICAL ASPECTS IN THE NEUROLOGY DEPARTMENT OF THE YAOUNDÉ CENTRAL HOSPITAL.

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[1]Yaounde Central Hospital, Yaounde, Cameroon, [2]Yaounde Central Hospital, Neurology, Yaounde, Cameroon

Aims: Movement disorders (MDs) are a group of pathologies that significantly impact an individual's functional and aesthetic prognosis, with notable socio-professional repercussions. Therefore, we sought to determine these disorders' epidemiological and clinical aspects.
Methods: A descriptive cross-sectional study was conducted during a period of nine months at the Neurology Department of the Yaoundé Central Hospital.
Results: A total of 45 patients were enrolled in the study, with an age range of 7 to 83 years and a mean age of 48.9 ± 19.6 years. There was a male preponderance (M/F=1.25). The prevalence of hyperkinetic movement disorders at Yaoundé Central Hospital was 1.5% (45/2993), with tremors and dystonias representing the most common presentations at 33.3% each. Myoclonus and choreas were observed in 8.9% of cases each, followed by dyskinesias (6.7%), hemifacial spasms (4.4%), tics and ballismus (2.2% each). The most common presentation of tremors was bilateral upper extremity tremors, occurring in 66.7% of cases. Focal dystonias, including writer's cramp and blepharospasm, were the most prevalent form of dystonia (73.3%). In the majority of cases (53.3%), a genetic cause was strongly suspected, while in 24.4% of cases, the cause was unknown and in 13.3% of cases, the cause was iatrogenic. The most frequently prescribed medication was a benzodiazepine (35.6%).
Conclusions: Hyperkinetic MDs are observed with a diverse range of clinical manifestations. The most prevalent MDs are tremors and dystonias. The underlying etiology remains poorly understood, although genetic factors appear to be a prominent.

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PATH TO PREVENTION (P2P) THERAPEUTICS PLATFORM TRIAL DISEASE IN NSD STAGE 2B : STUDY UPDATE

Tanya Simuni[1], Christopher Coffey[2], Andrew Siderowf[3], Caroline Tanner[4], Sohini Chowdury[5], Catherine Kopil[6], Todd Sherer[5], Michael Brumm[2], Karl Kieburtz[7], Kimberly Fabrizio[8], Lianne Ramia[8], Heidi Whalen[8], Cecilia Reyes[8], Erika Merriam[8], Cornelia Kamp[7], Cora Allen-Savietta[9], Barbara Wendelberger[9], Amy Crawford[9], Ken Marek[8]
[1]Northwestern University Feinberg School of Medicine, Neurology, Chicago, United States of America, [2]University of Iowa, Clinical Trials Statistical And Data Management Center, Iowa City, United States of America, [3]University of Pennsylvania, Philadelphia, PA, United States of America, [4]University of California San Francisco, San Francisco, United States of America, [5]The Michael J Fox Foundation for Parkinson's Research, NYC, United States of America, [6]The Michael J. Fox Foundation for Parkinson's Research, New York City, United States of America, [7]University of Rochester, Rochester, United States of America, [8]Institute for Neurodegenerative Disorders, New Haven, United States of America, [9]Berry Consultants, LLC, Austin, United States of America

Aims: To provide an update on the first interventional study in Neuronal α-Synuclein Disease (NSD) stage 2B. **Background:** P2P aims to recruit qualified participants with **NSD Stage 2B** (Figure 1). The study is embedded within the PPMI and sponsored by the MJFF.

Figure 1. P2P target population: biologically defined cohort. Stage 2B NSD-ISS

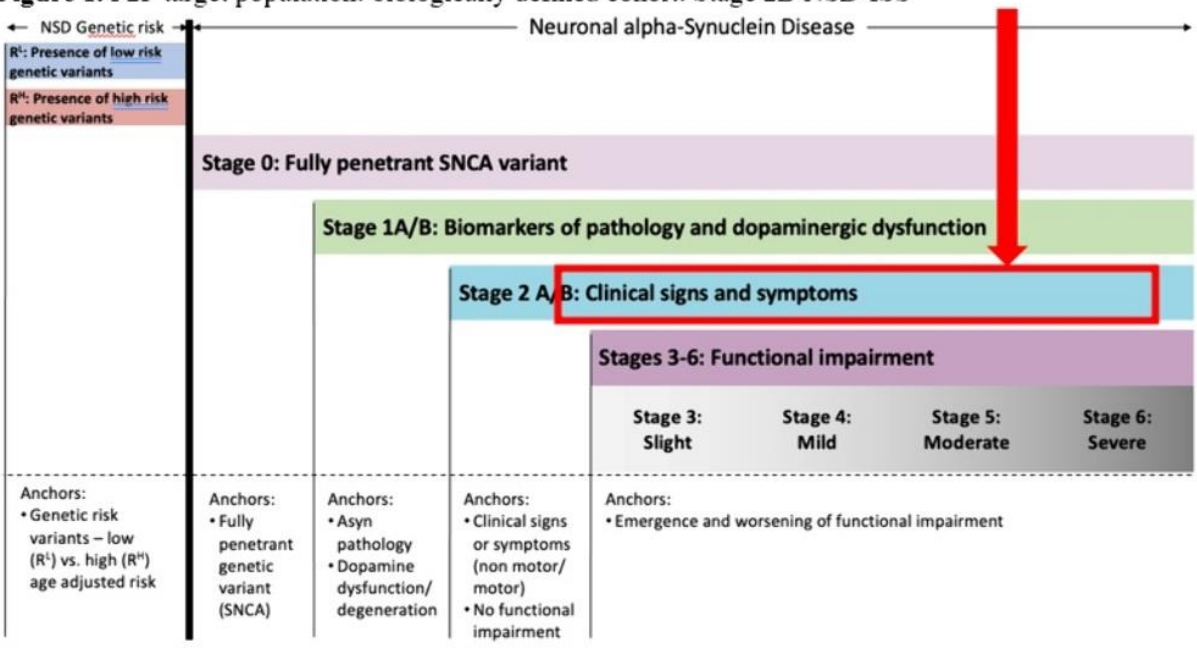
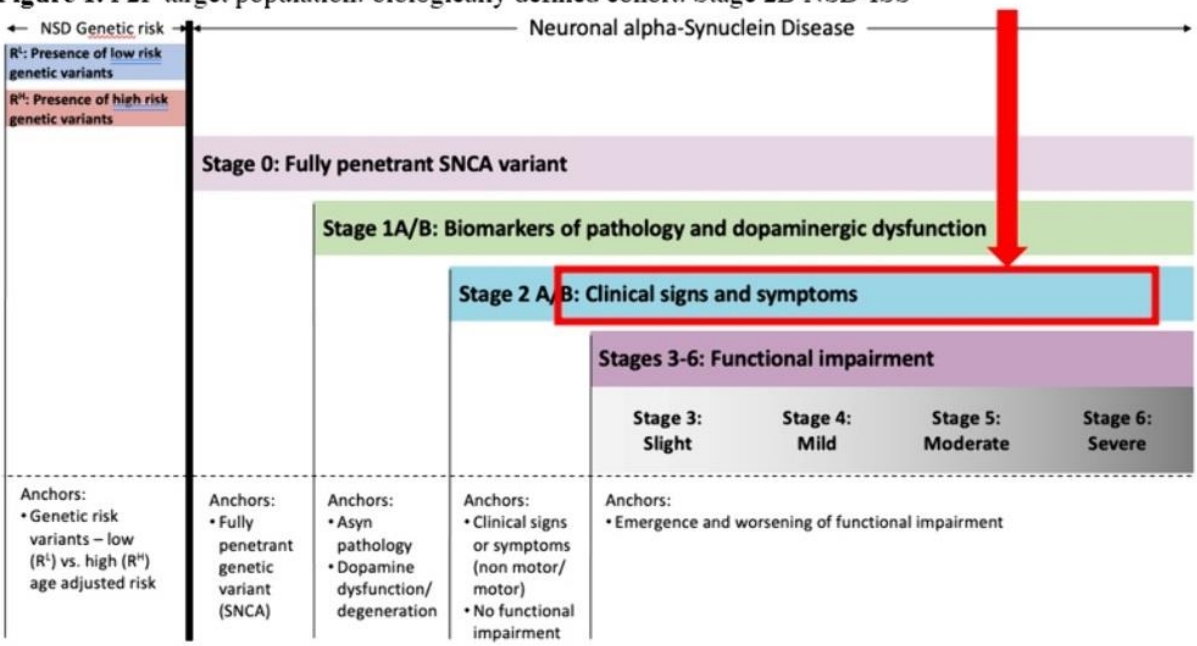
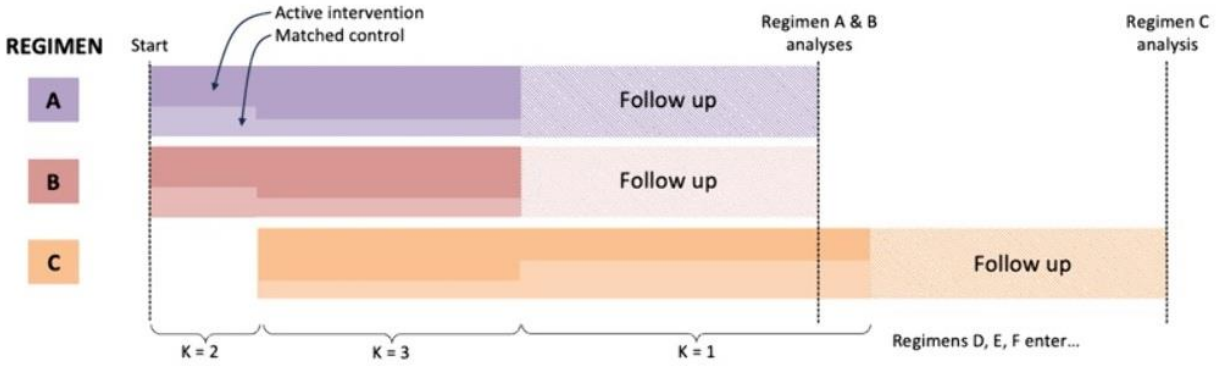


Figure 1. P2P target population: biologically defined cohort. Stage 2B NSD-ISS



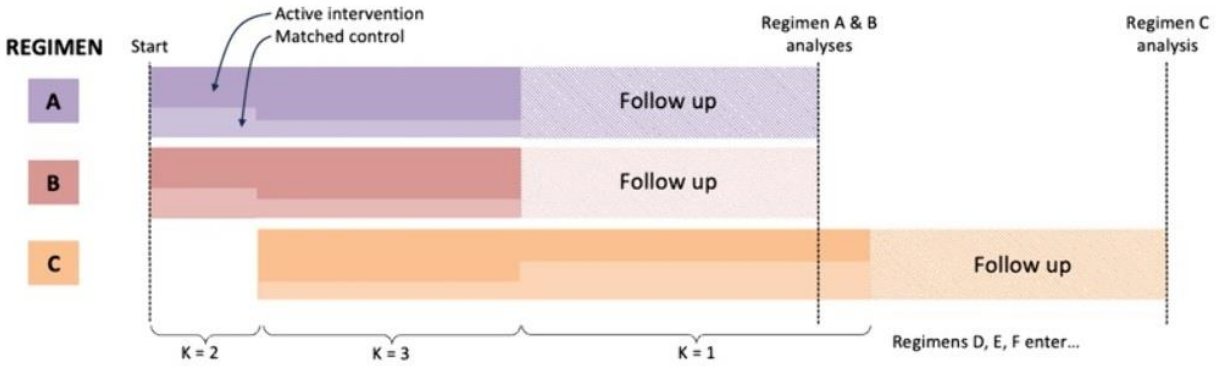
Methods: P2P is a Phase 2 randomized, double-blind, multi-center, multi-regimen perpetual platform trial with a master protocol dictating its conduct. Regimen-specific subprotocols provide detailed information for a single intervention and its matched control. Regimens can enter and exit the platform trial modularly (Figure 2). The study has two primary efficacy endpoints: 1) DAT imaging mean striatum Specific Binding Ratio and 2) MDS-UPDRS part III score. The primary efficacy analysis evaluates the progression rate for each endpoint and leverages progression data from the PPMI observational registry through Bayesian borrowing. Secondary endpoints include measures of safety, tolerability, and feasibility. The study includes an array of exploratory clinical (including digital) and biomarker measures. Randomization and consent occurs in two stages: 1) participants are randomized to a regimen (each regimen includes an active intervention and matched control), and 2) participants are randomized within their regimen to either the active intervention or placebo arm. Each active intervention will be allocated 125 participants and has 83% power to detect a 30% slowing in the progression rate of either primary efficacy endpoint.

Figure 2. Example of the P2P platform trial design.



Participant randomization
Stage 1: equal randomization to open regimens
Stage 2: K:1 randomization to active intervention or matched control
K = # of regimens enrolling

Figure 2. Example of the P2P platform trial design.



Participant randomization
Stage 1: equal randomization to open regimens
Stage 2: K:1 randomization to active intervention or matched control
K = # of regimens enrolling

Results: Final therapeutics are being selected from more than 15 industry-submitted applications. Study prelaunch activities and site selection are ongoing, and enrolment is expected to start at the end of 2025.
Conclusions: We report the design of the first platform study targeting the NSD Stage 2B population. Innovative recruitment into PPMI will enable this study.

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BASELINE NEURONAL SYNUCLEIN DISEASE STAGE PREDICTS LONG TERM PROGRESSION IN SPORADIC PARKINSON'S DISEASE: AN 11-YEAR FOLLOW-UP STUDY

Tanya Simuni[1], Paulina Gonzalez Latapi[1], Caroline Gochanour[2], Hyunkeun Cho[2], Seung Ho Choi[3], Chelsea Caspell-Garcia[2], Christopher Coffey[4], Michael Brumm[2], David-Erick Lafontant[2], Yuge Xiao[5], Caroline Tanner[6], Charles Venuto[7], Karl Kieburtz[8], Lana Chahine[9], Kathleen Poston[10], Andrew Siderowf[11], Ken Marek[12]
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Aims: To describe long-term outcomes in Parkinson's Disease (sPD) participants who met Neuronal Synuclein Disease (NSD) criteria from PPMI cohort and assess the impact of NSD Integrated Staging System (ISS) baseline stage on progression.
Methods: We analyzed longitudinal data from PPMI participants enrolled before 2020 in the sPD cohort, who met NSD criteria, defined as synuclein seeding amplification assay positive (SAA+) and DAT+ at baseline visit. Participants were assessed using comprehensive motor/non-motor scales, DAT imaging, and biofluid biomarkers. We used Cox proportional hazards models to assess the association between baseline NSD-ISS stage and time to key outcomes, including survival, postural instability, loss of independence, cognitive decline, domain-based milestones including walking, motor complications, cognition, autonomic dysfunction, and activities of daily living.
Results: 344 participants met NSD criteria from the 423 individuals recruited into PPMI as untreated, recently diagnosed sPD. At baseline NSD-ISS stages were: 23% Stage 2b, 67% Stage 3, 10% Stage 4. There was substantial time dependent change in stages (Figure 1). Median time to key outcomes differed significantly for baseline NSD-ISS stage (Figure 2). 35 participants died over the follow up period. Retention was 80% at 5 years, 49 % at 11 years and inversely correlated with the baseline stage. Biofluid biomarkers available for 5 years showed no clear trends, except for increasing serum NfL over time.

Figure 1. NSD stage by visit

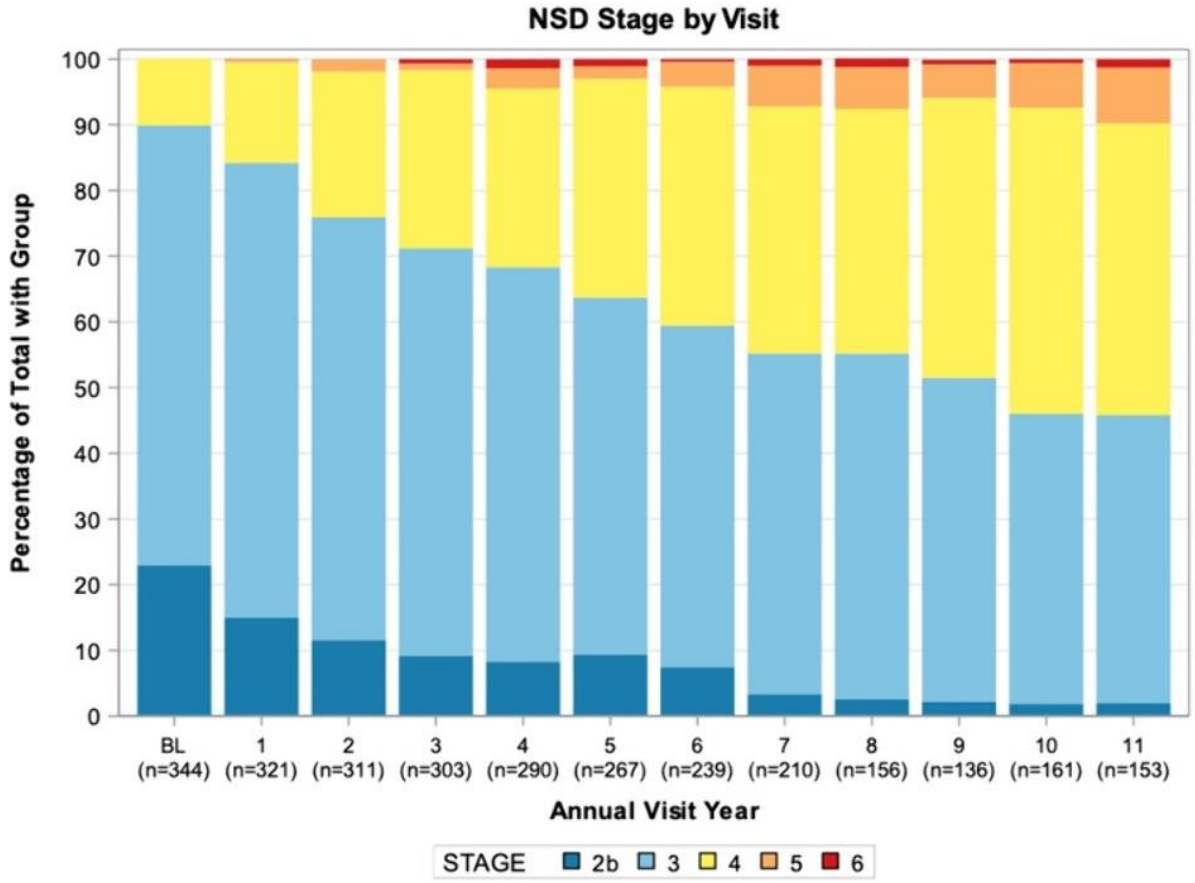


Figure 2. Time to clinically meaningful milestones (adjusted by age, sex and education)

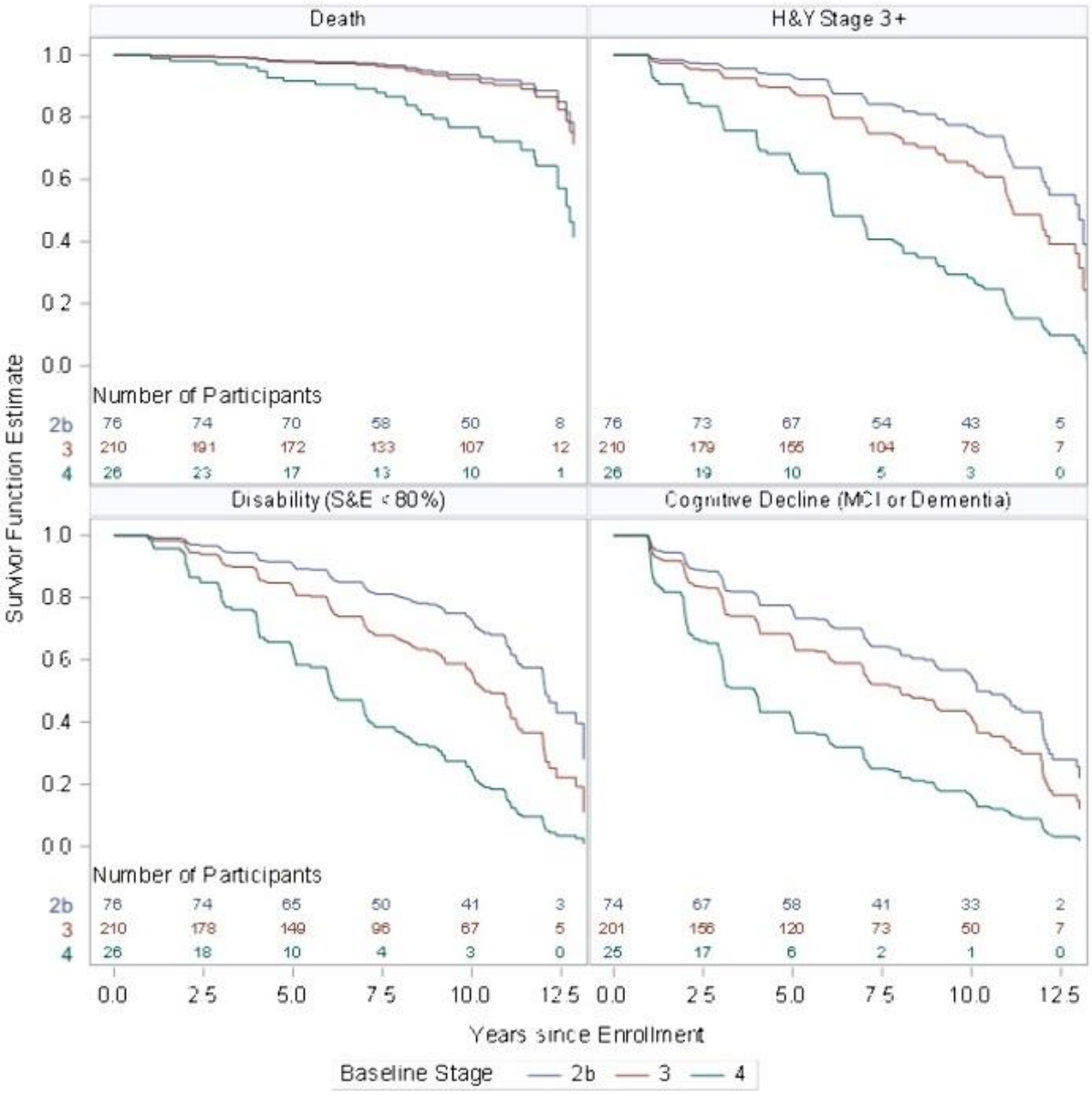


Figure 1. NSD stage by visit

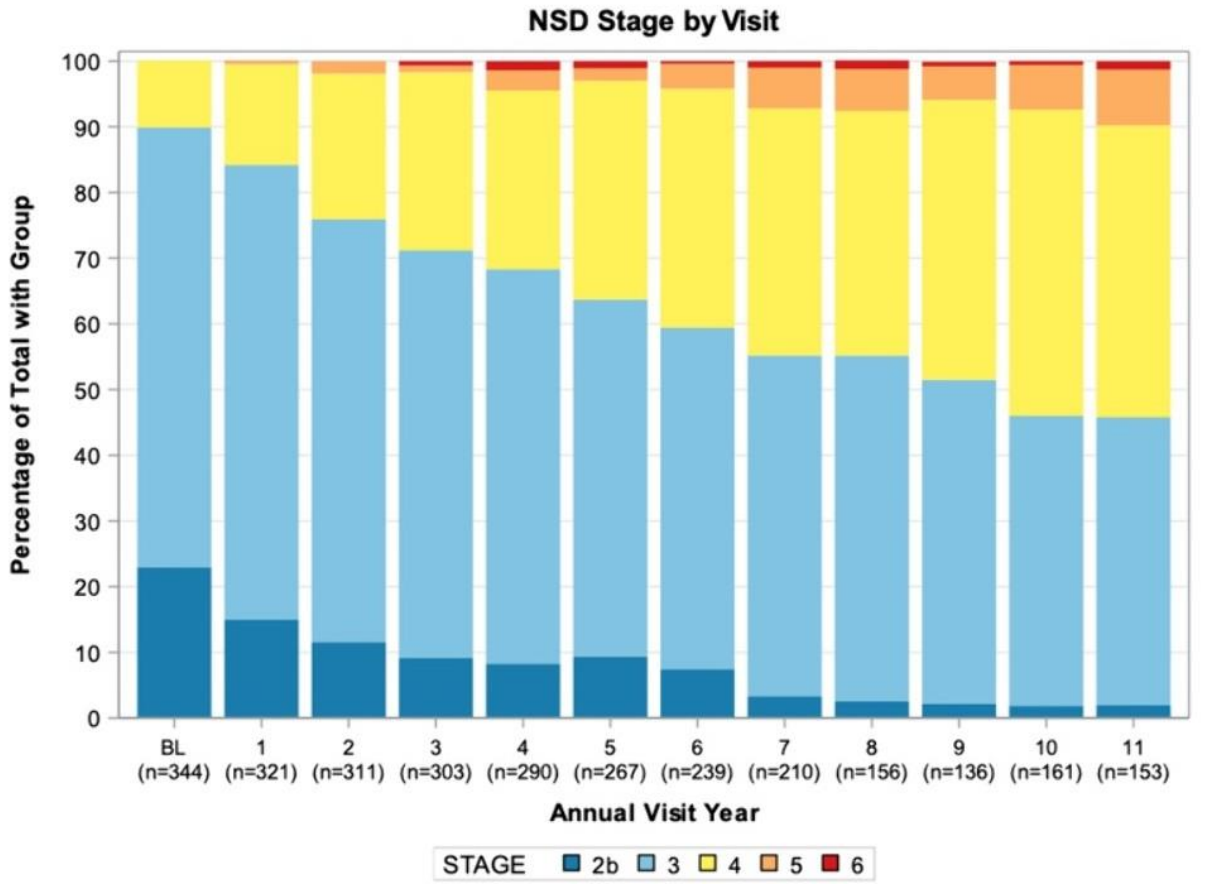
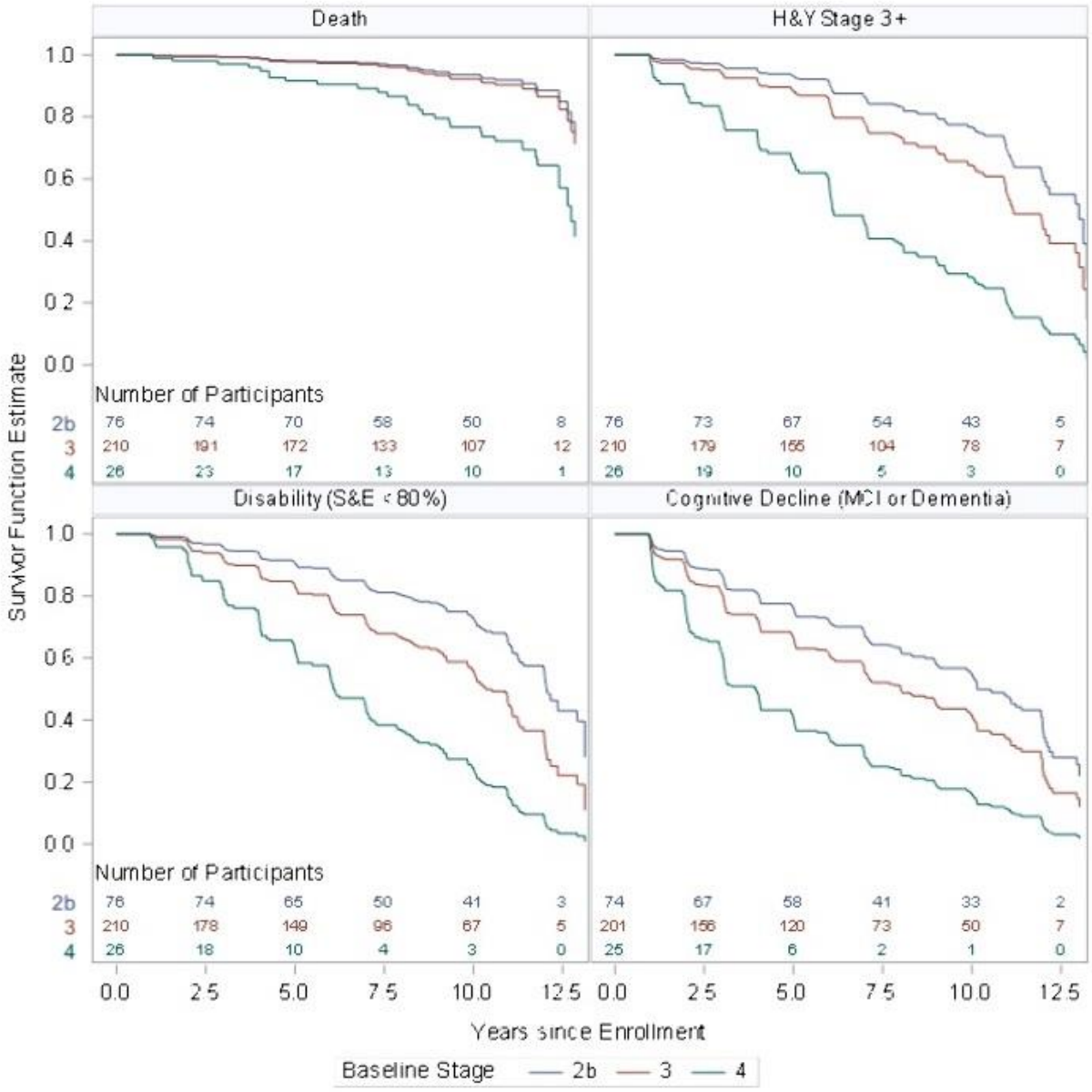


Figure 2. Time to clinically meaningful milestones (adjusted by age, sex and education)



Conclusions: We present data on long-term outcomes in NSD participants from the PPMI sPD cohort. We observed better long-term outcomes in this contemporary observational study cohort. Baseline NSD-ISS stage was a strong predictor of progression. Future work exploring other biomarkers, including omics data, as well as co- pathology, will be necessary to identify biomarkers of progression within the NSD-ISS. Note: Part of data presented MDS2024

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SARS-COV-2-INDUCED BRAIN DAMAGE OCCURS IN MULTIPLE NEURAL TYPES AND ACTIVATES INTRINSIC REPAIR MECHANISMS IN HUMAN BRAIN ORGANOIDS

Andrea Martí-Sarrias[1], Mari Carmen Puertas[2,3,4], Isabel Turpín[1], Lidia Garrido[2,3], Ramón Lorenzo-Redondo[5,6], Ángel Bayón[2], Javier Martínez-Picado[2,3,4,7,8], Sandra Acosta[1,9]
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Aims: SARS-CoV-2 infects human brain and can have long-term effects on brain function. However, the molecular processes triggered by the viral infection and the subsequent tissue response remain poorly understood. Here, we aim to elucidate the consequences of SARS-CoV-2 infection across diverse neural cell populations.
Methods: Three-month-old human brain organoids were exposed to SARS-CoV-2 for 24 hours and subsequently analysed using histological techniques and single-cell RNA sequencing 5 days post-infection.
Results: SARS-CoV-2 virus infects neural progenitors, mature neurons, astrocytes, and choroid plexus cells. Using a recombinant SARS-CoV-2-mCherry virus, we confirmed viral replication in mature neurons, astrocytes, and choroid plexus cells. At the molecular level, highly infected cells showed decreased **cytoplasmic translation**, **mitochondrial respiration**, and **protein folding** along with upregulated **protein ubiquitination**, **autophagy**, and **chromatin organization**, suggesting endoplasmic reticulum stress in infected cells. Moreover, highly infected neurons showed upregulation of interferon type I (IFN-I) genes. The mature neuron population, including the non-infected, showed evidence of cellular **stress** and **apoptosis**. Concurrently, signs of neuronal **regenerative response** were detected, characterized by **neuron projection morphogenesis**, **Wnt signalling pathway activation**, **DNA repair**, and increased mitosis in neural progenitors, suggesting a global tissue response to SARS-CoV-2 infection. Finally, we observed an increase in Macrophage Migration Inhibitory Factor (MIF) throughout the tissue. Organoid exposure to exogenous MIF suggests its role in activating dendritic regeneration.
Conclusions: Overall, our findings demonstrate that SARS-CoV-2 infection in the brain induces significant cellular stress, characterized by protein accumulation, DNA damage, and apoptosis. These pathological alterations establish a potential link between SARS-CoV-2 pathogenesis and neurodegenerative diseases.

Consequently, the infection elicits a regenerative response in both mature neurons and neural progenitor cells.

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THE LDL RECEPTOR-RELATED PROTEIN 1 (LRP1) FACILITATES ACE2-MEDIATED ENDOCYTOSIS OF SARS-COV2 SPIKE PROTEIN-CONTAINING PSEUDOVIRIONS.

Mashhood Wani[1], Joanna Cooper[2], Mary Migliorini[2], Dudley Strickland[2]
[1]University of Maryland. Baltimore, Cvid, Baltimore, United States of America, [2]University of Maryland School of Medicine CVID, Baltimore, United States of America

Aims: Several neurological complications are associated with COVID-19 infection, and one mechanism underlying these complications may be neuro-infiltration of SARS-CoV-2 into the brain. The ACE2 receptor is a major host factor for SARS-CoV-2, but questions remain about additional host factors that facilitate cell entry. In the current investigation, we sought to test the hypothesis that LRP1 may function as a co-receptor with ACE2 to facilitate viral entry of SARS-CoV-2.
Methods: We examined the binding between recombinant trimeric spike protein, spike S1 subunit, and the receptor binding domain (RBD) of spike protein to LRP1, VLDLr and LRP2 using surface plasmon resonance (SPR). Cellular internalization assays were performed using ^{125}I-labeled SARS-CoV-2 S1 subunit. Lastly, pseudovirions particles expressing spike protein on their surface were generated and utilized for studies.
Results: We confirm high affinity binding of trimeric spike and the S1 spike protein to LRP1. We also found high affinity binding of S1 to VLDL receptor and LRP2. We observed that chemical modification of lysine residues within the RBD of the spike protein ablates binding. We found that LRP1-expressing cells mediate the endocytosis of SARS-CoV-2 S1 subunit, while LRP1 enhances ACE2-mediated endocytosis of ^{125}I-labeled SARS-CoV-2 S1 subunit. Generation of spike protein-expressing pseudovirions showed that LRP1 expression enhances ACE2-mediated endocytosis of this protein.
Conclusions: Overarchingly, these results identify the potential of LRP1 to enhance ACE2-mediated SARS-CoV-2 viral entry. Given that LRP1 is highly expressed in the brain and neurovascular unit, and a well-known mediator of transcytosis across the blood-brain barrier, these findings raise poignant questions regarding the roles LRP1 could play in neuro-infiltration of SARS-CoV-2.

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COMPARING THE PERFORMANCE OF ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY IN DEMENTIA WITH LEWY BODIES ACROSS EUROPEAN COUNTRIES

Rakesh Kumar[1], Stephanie Gravett[1], Vesna Jelic[1], Johannes Lange[2], Linn Oftedal[2], Merve Bacinoglu[3], Arianna Ciullini[3], Chiara Maria Giulia De Luca[3], Lola Hamied[4], Catherine Birck[4], Frederic Blanc[4], Oliver Bousiges[4], Fabio Moda[3], Jodi Maple-Grødem[2], Axel Abelein[5], Daniel Ferreira[6]
[1]Karolinska Institutet, Department Of Neurobiology Care Sciences And Society, huddinge, Sweden, [2]Stavanger University Hospital, Stavanger, Centre For Movement Disorders, Stavanger, Norway, [3]Fondazione IRCCS Istituto Neurologico Carlo Besta, Department Of Neurology 5 - Neuropathology,, Milan, Italy, [4]University Hospital of Strasbourg, Laboratory Of Biochemistry And Molecular Biology, strasbourg, France, [5]Karolinska Institutet, Department Of Medicine, Huddinge, Huddinge, Sweden, [6]Karolinska Institutet, Neurobiology, Care Sciences, And Society, Stockholm, Sweden

Aims: Our goal was to test the performance of SAA across five different labs in Europe using different SAA protocols on same CSF samples from patients.
Methods: The study included 20 DLB patients (all DAT scan positive, 10 Abeta positive, 10 Abeta negative, 67.6 years old, 60 % male, with mild to moderate dementia) and 10 age- and sex-matched cognitively unimpaired controls, analysed at all labs. The SAA assay was run in 96 well plates, and Thioflavin T fluorescence was analysed for the CSF-seeded samples.
Results: Our interim result from three labs showed that the diagnostic performance of SAA varied across laboratories. Lab A achieved 100% sensitivity and 100% specificity, although there were two cases with an unclear SAA result (excluded from the calculation of diagnostic performance). Lab B achieved 85% sensitivity and 90% specificity. Lab C achieved 80% sensitivity and 60% specificity. The SAA result was statistically comparable between the Abeta positive and Abeta negative DLB groups.
Conclusions: The analysis of SAA data showed an average sensitivity of 88 % and specificity of 83 % across the three labs. The result highlights the overall effectiveness of SAA in diagnosing DLB. Our next step is to propose an ad-hoc harmonization to reduce variation in assay performance across centres and clinics.

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IN SITU AMPLIFICATION OF A-SYNUCLEIN AGGREGATES WITHIN TISSUE SECTIONS

Hengxu Mao[1], Yaoyun Kuang[1], Wei Dai[2], Pingyi Xu[1]
[1]the first affiliated hospital of Guangzhou Medical University, Guangzhou, China, [2]People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

Aims: This study introduces a new α-synuclein (αSyn) amplification technique called the quiescent seed amplification assay (QSAA), which facilitates in situ amplification of αSyn aggregates directly within tissue sections.
Methods: We investigated the role of seeding in synucleinopathy pathogenesis using a mouse model of PD, initiated by intrastriatal injection of αSyn preformed fibrils (PFFs). Additionally, brain and skin tissues from PD patients were analyzed using QSAA.
Results: QSAA was conducted under quiescent conditions using a reaction buffer with mouse-derived αSyn monomers and anionic components to promote fibril elongation at 70°C. Thioflavin T fluorescent imaging was used to detect β-sheet-rich structures in newly formed αSyn fibrils. Our results show that QSAA can identify endogenous pathological αSyn seeds in brain and skin sections. Furthermore, we developed a combined technique called IF-QSAA, which integrates QSAA with immunofluorescence. This method allowed for the colocalization of QSAA products with neuronal markers, such as NeuN and GFAP, enabling precise spatial localization of specific seeds. Notably, IF-QSAA supports the use of various anti-αSyn antibodies to study the connections between αSyn phosphorylation, aggregation, and seeding activity. Our findings reveal that, while pS129—an established pathological modification in αSyn—often correlates with seeding activity, there are cases where seeding occurs without pS129, and instances where pS129 does not promote seeding.
Conclusions: The QSAA method provides researchers with a tool to explore the spatial distribution of misfolded protein seeds within tissue sections, broadening the capacity for studying αSyn pathology. QSAA thus contributes to a more detailed and multi-dimensional understanding of the mechanisms driving synucleinopathies, paving the way for novel therapeutic strategies targeting misfolded proteins in neurodegenerative diseases.

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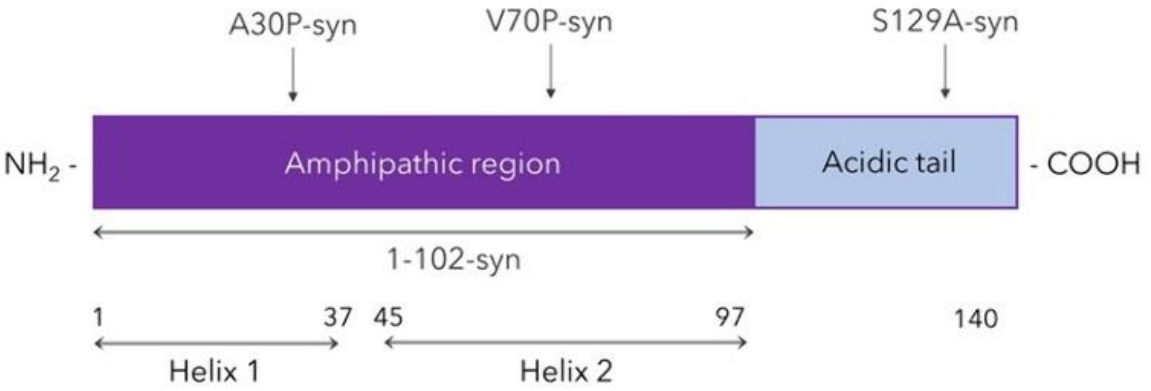
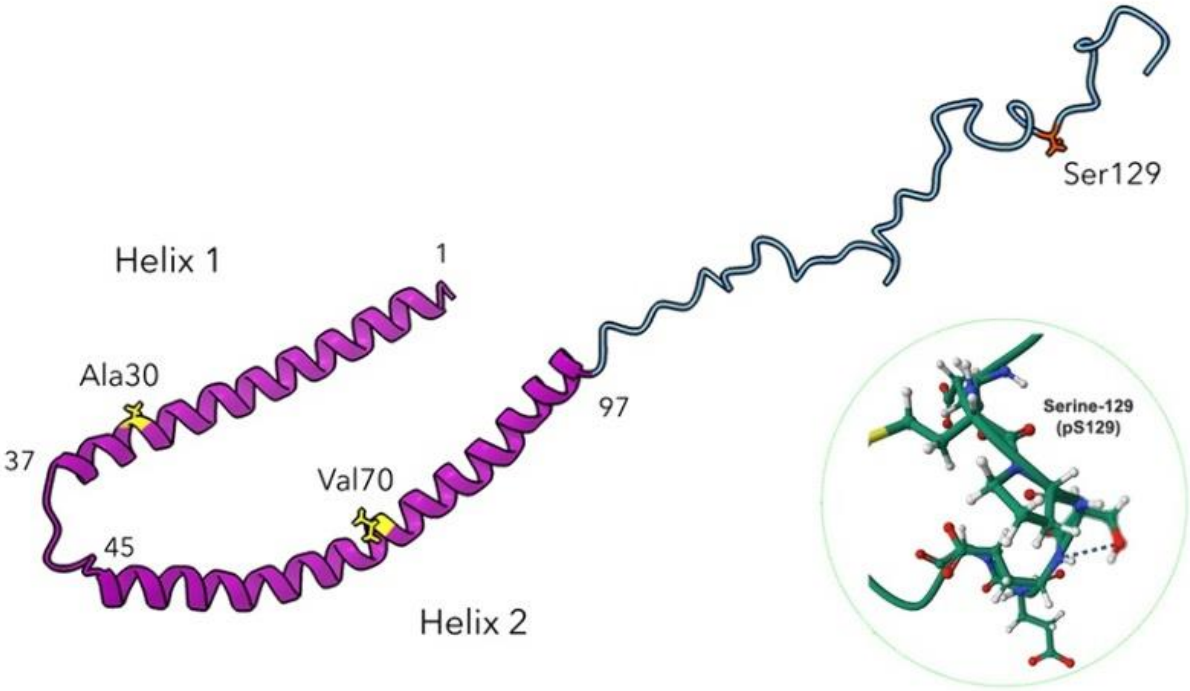
CONFORMATION CHANGES OF ALPHA-SYNUCLEIN RELEVANT FOR PARKINSON DISEASE

Markéta Procházková[1,2], Jozef Hritz[3,4]
[1]Masaryk University, Department of Chemistry, Faculty Of Science, Brno, Czech Republic, [2]CEITEC Masaryk University, Brno, Czech Republic, [3]Central European Institute of Technology, Centre For Structural Biology, Brno, Czech Republic, [4]Masaryk University; Faculty of Science, Department Of Chemistry, Brno, Czech Republic

Aims: The α-Synuclein is a presynaptic neuronal protein that is genetically and neuropathologically linked to Parkinson's disease. The α-Synuclein and its conformational changes play a key role in in the early stages of this progressive central nervous system disease with a complex mechanism. Its oligomeric conformations, are toxic and mediate disruption of cellular homeostasis and neuronal death through effects on various intracellular targets, including synaptic function. Targeting the conformational changes cause this protein's dysregulation in brain can lead to new therapeutic strategies not only in case of Parkinson's disease but also in research of other neurodegenerative diseases. Our research is focused on study of the specific conformational changes of the α-Synuclein, especially associated with phosphorylation of amino acids at specified positions in the protein structure. Especially the α-Synuclein with phosphoserine at position 129 in protein structure (Fig. 1) has become significant for research and moreover could serve as an important biomarker for improving the diagnosis of the early stages of Parkinson's disease in patients liquor or potentially also in their blood.


A30P-syn
V70P-syn
S129A-syn
NH2 -
Amphipathic region
Acidic tail
- COOH
1-102-syn
1
37
45
97
140
Helix 1
Helix 2


Ser129
Helix 1
1
Ala30
37
97
Val70
45
Helix 2
Serine-129
(pS129)

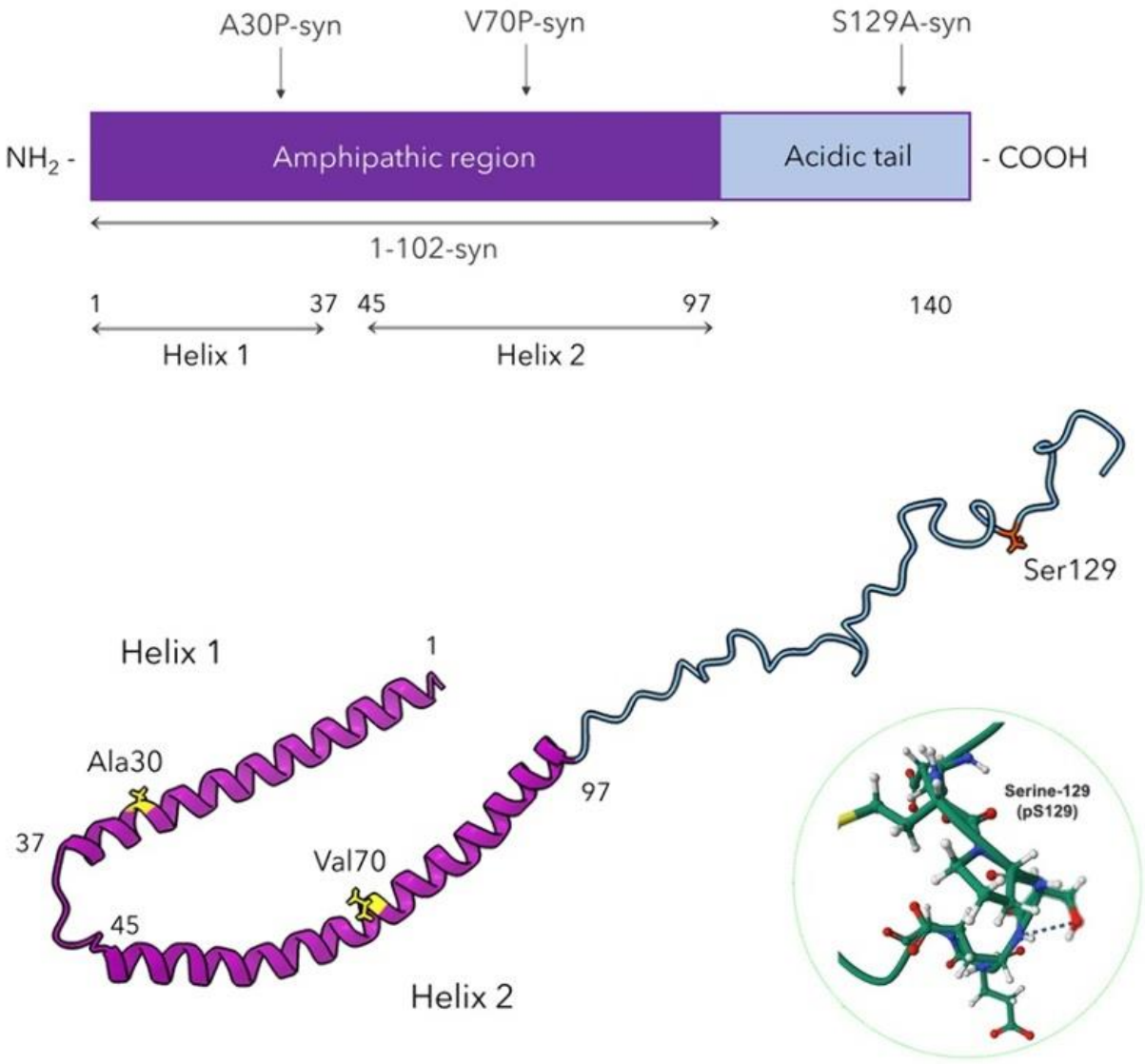


Figure 1 The pSer129 α-Synuclein structure scheme.

Methods: Specifically phosphorylated variants of the α-Syn protein in various selected structural positions prepared using new biochemical methods will be studied by bioanalytical techniques: CD spectrometry, NMR, MALDI-TOF MS, MS-MS, UV-Vis spectroscopy.

Results: Study of α-Synuclein conformational changes in human and mouse variant with phosphorylated selected amino acids at different specific structural positions prepared using new biochemical methods and technologies with the aim of a deeper understanding of aggregation mechanisms in the early stages of Parkinson's disease.

Conclusions: Research of the specifically phosphorylated variants of α-Synuclein can lead to deeper understanding not only the mechanisms but also the better diagnosis of the early stages of α-Synucleinopathies.

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A MECHANISTIC MODEL OF PURE AND LIPID-MEDIATED ALPHA-SYNUCLEIN AGGREGATION FOR ADVANCING PARKINSON'S DISEASE THERAPIES

Federico Reali[1], Elena Righetti[1,2], Luca Marchetti[1,2], Enrico Domenici[1,2]
[1]Fondazione The Microsoft Research - University of Trento Centre for Computational and Systems Biology, Rovereto, Italy, [2]University of Trento, Department Of Cellular, Computational And Integrative Biology – Cibio, Povo, Italy

Aims: The neuronal protein alpha-synuclein (aSyn) holds a crucial role in the intricate molecular landscape of Parkinson's disease. Indeed, recent advances in aSyn-based biomarkers have led to the definition of a new biological framework for the disease. Aggregates such as oligomers and fibrils have also been suggested as key pathogenic triggers and potential therapeutic targets. However, many unclear aspects and mechanisms linked to aggregation hamper the quest for effective disease-modifying therapies. To address these knowledge gaps, experimental research calls for a quantitative systems pharmacology approach [1].
Methods: We propose a mathematical model of the complex chemical reaction network underlying aSyn aggregation. The ordinary differential equation system captures a nucleation-conversion-polymerization process with toxic oligomers at the core and self-amplifying loops, including all the microscopic events explicitly related to aSyn in the literature. Model calibration and validation rely on experimental data from *in vitro* aggregation assays [2, 3]. To assess parameter reliability, we also performed local-at-a-point and structural identifiability testing and uncertainty quantification
Results: The model can capture multiple scenarios of aSyn accumulation mimicking *in vivo* settings in agreement with the underlying biological processes. In addition, our model enables a broad spectrum of *in silico* experiments exploring the impact of risk factors such as aging and gene mutations through specific proxies in the model, *e.g.*, lipid-to-protein ratio, pH level, and monomer concentration. Finally, model predictions and results of local sensitivity analysis are associated with the effects of compounds currently under investigation, suggesting candidate target mechanisms to counteract aggregation.
Conclusions: Overall, this work provides a robust mathematical framework for investigating disrupted aSyn homeostasis and a virtual lab for testing anti-aSyn aggregation therapies. **References** [1] DOI/10.3389/FAMS.2022.1060489 [2] DOI/10.1073/PNAS.1524128113 [3] DOI/10.1038/NCHEMBIO.1750

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A CASE OF LEWY BODY DISEASE WITH ATYPICAL NEUROPATHOLOGIC CHARACTERISTICS

Masafuchi Ryo[1], Kazuko Hasegawa[2], Ikuo Saitoh[3], Saburo Yagishita[4]
[1]Social Welfare Organization Saiseikai Imperial Gift Foundation,Inc. ShonanHiratsuka Hospital, Neurology, Hiratsuka Kanagawa, Japan, [2]National Hospital Organization Sagamihara Hospital, Department Of Neurology, Sagamihara, Japan, [3]National Hospital Organization Sagamihara Hospital, Pathology, Sagamihara, Japan, [4]National Hospital Organization, Sagamihara National Hospital, Clinical Research Center, Sagamihara, Japan

Aims: We report a case in which Lewy bodie(LB)s showed a somewhat unusual distribution and did not exhibit CA2/3 findings characteristic of Dementia with Lewy Bodies(DLB).
Methods: 【CASE】 A man who died at the age of 59. He suffered from a rest tremor of his left hand from about the age at 50. He then visited the neurologic and psychiatric department of a nearby hospital, and within a few year bradykinesia appeared. 51yo, he visited University Hospital because of his akinesia. He was shown to have akinesia, rigidity, postural instability. Following the diagnosis of Parkinson's disease (PD), L-dopa treatment was started, and the effect was confirmed. A 123I MIBG myocardial scintigraphy H/M showed early 1.92 late 1.29. Among the symptoms he experienced were hallucinations, especially visual hallucinations, and he was moved to a dementia clinic. 57yo, due to deterioration of motor function and severe dyskinesia, he admitted our hospital. His motor performance and mental status were improved, so he discharged nursing home to his home. 58yo, following a lapse into dyspnea with sputum clogging, he was taken into hospital by ambulance. A head MRI showed moderate atrophy in the frontal lobe. The DAT scan showed SBR right 1.00 left 1.22. 59yo, death was confirmed.
Results: Severe neuronal cell loss was observed in the substantia nigra and locus coeruleus, with the presence of LBs. LBs and α-synuclein positive structures were observed in the Brain stem and cerebral cortex including occipital cortex. Despite the fact that findings in CA2/3 is one of the characteristic features of DLB, in this case there were no findings in CA2/3.
Conclusions: We report a very rare and important case from the neuropathologic point of view in DLB.

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ULTRASTRUCTURAL ANALYSIS OF LEWY BODY PATHOLOGY IN CORTICAL AND DOPAMINERGIC NEURONS IN DEMENTIA WITH LEWY BODIES AND COMPARING WITH PARKINSON'S DISEASE

Notash Shafiei[1], Wilma Van De Berg[2,3], Henning Stahlberg[4], Amanda Lewis[1]
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Aims: This study aims to analyze the ultrastructure of phosphorylated alpha-synuclein aggregates to understand the pathological mechanisms that lead to DLB comparing to PD.we investigated the structure and composition of cortical and nigral LBs. from post-mortem brain tissue.
Methods: We employed a correlative light and electron microscopy protocol to examine postmortem human brain tissue. Fluorescent immunolabeling was applied to 60-micron-hick, free-floating brain sections that were chemically fixed. ROIs were imaged with fluorescent microscopy and sections were then prepared for electron microscopy with heavy metal staining and resin embedding. Using laser capture microdissection, we excised regions of interest, thinned them to 150-nm with an ultramicrotome, and correlated the fluorescent and EM images.
Results: In the substantia nigra (SN), neuronal LB structures in DLB resembled those in PD, and included pale bodies, single-layer halo LBs, and two-layer halo LBs containing dense fibrils. In enthorinal (ENT) and cingulate gyrus (CG) regions, however, only two types of neuronal LBs were observed in both PD and DLB: 1) LBs with clusterd mitochondria intermixed with low-density fibrils, and 2) single-layer halo LBs. Pathological neurons in SN, ENT and CG also exhibited a two-fold increase in mitochondria compared to healthy neurons.
Conclusions: LBs in PD and DLB show similar ultrastructures across neuron types, with denser alpha-synuclein fibrils in dopaminergic neurons than in cortical neurons. Cortical Lewy bodies appear less mature than those found in SN, which may reflect different stages in LB maturation and confirm begins in the brainstem and later spreads to the limbic and cortical regions. This difference may be also influenced by dopamine, neuromelanin, or neuron type, potentially promoting fibril formation. The higher number of mitochondria in alpha-synuclein-positive neurons suggest impaired mitophagy.

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SELECTIVE VULNERABILITY OF MONOAMINERGIC NEURONS AND NETWORK SPREAD OF ALPHA-SYNUCLEIN

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[1]University of California San Francisco, Neuroscience, San Francisco, United States of America, [2]University of California San Francisco, San Francisco, United States of America

Aims: Reconciling the mechanisms of network-based spread of alpha-synuclein oligomers in Parkinson's disease (PD) and the observed selective vulnerability of certain cells to alpha-synuclein remains challenging. Here we took a computational approach, applying the previously published Nexopathy in silico (NexIS) model[1] to jointly explore these two mechanisms at a whole-brain level.
Methods: Two models of PD, mouse- and human-derived preformed fibrils for seeding[2], were optimized by this model using: 1) directional spread and 2) the locations of monoaminergic neurons. Cell receptor type density maps were created using the Matrix Inversion and Subset Selection algorithm, which uses data from the Allen Gene Expression Atlas and RNA sequencing data from Zeisel, et al. 2018. 2.Mezias C, Neural connectivity predicts spreading of alpha-synuclein pathology in fibril-injected mouse models: Involvement of retrograde and anterograde axonal propagation. Neurobiol Dis. 134, 104623 (2020).
Results: Midbrain dopaminergic-1 (Human PFF R^2 = 0.29, Mouse R^2= 0.42) and hindbrain noradrenergic receptor (Human PFF R^2 = 0.43; Mouse R^2 = 0.42) regional data created models most similar to actual pathology spread. There was a net retrograde bias in alpha-synuclein spread which provided an additive effect of regional receptor data. The effect of these parameters was most significant 6 months after seeding for both human PFF (Global: R = 0.55; HBNOR: R = 0.60; MBDOP1: R = 0.57) and mouse PFF (Global: Pearson's R = 0.44; HBNOR: R = 0.49; MBDOP1: R = 0.47) models.
Conclusions: The NexIS model was able to fit two mouse synucleinopathy models with high accuracy, and identify neuronal mediators of alpha-synuclein spread, demonstrating that computational methods provide a necessary, complementary approach to bench studies to elucidate disease mechanisms and find avenues for the treatment of PD.

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A GUT FEELING: ELUCIDATING THE ROLE OF GUT MICROBIOTA IN ALPHA-SYNUCLEIN PATHOLOGY AND PARKINSON'S DISEASE

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Aims: Gastrointestinal (GI) dysfunction is a salient preclinical indicator of Parkinson's disease (PD), associated with alpha-synuclein (αSyn) accumulation in the GI tract and microbiome imbalance, or dysbiosis. However, mechanistic underpinnings of gut-brain contributions to disease remain elusive. This study expands on behavioral motor deficits observed in αSyn-overexpressing (ASO) mice to delineate distinctions in αSyn pathology due to variations in gut microbiota. We conduct a holistic investigation to characterize the relative presence of S129 phosphorylated αsynuclein (pSyn) in mice with diminished microbes and to elucidate specific brain regions most affected by depleted gut microbes. Finally, we evaluate cognitive behavioral symptoms in mice with amplified pSyn pathology to corroborate neurobiological evidence.
Methods: Using Y-maze cognitive testing in conjunction with western blot and immunofluorescence staining, we effectively characterized αSyn levels in conventional specific-pathogen free (SPF), microbiota-depleted germ-free (GF), conventionalized germ-free (ConvGF), and antibiotic-treated (ABX) ASO mice.
Results: We observed significantly elevated pSyn in PD-implicated regions of GF and ConvGF mice, suggesting the potential role of microbiota in mitigating pSyn pathology in this model. Furthermore, Y-maze spatial memory test results revealed exacerbated cognitive deficits in SPF ASO mice compared to SPF wild type mice, aligning with increased αSyn pathology in brain areas involved in PD-related dementia and cognition. We will elaborate on the implications of ABX conditions on pSyn levels by completing analysis of additional cohorts.
Conclusions: Findings from this project lay the groundwork for the role of microbial dysbiosis in αSyn aggregation, substantiating the gut-first hypothesis and potential avenues for enteric-neuroprotective therapies to delay PD progression.

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PATHOGENIC LRRK2-R1441G MUTATION OF PARKINSON'S DISEASE ABOLISHES DEPOLARIZATION-INDUCED MITOCHONDRIAL CA2+ RESPONSE AND CAMKII/ERK ACTIVATION ASSOCIATED WITH IMPAIRED MITOPHAGY

Eunice Eun Seo Chang[1], Huifang Liu[1], Zoe Yuen-Kiu Choi[1], Shirley Yin-Yu Pang[2], Shu-Leong Ho[2], Philip Wing Lok Ho[1]
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Aims: Stress-induced activation of ERK/Drp1 via cytosolic calcium mediates the segregation of damaged mitochondria for mitophagy. This process is altered in Parkinson's disease (PD) with leucine-rich repeat kinase 2 (LRRK2) mutations, contributing to mitochondrial dysfunction. How pathogenic LRRK2 mutation dysregulates Ca^{2+} signaling remains unclear. We aimed to elucidate mitochondrial Ca2+ response and CaMKII-MEK-ERK-Drp1 activation under mitochondrial depolarization in LRRK2-R1441G mutant mouse embryonic fibroblasts (MEFs).
Methods: Mitochondrial depolarization was induced by artificial uncoupler (FCCP) in wildtype (WT) and $LRRK2^{R1441G}$ mutant knockin (KI) MEFs. Cytosolic Ca^{2+} flux was assessed using live-cell Ca^{2+} imaging. The role of mitochondria in FCCP-induced cytosolic Ca^{2+} surge was confirmed by co-treatment with NCLX-inhibitor. Mitochondrial bioenergetics were evaluated by Seahorse™ metabolic analyzer, flow cytometry, and confocal imaging. Activation (phosphorylation) of stress response pathways were assessed by immunoblotting.
Results: FCCP caused rapid mitochondrial depolarization and cytosolic Ca^{2+} surge, mediated via mitochondrial-NCLX. Such response was abolished in LRRK2 KI MEFs. This loss of response was associated with impaired activation of CaMKII, MEK, and ERK. Inhibition of mutant LRRK2 hyperactivity did not rescue this phenotype. KI MEFs exhibited depolarized mitochondria and reduced mitochondrial Ca^{2+} store and calcium uniporter (MCU) expression. KI cells also exhibited lower cellular ATP:ADP ratio albeit higher basal respiration than WT. These defects may hinder cellular stress response and signals to Drp1-mediated mitophagy, as evident by impaired mitochondrial clearance in the mutant.
Conclusions: Pathogenic $LRRK2^{R1441G}$ mutation abolished mitochondrial stress-induced Ca^{2+} response and impaired mitochondrial clearance. Inherent defects from LRRK2 mutation may weaken the scavenge of damaged mitochondria that may further aggravate mitochondrial dysfunction and neurodegeneration in PD.

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INHIBITORS TARGETING THE DISORDERED REGION OF A-SYNUCLEIN FIBRIL TO REDUCE PATHOLOGICAL ACTIVITIES IN PARKINSON'S DISEASE

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Aims: Parkinson's Disease (PD), the second-most common neurodegenerative disorder, primarily impacting dopaminergic neurons in the substantia nigra, leading to motor symptoms. A crucial aspect of PD pathology involves the aggregation of α-synuclein (α-syn) fibrils, which form the core of Lewy bodies and disrupt neuronal function. These fibrils, particularly through their C-terminal intrinsically disordered region, play a key role in neuron-to-neuron transmission and neuroinflammation by interacting with specific receptors on neurons and microglia. Targeting these interactions presents a promising therapeutic approach to mitigate α-syn related pathologies.
Methods: We employed a robust high-throughput screening assay to identify compounds that inhibit the interaction between α-synuclein fibrils and their receptors. A structure-activity relationship study was then conducted to enhance the inhibitory activity of the selected candidate. Solution and solid-state NMR spectroscopy, along with cryo-EM, were used to elucidate the inhibitor's binding mechanism to α-synuclein fibrils.
Results: Givinostat (GS) proved highly effective, nearly eliminating the binding of α-syn PFFs to LAG3 D1 with an IC50 of 8.99 μM. GS also disrupted the interaction with vRAGE, another key receptor in PD pathology, showing even greater efficacy. To enhance GS's activity, structural modifications were made to reduce toxicity and improve selectivity against α-syn fibril-receptor interactions. Mechanism studies revealed that GS binds primarily to the C-terminal intrinsically disordered region of α-syn, supporting the idea that targeting this region could significantly impact PD pathology.
Conclusions: Our findings underline the potential of GS and its derivatives as promising candidates to prevent PD progression by specifically targeting and modulating α-syn fibril interactions with key receptors. This represents a significant advancement in developing targeted therapies for PD, offering hope for more effective treatments that address the disease's underlying mechanisms.

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REBALANCE OF MITOPHAGY BY INHIBITING LRRK2 IMPROVES COLON ALTERATIONS IN AN MPTP IN VIVO MODEL

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Aims: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are common genetic causes of Parkinson's disease (PD). Studies demonstrated that variants in LRRK2 genetically link intestinal disorders to PD. We aimed to evaluate whether the selective inhibitor of LRRK2, PF-06447475 (PF-475), attenuates the PD in central nervous system (CNS) and in the gastrointestinal system.
Methods: The nigrostriatal degeneration was induced by intraperitoneal injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (20 mg/kg, total dose of 80 mg/kg) at 2 h intervals. After 24 h PF-475 was administered intraperitoneally at the doses of 2.5, 5, and 10 mg/kg for seven days.
Results: In this study, LRRK2 inhibition reduced α-synuclein and modulated mitophagy pathway in the CNS. Moreover, LRRK2 inhibition reduced pro-inflammatory markers and α-synuclein aggregates in colonic tissues through the modulation of mitophagy proteins. In addition, LRRK2 inhibition suppressed MPTP-induced enteric dopaminergic neuronal injury and protected tight junction in the colon.
Conclusions: Results suggested that LRRK2 inhibition by PF-475 may attenuate gastrointestinal dysfunction associated to PD.

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NEUROPROTECTIVE EFFECTS OF GIT27 VIA TLR4 PATHWAY MODULATION IN AN IN VIVO MODEL OF PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder marked by the progressive degeneration and loss of dopaminergic neurons in the substantia nigra, leading to selective neuronal injury and cell death in the brain. This neuronal loss disrupts dopamine signaling pathways, resulting in the hallmark motor symptoms of PD, such as tremors, rigidity, and bradykinesia, alongside various non-motor symptoms. Recent studies have provided accumulating evidence for a significant role of the immune system and neuroinflammation in PD pathogenesis. In particular, it has been highlighted the important role of toll like receptor (TLR) 4 in the etiology and progression of PD. On this basis, this study aimed to evaluate the neuroprotective effect of TLR4 inhibition, using the immunomodulatory compound GIT27, in a mouse model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal degeneration.
Methods: The nigrostriatal degeneration was induced by intraperitoneal injections of MPTP (80mg/kg). GIT-27 was administered intraperitoneally daily at doses of 5 and 10 mg/kg starting 24 h after the first administration of MPTP, and mice were sacrificed 7 days after MPTP induction.
Results: In this study, treatment with GIT-27 significantly reduced the alteration of PD hallmarks such as motor and non-motor symptoms, also increasing both tyrosine hydroxylase (TH) and dopamine transporter (DAT) expression and reducing the number of alpha-synuclein positive neurons. In addition, GIT-27 treatment attenuated the neuroinflammatory state modulating TLR4/NF-kB pathway and reduced reactive astrocytes and microglia as demonstrated by the modulation of GFAP and IBA-1 markers in brain samples.
Conclusions: In conclusion, this study consolidates the pathological role of TLR4 in driving neuroinflammation and highlights GIT-27 as a promising therapeutic candidate for treating neurodegenerative disorders like PD.

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REVEALING ALTERATIONS IN PROTEASOME AND IMMUNE RESPONSE IN THE SUBSTANTIA NIGRA OF PARKINSON'S DISEASE: INSIGHTS FROM GEO DATABASE AND EXPERIMENTAL MODELS

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Aims: To investigate alterations in proteasome function and immune responses in Parkinson's disease (PD) by integrating transcriptomic data from GEO. Additionally, to elucidate whether these changes are linked to the response mechanisms of neurons and PD neurons to influenza virus infection.
Methods: Gene expression data from the substantia nigra of PD patients and controls were analyzed using the GEO datasets GSE8397 and GSE20292. Batch effects were corrected using the "Combat" algorithm, and differentially expressed genes (DEGs) were identified with the "limma" package in R. GO/KEGG pathway enrichment and immune infiltration analysis of 29 immune cell types was performed. A LUHMES PD cell model was co-cultured with HMC3 microglia and infected with the A/WS/33 H1N1 influenza strain. Flow cytometry was used to analyze immune cell populations, HLA class I/II expression, and viral infection. Cytokine profiles were assessed via ELISA, while Western blotting measured alpha-synuclein phosphorylation, dopaminergic neuron death, and proteasomal/lysosomal protein degradation.
Results: DEG analysis revealed significant downregulation of CCL5, UBA7, and PSMB5, related to immune and proteasome system. GO/KEGG analysis highlighted alterations in the proteasome pathway, and immune infiltration analysis showed increased HLA-I expression in PD patients. In the PD model, flow cytometry showed reduced influenza nucleoprotein levels compared to controls (healthy neurons), while virus infection led to increased HLA-I expression in the PD group, which was in line with GEO data. ELISA data revealed elevated IL-6 and CCL2 levels in both control and PD groups following infection, while TNF-α, IL-10, IL-1β, and IL-12p70 levels remained unchanged.
Conclusions: Increased HLA-I expression in PD suggests an enhanced immune response and altered viral susceptibility. HMC3 microglia potentially protect neurons and PD cells from viral infection by regulating IL-6 and CCL2.

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PLASMATIC EXTRACELLULAR VESICLES OF PATIENTS WITH PARKINSON`S DISEASE EXACERBATE NEUROINFLAMMATION IN CELLULAR MODELS OF PARKINSON`S DISEASE

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Aims: Plasma-derived extracellular vesicles (EVs) have emerged as critical mediators in neuroinflammation, particularly in neurodegenerative diseases such as Parkinson's (PD). Much is not understood about their effect on neuronal cells and their impact on more complex models of neurodegenerative diseases. This present study explores the functional role of plasma-derived EVs in inducing neuroinflammation in SHSY5Y cells. It outlines a planned investigation into the progression of pathology and neuroinflammation by plasma-derived EVs in midbrain organoids (hMORGs) treated with preformed fibrils (PFF).
Methods: Using SEC, EVs are isolated from the plasma of PD patients (PD-EVs) and healthy control (HC-EVs) and characterized by NTA and western blot. Differentiated SHSY5Y cells were exposed to EVs from PD patients and healthy control, and neuronal viability and axonal length were evaluated using flow cytometry and immunofluorescence. We outline the experimental design for future studies involving human midbrain organoids, where preformed fibrils will be used to model Parkinson`s disease pathology, neuroinflammation will be assessed by measuring pro-inflammatory cytokines through RNA sequencing, and signalling pathways will be identified using g: Profiler. Dopaminergic neuron viability and alpha-synuclein aggregation will be analyzed.
Results: Preliminary studies on differentiated SHSY5Y cells indicate that PD-EVs displayed a higher uptake, altered neuronal viability and axonal length, and enhanced pro-inflammatory response by activating microglia. The forthcoming experiment with PFF-hMORGs is expected to reveal how PD-EVs influence PFF-induced pathology, potentially offering insights into their role in exacerbating neuroinflammation and disease progression
Conclusions: This study supports the hypothesis that peripheral, plasmatic EVs of PD patients exhibit notable neuroinflammation and neuronal degeneration, which have detrimental effects on the brain. Further research is needed to decipher their role in neuroinflammation and their overall impact on neurodegenerative disease utilizing midbrain organoid technology.

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PHYLUM VERRUCOMICROBIOTA AS A PROVOCATEUR OF PARKINSON'S DISEASE: LOWERING FAECAL SHORT CHAIN FATTY ACIDS MAY COMPOUND MUCOLYTIC ACTIVITY IN GUT.

Jennifer Yick[1], Chianna Umamahesan[1], Wenjing Wang[2], Kieran Baker[3], Bu'Hussain Hayee[4], Polychronis Pavlidis[4], David Taylor[2], Melvyn Smith[5], Sylvia Dobbs[6], R John Dobbs[2], André Charlett[7]
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Aims: To determine relationship between low faecal concentrations of short chain fatty acids (SCFAs) in Parkinson's disease (PD) and bacteriome, and whether traditional probiotics are likely to be useful.
Methods: We examined bacterial predictors of PD at phylum level in 75 participants with diagnosed-PD, 112 without. We characterised a subset (42 with PD, 74 without) by faecal SCFA concentrations, allowing for false discovery rate. A 5-day dietary diary and supplement analysis showed no probiotic use.
Results: Verrucomicrobiota had a non-linear association with PD-status in a pylum-level model containing *Pseudomonadota* and *Actinobacteriota* as positive predictors (ROC area acceptable at 0.74). Predicted probability of PD was around 0.2 when Verrucomicrobiota absent or its relative abundance <2%, rapidly rising to, and stabilising at, 0.5 for higher abundances. Of phyla in this model, Verrucomicrobiota had the strongest association with the SCFAs, butyric, proprionic and acetate, the more abundant the Verrucomicrobiota the lower the SCFAs (significant reductions of 6.7%, 4.2%, and 7.2%, respectively, for 1% increase in relative abundance). The relationship extended down to class (Verrucomicrobiae (6.6%, 4.1%, and 7.0 reductions), and from order Verrucomicrobiales to genus *Akkermansia* (6.2%, 3.9%, and 6.5% reductions, order to genus being identical in terms of reads). Size of effect for order Opitutales was greater (17.0%, 10.2%, and 19.1% reductions). Of bacteria conventionally used in probiotics, neither genus *Lactobacillus* (phylum Bacillota) nor *Bifidobacteria* (Actinomycetota) was significantly associated with SCFAs.
Conclusions: Systematic review supports *Verrucomicrobiota* being predictive of PD. Net effect of phylum was a decrease in SCFAs, despite *Akkermansia* producing SCFAs by fermenting mucin. Moreover, mucolytic activity may be harmful in PD where colitis features and there is evidence for barrier dysfunction and translocation of microbes and their products.

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MIDBRAIN ORGANOIDS INTEGRATED WITH MICROGLIA PRODUCE INFLAMMATORY RESPONSES IN AN SNCA TRIPLICATION MODEL

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Aims: Microglia are the resident immune cells of the brain and changes in microglial states play a critical role in Parkinson's disease (PD) pathology. However, 2D microglial models have been shown to have drastic transcriptional differences compared to their *in vivo* counterparts, proving problematic when used to model *in vivo* systems in PD research. In recent years, new technology has allowed for the generation of 3D human-derived midbrain organoids (hMOs) from induced pluripotent stem cells (iPSCs). We have developed an optimized protocol for integrating microglia into hMOs, yet to date no studies assessing microglia mediated pathology in hMO models of PD have been reported. Here, **our objective is to investigate microglia induced inflammatory pathology in PD using our optimized hMO-microglia model.**
Methods: For this we will assess microglia inflammatory responses in our PD hMO model through cytokine/chemokine expression and release assays assessed via qPCR and secretomic analysis respectively. We will then determine how microglial pro- and anti- inflammatory states affect PD pathology in hMOs by looking at expression of toxic synuclein aggregates and dopaminergic cell loss through immunofluorescent analysis. Additionally, pharmacological manipulation of hMOs will be performed to induce a pro- or anti-inflammatory microglia state. This will be done to assess how the enhancement or reversal of microglial inflammatory responses change the observed pathology.
Results: Preliminary results indicate an increased immune response from microglia integrated into PD hMOs both at baseline and when stimulated with LPS. Furthermore, we see decreased levels of insoluble synuclein in hMOs containing microglia indicating possible synuclein clearance.
Conclusions: The results of these experiments will deduce how PD hMOs induce microglia inflammatory responses and pathology, and how our hMO-microglia model can be applied in PD research to capture disease pathology.

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CONTRIBUTION OF CREB2 IN MEDIATING GLUTAMATE-INDUCED FERROPTOSIS IN NEURONAL CELLS

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Aims: Neuronal oxidative stress, an important factor in neurodegeneration, can be caused by different cellular mechanisms. Glutamate, an excitatory neurotransmitter in the central nervous system, is neurotoxic at high concentrations, via two different pathways, the receptor-mediated excitotoxicity and the non-receptor-mediated oxidative cytotoxicity. In the present study, we seek to examine the role of CREB2 in mediating glutamate-induced ferroptosis in neuronal cells.
Methods: HT22 cells, a mouse hippocampal neuronal cell line, were treated with glutamate to induce ferroptosis in vitro. Kainic acid-induced oxidative damage to the hippocampus in rats was used as an in vivo model. The signaling molecules along the p53-CREB2-GADD45α signaling cascade were probed with various means to determine their contributions to ferroptosis.
Results: We find that treatment of HT22 cells (a mouse hippocampal neuronal cell line) or the mouse primary neuronal culture with glutamate markedly increases CREB2 protein levels. Also, the CREB2 protein level is increased in the damaged hippocampal CA3 region of male rats following direct injection of kainic acid into this brain region. Glutamate-induced CREB2 activation in HT22 cells is preceded by accumulation of reactive oxygen species (ROS), and joint treatment with *N*-acetyl-cysteine (NAC) inhibits glutamate-induced CREB2 expression. In addition, the increase in CREB2 and GADD45α protein level following glutamate treatment is strongly reduced by PFTα (a p53 inhibitor) or p53 siRNA. Knockdown of CREB2 abrogates glutamate-induced GADD45α activation.
Conclusions: These results demonstrate that CREB2 plays an important role in mediating glutamate-induced ferroptosis in hippocampal neurons, likely via activation of the p53-CREB2-GADD45α signaling cascade.

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SPATIAL TRANSCRIPTOME ANALYSIS OF THE MYENTERIC PLEXUS AND INTESTINAL EPITHELIUM OF THE COLON IN PATIENTS WITH PD

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Aims: To investigate the gene expression profiles of the myenteric pelxus and intestinal epithelium of patients with Parkinson's disease (PD).
Methods: Five patients with PD and five normal controls who underwent radical surgery of the colon or rectum due to colorectal cancers were included in this study. Alpha-synuclein (AS) accumulation was found in the myenteric plexus in all patients with PD. We analyzed spatial-specific transcriptomic profiling on the myenteric plexus and epithelium of paraffien-embedded surgical specimens using the GeoMX Digital Spatial Profiler.
Results: Forty-one differentially expressed genes (DEGs) (36 up-regulated and 5 down-regulated) were identified in the myenteric plexus of patients with PD compared to controls. In the intestinal epithelium, 240 DEGs (81 up-regulated and 159 down-regulated) were identified. Pathway analysis showed upregulation of cytoplasmic translation, peptide biosynthetic process, and macromolecule biosynthetic process in the myenteric plexus, and upregulation of response to type II interferon, regulation of RNA metabolic process, and lymphocyte activation in the intestinal epithelium in patients with PD. In the network analysis, genes with the highest probability were CD81, LAMP1, TUBB2A, S100B, and BTF3 genes in the myenteric plexus, and AGR2, SPPL3, EGLN3, CANX, and MT1M in the intestinal epithelium. Among upregulated genes in the myenteric plexus, LAMP1 is involved in protection against oxidative stress, TUBB2A is a microtubular protein, and S100B is involved in neuronal proliferation.
Conclusions: The results suggest that simultaneous alterations of gene expression occur in both myenteric plexus and intestinal epithelium of patients with PD. Of note, neuronal regeneration mechanisms are active in the myenteric plexus, while an inflammatory process is underway in the intestinal epithelium. A spatial transcriptomic analysis of the brain and GI tract will provide a better understanding of the gut-brain axis in PD.

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MOLECULAR DRIVERS OF NEURODEGENERATION IN PARKINSON'S DISEASE: INSIGHTS FROM A DUAL GENETIC-ENVIRONMENTAL ZEBRAFISH MODEL

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Aims: Parkinson's disease is the second most common neurodegenerative disorder. There is no cure for PD, largely due to a limited understanding of early neurodegenerative mechanisms. Identifying these mechanisms is crucial for early diagnosis and treatment before excessive damage occurs. This study aims to explore these early molecular changes by investigating the synergistic effects of the *DNAJC6* F839Lfs mutation, known to cause early-onset PD in humans, and the mitochondrial toxin rotenone in a zebrafish model.
Methods: We created a knock-in zebrafish model of *DNAJC6* F839Lfs by introducing the equivalent mutation in the endogenous zebrafish gene, *dnajc6* F782fs. Zebrafish (*Danio rerio*) were selected due to their genetic similarity to humans and their capacity for intrafamily comparisons, allowing analysis of mutant and wild-type siblings raised in the same conditions. Recognising the variability in phenotypic severity and penetrance in genetic models, we implemented a dual genetic-environmental approach by exposing wild-type and mutant sibling fish to low doses of rotenone, a pesticide and mitochondrial complex I inhibitor. RNA sequencing (bulk, polyA selected) and gene-set enrichment analysis were used to explore cellular pathways disrupted across environmental (rotenone-only), genetic (*dnajc6*-only), and combination models compared to their untreated wild-type siblings.
Results: The gene-set enrichment analyses revealed that all models exhibited alterations in the proteasome pathway, amino acid metabolism, and complement activation. Notably, changes in fatty acid metabolism were observed in the genetic model, which became more pronounced in the combination model, suggesting a synergistic effect.
Conclusions: Our findings align with recent studies on *DNAJC6* knockout models and emphasise the emerging role of lipid metabolism in PD. The observed synergistic effect between the genetic mutation and environmental exposure underscores the importance of considering both factors to produce a robust PD model applicable to real-world cases.

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ANIMAL MODEL TO STUDY THE THRESHOLD OF BENEFICIARY MECHANISMS OF EXERCISE IN EARLY PARKINSON'S DISEASE

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Aims: Regular, intense exercise is recommended for PD treatment, improves motor functioning and has a potential to slow down the degeneration progress. The exact mechanisms are unknown. Up to the certain threshold of nigrostriatal system degeneration surviving dopaminergic neurons are able to compensate and maintain almost normal system functioning. Exercise could help to naturally move this threshold. The aim was to create reliable animal model of adaptation to nigrostriatal degeneration in fully controlled parameters to study particular compensation and regeneration mechanisms induced by training.
Methods: Regular training was performed for 4 weeks before and 4 weeks after unilateral 6-OHDA injection into the medial forebrain bundle. Dopaminergic nigrostriatal system was selectively and progressively lesioned in medium or large size. Locomotor activity, asymmetric paw use, apomorphine induced rotation tests, DA level and metabolism were assessed. Efficacy of training was monitored.
Results: Trained animal locomotion was not different than control already 2 weeks after lesioning. Sedentary rats locomotion was decreased permanently after large lesion and reversibly after medium lesion showing smaller potential to compensate. Level of motor dysfunction is lower in running rats than in sedentary. Asymmetric paw use showed that large lesioned, training animals did not show improvement, in contrast to medium ones. DA levels in striatum were depleted in all lesioned rats but large lesions showed much higher turnover.
Conclusions: Size of dopaminergic lesion dictates effectiveness of intense treadmill training to ameliorate some behavioral deficits in rat. Understanding of the compensatory mechanisms is necessary to prolong independent functioning of patients in multiple neurodegenerative diseases. Dopamine level does not necessarily correlate with motor function. Funding: supported by NCN 2019/35/B/NZ7/02862 and statutory funds of Maj Institute of Pharmacology PAS, Poland.

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A2-ASTROCYTE ACTIVATION BY SHORT TERM HYPOXIA RESCUE A-SYNUCLEIN PREFORMED FIBRIL INDUCED NEURONAL CELL DEATH

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Aims: In this study, we aimed to investigate whether hypoxic conditions can activate cerebral astrocytes and explore their protective effects on α-synuclein pre-formed fibril (PFF)-treated cortical neurons.
Methods: We investigated the activation levels of primary cortical astrocytes depending on various hypoxic conditions and determined the appropriate conditions for this study. Hypoxia-exposed astrocyte-conditioned medium (hypoxic-ACM) was treated on α-synuclein PFF-treated primary cortical neurons. Cell viability and α-synuclein and p-α-synuclein levels in the neurons were examined. Furthermore, we analyzed DNA expression patterns of hypoxia-exposed astrocytes.
Results: We found that short-term rather than long-term exposure to hypoxic conditions dramatically activated cortical astrocytes. The hypoxic-ACM significantly reduced the death of α-synuclein PFF-treated cortical neurons and toxic p-α-synuclein formation compared to control-ACM. Further, hypoxia-exposed astrocytes demonstrated a different DNA expression profile compared to control astrocytes.
Conclusions: Mild hypoxic condition activated cortical astrocytes, which demonstrated a protective effect on α-synuclein PFF-treated cortical neurons, at least in part, by modifying astrocyte DNA expression. Our findings provide a possible explanation on the protective effects of smoking on PD pathogenesis and suggest that hypoxic conditions can be used clinically as a disease-modifying strategy.

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DEVELOPMENT OF A-SYNUCLEIN-SPECIFIC NANOBODIES FOR TARGETING AGGREGATION IN PARKINSON'S DISEASE

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Aims: Aims: Parkinson's disease (PD) is marked by the accumulation of α-synuclein (α-syn) aggregates, which form Lewy bodies and drive the progression of the disease and its associated neuropathological symptoms. Therefore, identifying molecules capable of preventing α-syn aggregation and inhibiting Lewy body formation is crucial for developing therapies. In this study, we aim to develop biomolecules, specifically nanobodies (Nbs) – the antigen-binding domains derived from heavy-chain-only antibodies, Nb-04 and Nb-40 and their bivalent forms. These nanobodies are designed to be conformation-specific, targeting the aggregated forms of α-syn.
Methods: Methods: We utilized our conformation-specific nanobodies, Nb-04 and Nb-40, to assess their specificity for α-syn monomers and fibrils across varying concentrations. We evaluated their binding to other proteins within the synuclein family as well as neuronal proteins exhibiting beta-sheet structures. To further investigate their therapeutic potential, we tested the nanobodies' ability to inhibit α-syn aggregation using the Thioflavin-S (Th-S) assay. Lastly, we examined the efficacy of our nanobodies in staining Lewy bodies (LB) and Lewy neurites (LN) across different brain regions in post-mortem samples from Parkinson's disease (PD) and dementia with Lewy bodies (DLB) cases.
Results: Results: Our nanobodies exhibited strong specificity for α-syn fibrils, with no cross-reactivity observed with α-syn monomers or other neuronal proteins. Additionally, the nanobodies effectively inhibited α-syn aggregation in the Thioflavin-S assay. Moreover, Nb-04 and Nb-40 successfully stained LB and LN across multiple brain regions in post-mortem samples from PD and DLB cases.
Conclusions: Conclusion: Our findings underscore the potential of Nb-04 and Nb-40 as promising candidates, demonstrating specificity for α-syn aggregates, while sparing monomers—critical for minimizing off-target effects and preserving the normal physiological functions of α-syn. These nanobodies show great promise for both therapeutic and imaging applications.

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STUDYING THE EFFECTS OF EXERCISE ON GASTROINTESTINAL HEALTH AND ALPHA-SYNUCLEIN AGGREGATION THROUGH HUMAN DERIVED FOXINSIGHT DATA AND MECHANISTIC STUDIES IN C. ELEGANS MODELS OF PARKINSON'S.

Minna Schmidt[1], Julie Andersen[1], Gordon Lithgow[1], Jeremy Tachiki[2], Seth Ashby[3], Suzanne Angeli[3]
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Aims: Research has shown that physical exercise (Ex) helps to mitigate the progression of Parkinson's disease (PD), an age-related neurodegenerative disorder involving alpha-synuclein (alpha-syn) aggregation. Our work currently involves studying the effect of Ex on gastrointestinal (GI) health in those with PD through FoxInsight, a program amassing patient and control questionnaire, microbiome, and genetic data. In addition, we aim to understand the underlying mechanisms invoked with Ex by working with *C. elegans*, which have been shown to experience Ex mechanisms similar to mammals. Our prior publication showed that a short bout of swimming Ex significantly reduced alpha-syn aggregation in a *C. elegans* model of PD. Currently, our work involves administration of lactate (LA) or lactic acid bacteria (LAB), which are increased with Ex, to *C. elegans* models of PD in order to assess alpha-syn.
Methods: In FoxInsight, we have analyzed patient questionnaire data concerning Ex and stool health. In *C. elegans* studies, worms are treated with LA or yogurt containing LAB and alpha-syn aggregation, swimming ability, lifespan, and dopaminergic neuronal health is assessed.
Results: Our analysis of FoxInsight data has shown that moderate Ex, versus light or strenuous Ex, correlates with reduced constipation, a common non-motor symptom of PD. Our studies in *C. elegans* show that LA and yogurt-based LAB treatment improve swimming ability, extend lifespan and protect dopaminergic neurons from alpha-syn proteotoxic stress.
Conclusions: Our results from FoxInsight suggest that Ex improves GI health and we aim to address whether this benefit may occur as a result of increased LAB and therefore bacterial derived LA production. Our future studies will aim to work with FoxInsight data to determine the effects of Ex on the microbiome, as well as the therapuetic effects of LA/LAB treatment for PD.

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A SYSTEMATIC DRUG REPOSITIONING PIPELINE FOR PARKINSON'S DISEASE TREATMENT USING GRAPH DEEP LEARNING ON MULTI-OMICS DATASETS

Zhihao Wan, Shaohua Qi, Bill Chan, Zheng Yin, Hong Zhao, Stephen Wong
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Aims: To leverage graphical deep learning and multi-omics datasets from 41 Parkinson's disease (PD) cell lines for identifying druggable targets that inhibit α-synuclein (α-Syn) aggregation and to validate these predictions using 3D dopaminergic neuronal cell culture and PD mice models.
Methods: We integrated extensive genetic, epigenetic, regulatory, cellular imaging, and transcriptomic datasets of 41 monogenic PD (LRRK2+, GBA1+, and SNCA+) cell lines provided by the Foundational Data Initiative for Parkinson Disease (FOUNDIN-PD). A deep learning pipeline incorporating Graph Neural Networks and autoencoders was developed to analyze multi-omics datasets for uncovering and modifying novel genetic and molecular risk factors. Using this pipeline, we identified PD-associated genotypes linked to α-synuclein aggregation ($R > 0.9$) across multiple time points during neuronal differentiation. We predicted four compounds with potential properties against α-Syn aggregation. Candidates and their combinations were validated *in vitro* using 3D dopaminergic neuronal cell cultures. A high content screening scanner (ImageXpress Micro, Molecular Devices) was used to assess α-Syn conformation and aggregation status. Pharmacokinetics and drug toxicity will be evaluated through PD mice models.
Results: Monogenic PD cell lines harboring LRRK2+, GBA1+, and SNCA+ mutations exhibited distinct forms of synucleinopathies, with unique conformation and aggregation patterns. The identified drugs regulate α-Syn's nucleocytoplasmic transport via ubiquitin-dependent proteasome degradation. These findings suggest potential therapeutic avenues for mitigating toxic α-Syn accumulation in PD.
Conclusions: Our systematic drug repositioning pipeline, based on graphical deep learning and multi-omics FOUNDIN-PD datasets, identified novel anti-α-Syn drug candidates targeting key pathogenic processes. Modulating these targets, either individually or in combination, offers promising strategies for optimizing α-Syn regulation to yield functional and neuroprotective outcomes. This research paves ground for further investigations, leveraging multi-omics data to advance our understanding of Parkinson's disease.

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FOCUSING ON THE INTERACTION BETWEEN A-SYNUCLEIN AND NEUROTRANSMITTERS: A KEY PATHWAY TO UNRAVEL THE PATHOGENESIS OF PARKINSON'S DISEASE

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Aims: α-syn and a series of neurotransmitters including catecholamine (catechol) play an important role in the PD's pathogenesis and the mutual effects between neurotransmitters and α-syn are complex and multifaceted. This study focused on the relationship between α-syn and various neurotransmitters, hoping to unravel the PD's pathogenesis and advance the diagnosis and treatment.
Methods: This study summarized previous literatures on the interaction between α-syn and various neurotransmitters, described their effects and mechanisms both in vivo and in vitro, and finally concluded that the interaction between α-syn and various neurotransmitters is an adjunct or helper for PD
Results: There is a strong and significant interaction between α-syn and neurotransmitters in PD. For the effects of α-syn on neurotransmitters, on the one hand, α-syn is involved in various synaptic vesicular trafficking processes in general, including release and reuptake. On the other hand, α-syn has specific effects on certain neurotransmitters. For example, α-syn modulated the synthesis of catechols by affecting key enzymes such as tyrosine hydroxylase(TH) and aromatic acid decarboxylase(AADC). Moreover, α-syn exerted different modulation effects on glutamate transporters'family in different cells. For the effects of neurotransmitters on α-syn, various catechols promoted oligomerization and inhibited fibrillation of α-syn in several mechanisms. Additionally, catechols regulated α-syn quinonylation. Also, serotonin and GABA were also involved in aggregation and secretion of α-syn, respectively. The interactions between α-syn and catechols are most important , however, it is still hard to tell whether the interactions are accomplices or helpers in PD.
Conclusions: It is worthwhile to conduct more profound research on interations between different types of α-syn and neurotransmitters to figure out what proportion and form of interactions that contribute to neurotoxic or neuroprotective effects in PD.

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REPAIR CELL THERAPY FOR COGNITION IN PARKINSON'S DISEASE: A CLINICAL TRIAL TARGETING THE NUCLEUS BASALIS OF MEYNERT

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Aims: The greatest unmet need for the neurodegenerative diseases of AD, DLB, PDD, and PD are therapies that can stabilize or maintain cholinergic and/or dopaminergic circuits. Memory and cognitive deficits observed in these disorders are largely attributable to a loss of cholinergic function in the brain, primarily within the nucleus basalis of Meynert (NBM). Our clinical trials have focused on delivering repair cell tissue (RCT), harvested from autologous sural nerves, to areas of the brain affected by neurodegenerative disease. *The major goal of this trial (*NCT06683378,1R01AG081356-01A1) *is to identify the feasibility and safety of bilateral implantation of RCT to the NBM to improve the function of cholinergic neurons in dementias*.
Methods: Twenty-four participants diagnosed with PD, selected, qualified, and agreed to undergo DBS surgery of the globus pallidus internus, will be followed for 24 months as part of a trial to receive, at the time of DBS surgery, RCT implanted bilaterally into the NBM (n=12) or an alternate target, the substantia nigra, that primarily controls motor function as control (n=12).
Results: Feasibility objectives will be based on the number of participants receiving PNT delivery and the number of participants completing the 12-month and 24-month study visits. For the safety objective, the number of serious adverse events related to the procedure will be collected for 24 months following surgery. Cognitive safety endpoints at 12 and 24 months following surgery will be defined as ≥ 1.5 standard deviation decrement relative to the participant's estimated pre-morbid functioning.
Conclusions: This study is a critical step for identifying the feasibility of this NBM vs. SN design for trialing in subsequent multicenter, Phase II studies and for continuing to investigate this approach as an eventual monotherapy for treatment of the AD Spectrum.

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NOVEL FINDINGS ON CCR1 RECEPTOR IN CNS DISORDERS: A PATHOGENIC MARKER USEFUL IN CONTROLLING NEUROIMMUNE AND NEUROINFLAMMATORY MECHANISMS IN PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is recognized as the second most common neurodegenerative disease worldwide. Even if PD etiopathogenesis is not yet fully understood, in recent years, it has been advanced that a chronic state of inflammation could play a decisive role in the development of this pathology, establishing the close link between PD and neuroinflammation. In the broad panorama of inflammation and its several signaling pathways, the C-C chemokine receptor type 1 (CCR1) could play a key pathogenic role in PD progression, and could constitute a valuable target for the development of innovative anti-PD therapies.
Methods: In this study, we probed the neuroprotective properties of the CCR1 antagonist BX471 compound in a mouse model of MPTP-induced nigrostriatal degeneration. BX471 treatments were performed intraperitoneally at a dose of 3 mg/kg, 10 mg/kg, and 30 mg/kg, starting 24 h after the last injection of MPTP and continuing for 7 days.
Results: From our data, BX471 treatment strongly blocked CCR1 and, as a result, decreased PD features, also reducing the neuroinflammatory state by regulating glial activation, NF-κB pathway, proinflammatory enzymes, and cytokines overexpression. Moreover, we showed that BX471's antagonistic action on CCR1 reduced the infiltration of immune cells, including mast cells and lymphocyte T activation. In addition, biochemical analyses carried out on serum revealed a considerable increase in circulating levels of CCR1 following MPTP-induced PD.
Conclusions: In light of these findings, CCR1 could represent a useful pathological marker of PD, and its targeting could be a worthy candidate for the future development of new immunotherapies against PD.

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ROLE OF THE CYTOKINE ENAMPT IN CONTROLLING NEUROINFLAMMATION IN PARKINSON DISEASES

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Aims: Parkinson's disease (PD), a chronic and progressive neurodegenerative movement disorder, is characterized by the deterioration of motor activities due to the impairment of the nigrostriatal dopaminergic system which in turn also negatively affects other neurotransmission systems. Lipid peroxidation, oxidative stress, mitochondrial dysfunction associated with inflammation are mediators of the progression of dopaminergic neuron degeneration. Recently, extracellular nicotinamide phosphoribosyltransferase (eNAMPT), a key enzyme involved in NAD synthesis has been identified as one of the most significant dysregulated genes in PD highly involved in neuroinflammation through the activation of Toll-Like Receptor Type 4 (TLR4). Based on these findings the aim of this study was to assess the possible neuroprotective effect of anti-eNAMPT antibodies called C269 in PD pathogenesis.
Methods: The nigrostriatal degeneration was induced by intraperitoneal injections of MPTP (80 mg/kg). C269 was administered intraperitoneally daily at dose of 1 mg/kg every 3 days 24 h after the first administration of MPTP, and mice were sacrificed 7 days after MPTP induction.
Results: In this study, treatment with C269 reduced MPTP-induced behavioral impairments and the alteration of PD hallmarks, reducing the number of a-synuclein positive neurons and increasing tyrosine hydroxylase expression. Moreover, C269 prevented dopamine transporter (DAT) depletion in the substantia nigra and in the striatum of MPTP mice. In addition, C269 significantly reduced eNAMPT levels e modulated different immune cell populations.
Conclusions: In conclusion, this study highlighted that inhibition of eNAMPT by C269 administration could be a potential therapeutic agent for the treatment of neurodegenerative disorders such as PD.

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THE CHAPERONE DOMAIN BRICHOS AS A TREATMENT FOR ALPHA-SYNUCLEINOPATHIES? IDENTIFYING THE MOLECULAR BINDING MECHANISM OF BRICHOS TO ALPHA-SYNUCLEIN

Willem Hendrik Molenkamp[1], Tanguy Le Marchand[2], Mathieu Coincon[3], Rakesh Kumar[1], Jan Johansson[1], Marta Carroni[3], Guido Pintacuda[2], Axel Abelein[1]
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Aims: BRICHOS is a domain of the Bri2 protein which is able to inhibit protein aggregation and associated cellular toxicity for the amyloid-β peptide and IAPP. Recently, we also showed its effectiveness against the aggregation of α-synuclein. By specifically inhibiting nucleation reactions catalyzed on the amyloid fibril surface, the generation of small and toxic oligomers is efficiently reduced, eventually leading to reduced toxicity *in vitro* and in treatment studies in animal models. BRICHOS apparently binds to specific sites on the fibrils, which act as aggregation hotspots for formation of new oligomers. In this project, we aim to determine how BRICHOS targets such catalytic sites and binds to α-synuclein fibrils.
Methods: Human full-length alpha-synuclein and the monomer mutant Bri2 BRICHOS R221E were recombinantly produced and incubated under different conditions. The structural characteristcs of alpha-synuclein fibrils formed with or without the presence of Bri2 BRICHOS were studied by solid-state nuclear magnetic resonance (ssNMR) with ^{1}H-detection, cryo-electron microscopy (cryo-EM) and proteinase K digestion.
Results: Our first results suggest that Bri2 BRICHOS is able modulate the alpha-synuclein fibril morphology, indicated by specific chemical shift changes in the ssNMR spectra. We are currently working on determining the fibril structures and identifying the binding site of Bri2 BRICHOS by combining solid-state NMR and cryo-EM.
Conclusions: Understanding how Bri2 BRICHOS binds to the fibril surface is important for the development of mechanism-based therapeutics. Moreover, since BRICHOS targets the sites where new toxic oligomers are formed, this study could provide novel molecular insights about the mechanism of toxicity in synucleinopathies.

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INVESTIGATING THE NEUROPROTECTIVE POTENTIAL OF SMALL MOLECULE REGULATORS OF THE BMP-SMAD PATHWAY IN IN VITRO MODELS OF RELEVANCE TO PARKINSON'S DISEASE

Rebekah Bevans[1], Aideen Sullivan[2,3,4], Gerard O'Keeffe[1,2,4], Louise Collins[1,2,5]
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Aims: Recent interest in neurotrophic factor therapy (NTF) has focused on delivering NTF genes or recombinant proteins to the midbrain for the treatment of Parkinson's Disease (PD). Despite initial *in vivo* success, all trials have failed to meet their primary endpoints. Consequently, there is growing interest in identifying alternative strategies to protect dopaminergic (DA) neurons from degeneration. A significant challenge with NTFs is that they require direct administration to the brain due to being rapidly metabolised *in vivo* and an inability to cross the blood-brain barrier (BBB) in adequate doses. One strategy is to identify small molecules or biologics that can cross the BBB and selectively activate downstream targets of specific NTFs. The BMP-Smad signaling pathway is known for its neuroprotective effects on midbrain DA (mDA) neurons. Here we aim to investigate the neuroprotective potential of small molecule activators of BMP-Smad signalling.
Methods: We investigated whether novel small molecule activators of BMP-Smad signalling could protect against PD-related insults *in vitro*. SH-SY5Y cells and embryonic day (E) 14 ventral mesencephalon (VM) cultures were treated with varying doses of two small molecules. Cells were also treated with the neurotoxin 6-hydroxydopamine (6-OHDA) or transfected with plasmids overexpressing alpha-synuclein (αSyn).
Results: Small molecule treatment significantly increased neurite length and protected against 6-OHDA and aSyn-induced insults. A BMP reporter assay revealed that both small molecules upregulated BMP-Smad-dependent transcription in SH-SY5Y cells.
Conclusions: These results indicate that novel small molecules enhance BMP-Smad-dependent transcription, exerting a neuroprotective effect against PD-related insults *in vitro*. This finding warrants further *in vivo* testing.

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RELATIONSHIP BETWEEN SLEEP QUALITY AND COGNITIVE FUNCTION IN PARKINSON'S DISEASE -2

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Aims: In PD, the frequency of cognitive decline increases with progression, but there are few studies on the pathological condition that concerned of the onset of cognitive impairment. As a sleep disorder in PD, RBD: REM sleep behavior disorders is well known, however, few studies were reported among sleep architecture abnormalities, frequency of sleep apnea and cognitive function on PD. The purpose of this study to clarify this relation between sleep disorders and cognitive decline by overnight-EEG analysis and the cognitive function test in PD.
Methods: We examined 45 people with PD who were admitted in our hospital for a purpose of having rehabilitation (female 35, male 20). Average duration of illness of PD is 9years and mean age of examination is 70.3 years old. They conducted a cognitive function test every year if possible. In their admission, they checked overnight -EEG with apnea-monitoring. Exclusion criteria are 1. over 85 years old, 2. MMSE: Mini-mental State Examination <25, 3. Duration of illness20<,5 advanced physical disability on language.
Results: People who did not revealed REM sleep and no deep sleep acknowledged a drop in points in MMSE compared to those showed both. Frequency of sleep apnea was same as normal aged people.
Conclusions: We investigated the relation between cognitive function and sleep qualities such as sleep architecture, positive or negative REM sleep, RWA, obtained from overnight-EEG for PD patients. In cases showing only shallow sleep with sleep fragmentation, cognitive deterioration was marked, however, cognitive function was obtained by improving sleep architectures. Important thing is improved sleep architecture for cognition.

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LONGITUDINAL ASSOCIATION BETWEEN DPP4 USE AND MORTALITY IN DIABETIC PARKINSON'S DISEASE PATIENTS

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Aims: The role of dipeptidyl peptidase 4 (DPP4) inhibitors in diabetes management is critical. However, it is still unclear whether the use of DPP4 inhibitors is associated with mortality in patients with Parkinson's disease (PD). This study evaluates the risk of death and survival probability among patients with PD, with or without DPP4 inhibitor treatment.
Methods: A retrospective cohort study using national claims databases of the 2009-2019 National Health Insurance Service (NHIS). Kaplan-Meier survival analysis and Cox proportional hazard regression model were utilized to examine the survival rates between the two groups. The study cohort consisted of 1,093 adults diagnosed with PD and also diagnosed with type 2 diabetes between 2009 and 2019. The study subjects were categorized into two groups: 1) those with PD and type 2 diabetes (n = 557) and those with PD and type 2 diabetes who were further treated with DPP4 inhibitors (n = 536).
Results: The average age of the study subjects was 73.40 years (SD = 7.67) and the majority were female (n = 676, 61.57%). Cox proportional hazard regression model revealed that patients who did not take DPP4 inhibitors had a higher risk of death compared to those taking DPP4 inhibitors (hazard ratio [HR] = 1.266, 95% confidence interval 1.036, 1.546). Female, older age at the PD diagnosis, and patients with more than two comorbidities were associated with a higher risk of death (all HR > 1.0, all p < 0.05).
Conclusions: The findings underscore the complexity of managing PD and diabetes, suggesting that DPP4 inhibitors could offer some protective effect against mortality in these patients, with implications for clinical practice and patient care.

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"NEUROTANGO AS A NON-PHARMACOLOGICAL THERAPY TO IMPROVE SYMPTOMS, AND QUALITY OF LIFE IN A COHORT OF PATIENTS WITH PARKINSON'S DISEASE"

Susana Montoya Jaramillo[1], Lucia Madrigal Zapata[1], David Aguillón[2], Francisco Lopera[2]
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Aims: Parkinson's disease is a neurodegenerative, progressive disorder characterized by the presence of bradykinesia, rigidity, resting tremor, and difficulty in performing manual tasks. Studies have shown that physical activity such as dancing brings benefits in physical performance and quality of life.We aim to evaluate the impact of Neurotango on motor, emotional, and quality of life levels in patients with Parkinson's disease.
Methods: Population and study design : Single group trial of 10 patients with Parkinson's disease who participate in tango classes for 12 months, once a week for 120 minutes. **Measures:** Outcome parameters were collected at three points in time (first, sixth, and twelfth months) and assess motor, emotional symptoms, and quality of life using standardized instruments: Parkinson's Disease Questionnaire-39 (PDQ-39), Beck Depression Inventory-II (BDI-II), Berg Balance Scale, and Time Up and Go test.
Statistical analysis: Baseline continuos data were presented as a mean standard deviation and T-test was employed to assess statistical differences at different points in time.
Results: No improvements were found for all outcomes with the exception of the **Timed Up and Go test (p=0.020)**, with an average time of 12.76 ± 2.89, 10.46 ± 1.30 and 9.42 ±1.66 at the first, second and third time points, respectively.The mean number of second of the Timed Up and Go test was reduced 3,3 between first and third intervention.
Conclusions: The improvements in gait demonstrated in the reduction of the Timed Up and Go test times may be due to its similarity to the walking movements performed constantly during classes. We consider that the other test that did not present statistically significant differences, could be due to lack of statistical power , and a larger cohort could help to better visualize actual differences.

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HIPPOCAMPUS-TO-VENTRICLE RATIO REVEALS STEEPER AGE-RELATED NEURODEGENERATION IN PARKINSON'S DISEASE COMPARED TO CONTROLS

Sofia Fernandez-Lozano[1,2], Victoria Madge[1,3], Madeleine Sharp[2], Alain Dagher[1,4], Ronald Postuma[4], Edward Fon[2], D Louis Collins[1,2,3]
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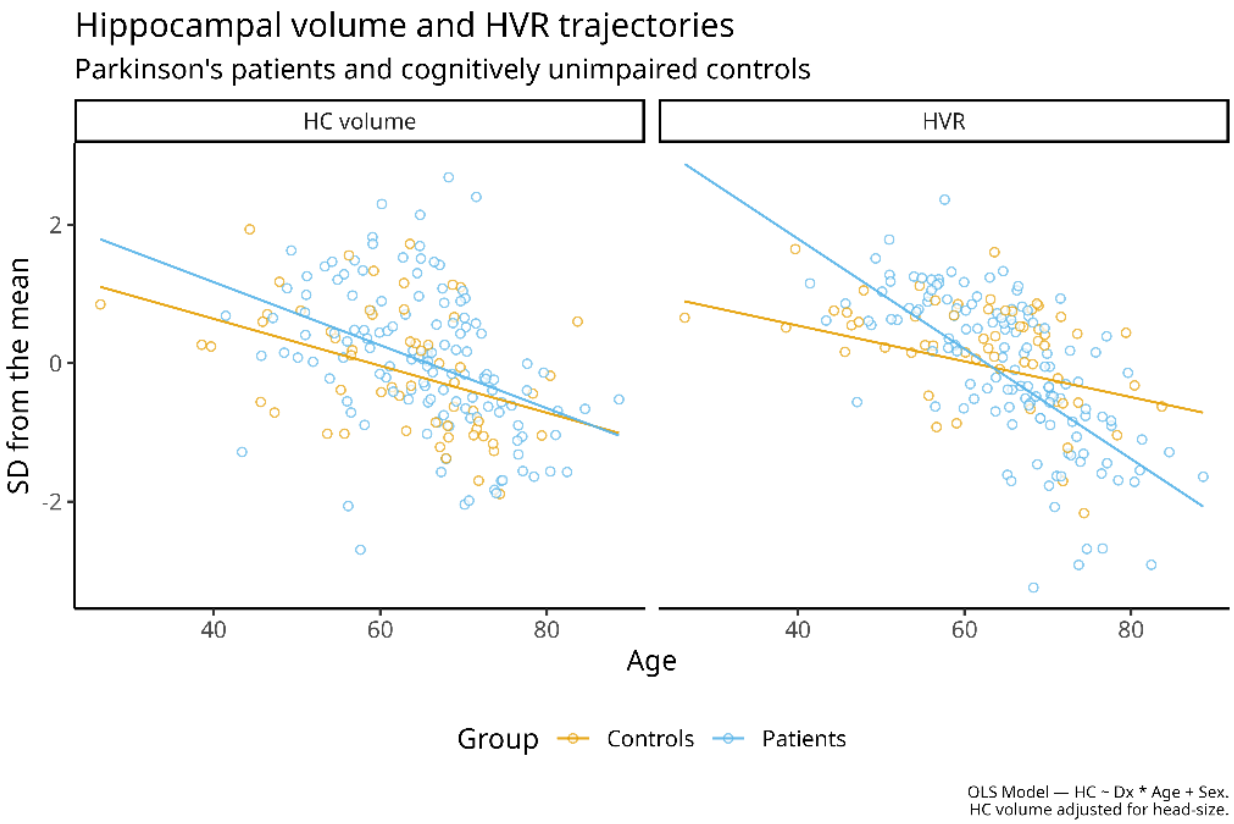
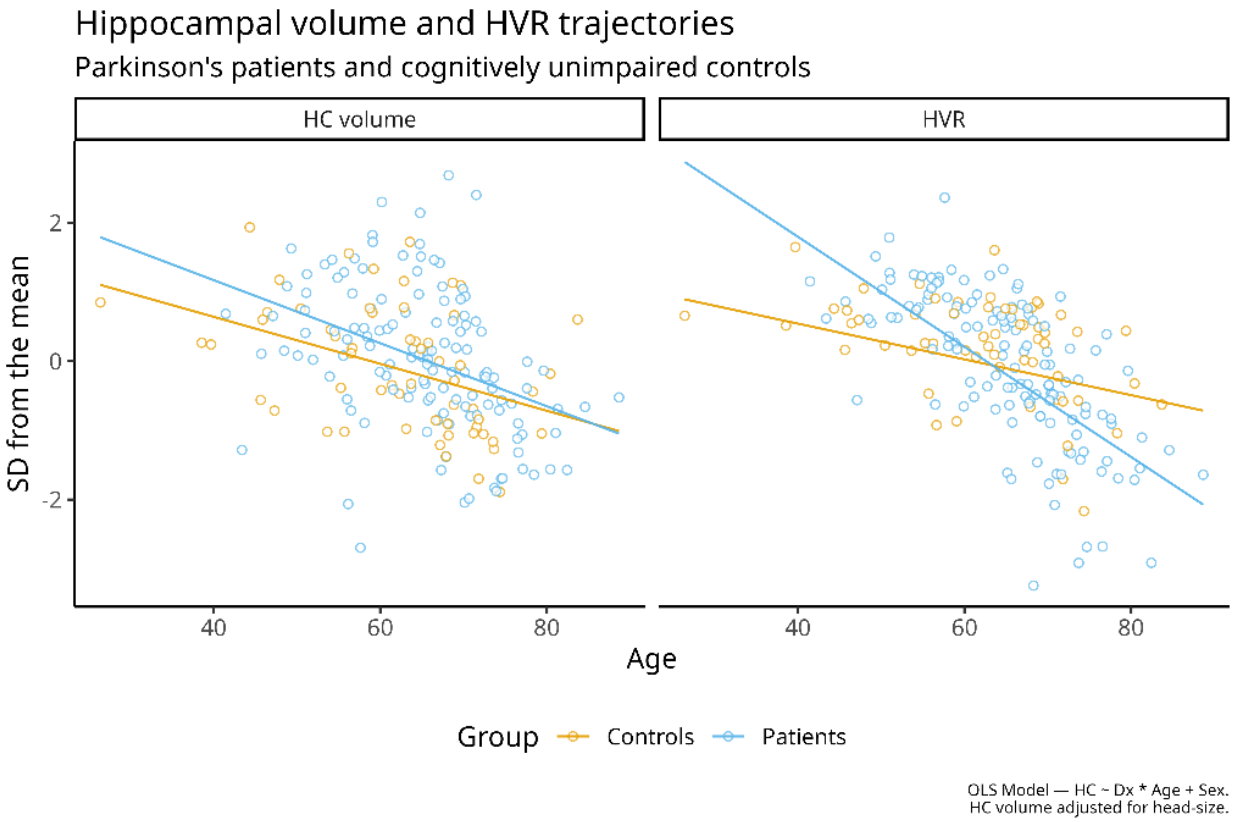
Aims: Objectives
Volumetric studies of the hippocampus (HC) have produced mixed results. We aimed to determine if the Hippocampus-to-Ventricle Ratio (HVR), a more sensitive measure than HC volume, clarifies the role of mediotemporal neurodegeneration in Parkinson's disease (PD) compared to cognitively unimpaired controls (UC).
Methods:
Using T1-weighted MRI from the Québec Parkinson Network (QPN) (131 PD patients and 58 UC subjects), we segmented the HC and surrounding temporal horns of the lateral ventricles (VC) with a Convolutional Neural Network. We calculated the HVR [HC / (HC + VC)]. We also adjusted the HC volume for head-size (HCvol). We assessed the interaction between age and PD diagnosis, by fitting linear regression models for both HCvol and HVR. Both HCvol and HVR were scaled, and age was centered; sex was added as a covariate.





Results: Our analyses revealed no significant between group difference in HCvol (β = 0.25, p = 0.11) or HVR (β = -0.05, p = 0.67). While both measures showed similar rates of HC degeneration with age (HCvol, β = -0.03; HVR, β = -0.03; p < 0.01), PD patients exhibited a greater rate of neurodegeneration in HVR compared

to UC (β = -0.05, p < 0.001), which was not observed with HCvol (β = -0.01, p = 0.41). The HVR also provided a better model fit compared to HCvol (adjusted R2: 0.44 vs 0.14; Residual SE: 0.75 vs 0.92).

Conclusions: Our results provide evidence of the HVR being a more sensitive metric for detecting age-related neurodegeneration in Parkinson's disease compared to traditional HC volume measurements. This finding underscores the HVR's potential as a valuable tool in neurodegeneration research.

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BINDING ADAPTABILITY OF CHEMICAL LIGANDS TO POLYMORPHIC A-SYNUCLEIN AMYLOID FIBRILS

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Aims: α-Synuclein (α-syn) assembles into structurally distinct fibril polymorphs seen in different synucleinopathies, such as Parkinson's disease and multiple system atrophy. Targeting these unique fibril structures using chemical ligands holds diagnostic significance for different disease subtypes. However, the molecular mechanisms governing small molecule interacting with different fibril polymorphs remain unclear.
Methods: Here, we investigated the interactions of small molecules belonging to four distinct scaffolds, with different α-syn fibril polymorphs. Using cryo-electron microscopy, we determined the structures of these molecules when bound to the fibrils formed by E46K mutant α-syn, and compared them to those bound with wild-type α-syn fibrils.
Results: Notably, we observed that these ligands exhibit a remarkable binding adaptability, as they engage distinct binding sites across different fibril polymorphs. This behavior sharply deviates from the typical ligand interactions observed with well-defined 3D pockets in native globular proteins. In addition to the adaptability observed, cryo-EM structures reveal that each molecule demonstrates a preference for specific binding sites and geometries when recognizing various polymorphs. While the molecular scaffold primarily steered the binding locations and geometries on specific sites, the conjugated functional groups further refined this adaptable binding by fine-tuning the geometries and binding sites.
Conclusions: Overall, our finding elucidates the adaptability of small molecules binding to different fibril structures, which sheds light on the diagnostic tracer and drug developments tailored to specific pathological fibril polymorphs.

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CLINICAL CHARACTERISTICS OF PARKINSON'S DISEASE PATIENTS WITH NORMAL FINDINGS ON I-123 MIBG SCAN

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Aims: It is well known that in Parkinson's disease (PD), I-123 MIBG scan shows reduced cardiac uptake from the early stages. This characteristic is used to differentiate PD from other parkinsonian syndromes. However, some PD patients show normal I-123 MIBG scan results. This study aims to analyze the clinical characteristics of PD patients with normal findings on I-123 MIBG scans.
Methods: The study included 194 PD patients. Patients were classified into normal and abnormal groups based on the delayed heart-to-mediastinal ratio (dHMR) of 1.8 from the I-123 MIBG scan. The two groups were compared regarding functional striatal activity (FSA) from the F-18 FP-CIT scan, neuropsychological, and autonomic function tests.
Results: Based on I-123 MIBG scan findings, 43 patients (22.2%) were classified in the normal group, and 151 patients in the abnormal group. There was a significant difference between the two groups in terms of dHMR (1.89 ± 0.20 vs 1.34 ± 0.14, $p < 0.001$) and washout rate (-1.56 ± 10.76 vs 22.36 ± 19.98, $p < 0.001$). FSA measured by F-18 FP-CIT PET significantly differed between the two groups (48.93 ± 16.94 vs 39.75 ±14.10, $p = 0.001$). No statistically significant differences were found between the two groups regarding gender, age, body mass index, MMSE, disease duration, HY stage, and UPDRS score. In autonomic function tests, the CASS score was significantly lower in the normal group (2.62 ± 1.73 vs 3.75 ± 2.25, $p = 0.005$), and the cardiosympathetic score showed a significant difference (0.98 ± 1.03 vs 1.49 ± 1.34, $p = 0.005$).
Conclusions: PD patients with normal I-123 MIBG scan findings showed no significant differences in motor function compared to those with abnormal findings but appeared to have better-preserved autonomic function.

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CHRONOBIOTIC USE OF MELATONIN IMPROVES DAT-BINDING IN IRBD

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Aims: Isolated REM-sleep behavior disorder (iRBD) is recognized as a prodromal state of clinical α-synucleinopathies such as Lewy-body dementia and Parkinson's disease. A pathophysiologic hallmark of α-synucleinopathies is nigrostriatal dopaminergic impairment, with dopamine-transporter(DaT)-SPECT imaging considered best available prognostic and monitoring marker. DaT-binding is reported to decrease with healthy aging by 4-10% per decade,accelerated to 4-12% per year iRBD patients. We have introduced melatonin as a treatment option for iRBD. Aim of the study was to evaluate effects of melatonin on DaT-SPECT imaging in iRBD patients.
Methods: In a prospective, longitudinal, observational, single-center study we performed at least two DaT-SPECTs in 97 iRBD patients treated with melatonin as a chronobiotic (i.e. administration always-at-the-the-same-clock-time;10-11p.m.-corrected for chronotype); 28 patients were excluded mainly due to change of psychotropic drugs known to influence DaT.
Results: After mean follow-up of 3.6yrs, only 21/69 patients (11female; mean age 71±6yrs) showed specific binding ratios (SBR) in most affected region (MAR, predominantly right posterior putamen) comparable to usually reported declines with iRBD. In contrast, 7 had declined SBR at a rate comparable to healthy aging, while 41 had actually improved SBR. Improvement after one year (SBR of MAR; $F_{1,31}$=23.748;p>0.001) and two years was significant ($F_{1,24}$=4.648;p=0.041). After four years half of the patients showed a higher SBR than baseline (23vs.24patients), though this was not significant. 47/69 of our patients at baseline met established criteria for an advanced state.
Conclusions: To the best of our knowledge, present data give first evidence for a consistent increase in DaT-binding ratios in nigrostriatum over time in a cohort of patients with iRBD. In addition, the previously reported persisting effect of melatonin on RBD symptoms suggest that melatonin, when used as a chronobiotic, may have a disease-modifying effect in prodromal α-synucleinopathies.

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EXPLORING THE RELATIONSHIP BETWEEN [11C]-DTBZ PET AND NEUROMELANIN-SENSITIVE MRI IN PARKINSON'S DISEASE, A PILOT STUDY

Victoria Madge[1,2], Lydia Chougar[1,3], Alain Dagher[1,3], Madeleine Sharp[3], Ronald Postuma[3], Edward Fon[3], Jean-Paul Soucy[1,4], D Louis Collins[1,2,3]
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Aims: This study explores the relationship between substantia nigra (SN) integrity, assessed using neuromelanin-sensitive (NM) MRI, and striatal dopaminergic density, measured with the [11C](+)-dihydrotetrabenazine (DTBZ) PET radiotracer, in individuals with Parkinson's Disease (PD), marking the first comparison of these imaging modalities in this context.
Methods: Eight PD patients (4 female; Age: 67.41 +/- 8.75, Disease duration: 6.44 +/- 6.17; UPDRS-III score: 26.25 +/- 11.78; Most-affected side: 4 right, H&Y: 2.13 +/- 0.35) underwent NM-sensitive MRI, and a 60-minute [11C]-DTBZ PET scan within three months, both during dopaminergic medication ON-state. DTBZ binding potentials from executive, limbic, and sensorimotor striatal subregions were calculated by normalizing to cerebellar grey matter in a compartmental modeling analysis. The SN was segmented using an in-house NM-MRI atlas. SN volume was calculated from voxels in the NM-MRI atlas with intensities above the 95th percentile of cerebral peduncle intensity (as reference region) and normalized to total intracranial volume. SN NM intensity was measured for the entire SN and the three functional subregions using the reference region for normalization. Statistical correlations were computed for both the most and least affected sides using Spearman's rank, controlling for age and sex.
Results: Significant correlations were observed between the DTBZ sensorimotor area of the striatum and SN volume ($R=0.96$; $p<0.005$) as well as SN NM intensity ($R=0.94$; $p<0.005$) on the most-affected side. While no significant correlations were found with other striatal subregions, especially on the least-affected side, trending correlations emerged between sensorimotor regions of the SN and striatum on the most-affected side ($R=0.78$; $p=0.06$).
Conclusions: SN integrity, measured by volume or intensity, is correlated with dopaminergic density in the sensorimotor region of the striatum (nigro-striatal pathway). Future work will test this in an increased sample size.

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DETECTION OF PRODROMAL SYNUCLEINOPATHIES USING A HIGHLY SENSITIVE SEEDING AMPLIFICATION IMMUNOASSAY IN IDIOPATHIC REM SLEEP BEHAVIOR DISORDER

Ilham Abdi[1], Indulekha Sudhakaran[1], Simona Ghanem[1], Nishant Vaikath[1], Vasilios Constantinides[2], Elizabeth Kapaki[2], Laura Parkkinen[3], Wilma Van De Berg[4], Daniel Erskine[5], Kostas Vekrellis[6], Britt Mollenhauer[7], Michael Schlossmacher[8], Omar El-Agnaf[1]
[1]Hamad Bin Khalifa University, Qatar Biomedical Research Institute, Doha, Qatar, [2]National and Kapodistrian University of Athens, Department Of Neuroscience, Athens, Greece, [3]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom, [4]Vrije Universiteit Amsterdam1081 HZ Amsterdam, Department Of Anatomy And Neurosciences, Amsterdam, Netherlands, [5]Newcastle University, Translational And Clinical Research Institute, Newcastle, United Kingdom, [6]Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece, [7]University Medical Centre Göttingen, Department Of Neurology, Göttingen, Germany, [8]Ottawa Hospital Research Institute, Ottawa, Canada

Aims: Idiopathic REM sleep behavior disorder (iRBD) is recognized as a prodromal state of Parkinson's disease and other synucleinopathies. The aim of this study was to assess the potential of the Seeding Amplification ImmunoAssay (SAIA) as a sensitive and specific diagnostic tool for detecting alpha-synuclein seeds in cerebrospinal fluid samples from individuals with iRBD.
Methods: We analyzed cerebrospinal fluid samples from 24 individuals with iRBD, drawn from two independent cohorts: the DeNoPa study and the Discovery Study, using SAIA. This novel immunoassay is designed to amplify and detect minute quantities of alpha-synuclein seeds. The assay's performance was evaluated in terms of its sensitivity and specificity for detecting alpha-synuclein seeds in these prodromal cases.
Results: SAIA successfully identified all 24 iRBD cases, achieving a sensitivity of 100 percent. Additionally, the assay maintained high specificity, demonstrating its capability to detect alpha-synuclein seeds associated with prodromal synucleinopathies.
Conclusions: This study highlights the potential of SAIA as a powerful and highly sensitive diagnostic tool for identifying prodromal synucleinopathies in individuals with iRBD. The ability to detect alpha-synuclein seeds in this at-risk population offers significant implications for early diagnosis, monitoring, and potential therapeutic intervention in the preclinical stages of synucleinopathies.

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MYELIN ALTERATIONS IN THE SKIN FROM SYNUCLEINOPATHIES

Marta Di Fabrizio[1,2], Bram Van Der Gaag[3], Mara Terzi[1,2], John Bol[3], Wilma Van De Berg[3], Henning Stahlberg[1,2], Amanda Lewis[1,2]
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Aims: Myelin is the lipidic membrane formed by oligodendrocytes and Schwann cells around neuronal axons, that allows rapid saltatory conduction of action potentials. Loss of myelin/demyelination in the central nervous system has been demonstrated to play a role in neurodegenerative diseases, but little is known about the integrity of the myelin-axon unit in the peripheral nervous system. We have used electron microscopy to thoroughly characterize the ultrastructure of myelin sheaths in human dermal nerve fiber bundles among subjects with synucleinopathies (Parkinson's Disease - PD, Dementia with Lewy Bodies - DLB, Multiple System Atrophy - MSA) and non-neurological controls, in order to assess whether myelin damage in the peripheral nervous system can be used as a biomarker for disease.
Methods: Post-mortem human skin tissue was obtained with short post-mortem delay (< 10 hours) from subjects with synucleinopathies and age-matched controls. Specifically, 3-mm cervical skin biopsies were chemically fixed at autopsy and processed for electron microscopy using heavy metal staining and resin-embedding. Ultra-thin sections (80 nm) were cut using an ultramicrotome and imaged using transmission electron microscopy.
Results: We classified over 1200 myelin sheaths and the Lewy group (PD and DLB) shows a significantly higher myelin damage compared to non-neurological control and MSA groups. We defined a total myelin damage score that can be used as a disease classifier, showing high sensitivity, specificity and accuracy.
Conclusions: The abnormalities we observed in the myelin sheaths surrounding the diseased nerve fibers may help to discriminate among subjects with synucleinopathies and control subjects and to understand the involvement of the peripheral innervation in the diseases. Quantification of myelin associated proteins will be performed to assess whether ultrastructural differences are associated to altered levels of myelin proteins.

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PRESENTATION OF THE EUROPEAN PROJECT VAMPIRE: VALIDATION OF A-SYNUCLEIN MODIFICATIONS IN PARKINSON'S DISORDER EVOLUTION

Sandra Rodriguez[1], Tiago Outeiro[2], Salvador Ventura[3], Mayca Marin Valero[4], Chiara Guerrera[5], Maurizio Ferrari[6], Raniero Romagnoli[7], Elda Judica[8], Tomasz Stępień[9], Maria Del Carmen Blanco Lopez[10], Raluca Badea[11], Savvas Petanidis[12], Murray Cairns[13], Marco Feligioni[14]
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Aims: Parkinson's disease (PD) affects >10M million people globally, yet early diagnosis remains challenging due to the lack of validated blood-based biomarkers. Current diagnostic methods (e.g., DaTscan, CSF α-Syn) are invasive, costly, or non-specific. The VαMPiRE project aims to develop an artificial intelligence (AI)-assisted in-vitro diagnostic (IVD) test targeting truncated α-Synuclein isoforms in neuronal-derived extracellular vesicles (NDEVs) to:

1. Detect PD before symptom arise (Early detection),
2. Monitor disease progression (Prognostic assessment),
3. Support precision medicine (PD evolution).

Methods: A longitudinal case-control study will enrol 600 PD and 600 non-PD participants, collecting blood samples at baseline and 24 months for PD, and only at baseline for non-PD. Non-PD participants will be longitudinally monitored for PD cases incidence (estimated 4% conversion rate) to potentially create a third cohort. The assessment of truncated α-Synuclein isoforms will be performed through multiple analytical approaches in blood-isolated NDEVs and results will be integrated in an AI-driven (Machine learning models integrating biomarker and clinical data for optimized diagnostic accuracy and PD evolution) IVD (conducted in collaboration with regulatory-aligned laboratories and IVD manufacturers) to produce a novel pathology biomarker.

Results: Expected Results:

1. Baseline validation of the IVD prototype's diagnostic performance using PD vs. non-PD samples (targeting >85% accuracy),

2. Comparative analysis of baseline vs. 24-month follow-up samples to assess PD progression and identify at-risk individuals before clinical symptoms manifest.

Conclusions: VαMPiRE offers a minimally invasive, scalable diagnostic tool with potential to improve diagnostic accuracy for 270,000 newly diagnosed PD cases annually, enable timely interventions, and reduce 5.8 million disability-adjusted life years (DALYs) by 2028. By supporting regulatory approval and commercialization, this project bridges research and clinical application, advancing precision medicine in PD.

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LIPO-FREE SEED AMPLIFICATION ASSAY FOR DETECTING SERUM A-SYNUCLEIN SEEDS IN PARKINSON'S DISEASE

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Aims: This study aimed to characterize the inhibitory effects of serum components on the detection of α-synuclein (αSyn) aggregates in seed amplification assays (SAAs) and to develop a modified approach that improves the accuracy of αSyn aggregate detection in serum, aiding in the diagnosis of Parkinson's disease (PD) and other synucleinopathies.
Methods: The inhibitory effect of serum on αSyn SAA was analyzed using serum fractionation, mass spectrometry, immunoassays, and αSyn SAA. Serum samples from 132 PD patients and 185 healthy controls were evaluated using this modified SAA.
Results: The high-molecular-weight (HMW) fraction of serum (>100 kDa) was found to inhibit αSyn aggregation, with apolipoproteins identified as the primary inhibitors. To reduce this effect, a lipo-free SAA was developed by removing apolipoproteins via dilution and centrifugation. The modified assay effectively distinguished PD cases from non-synucleinopathies, achieving a sensitivity of 73.48% and a specificity of 92.43% within 24 hours.
Conclusions: This study presents a novel approach to detect misfolded αSyn in serum by eliminating inhibitory apolipoproteins, thereby improving the diagnostic capability of serum-based SAAs for PD. The lipo-free SAA platform could potentially enable faster and accurate diagnosis of synucleinopathies using serum samples.

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NOVEL COMPOUND HETEROZYGOUS ATP10B MUTATIONS IN A FAMILY WITH EARLY ONSET PARKINSON'S DISEASE

Daeun Jeong
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Aims: Novel pathogenic gene, ATPase phospholipid transporting 10B (ATP10B) mutations are established casuse of autosomal
recessive early onset Parkinson's Disease(EOPD) or dementia with Lewy bodies (DLB). ATP10B mutations participate in
contribute to loss-of-function mechanism resulting in a dysregulated lipids glucosylceramide(GluCer) and phosphatidylcholine(PC) homeostasis. That induces lysosomal degradation, which contributes to the aggregation of alpha- synuclein.
Methods: We report the clinical and genetic findings of two members (son and his mother) of family affected by early-onset PD carrying novel ATP10B mutation who manifested young age onset (before <50 years old) early prominent lower-limb symptoms and gait disturbance with mild, slowly-progressive Parkinsonism.
Results: The mutation could affect the structural changes by the alternation of the intra-molecular interactions with other amino acids. 3D structure and interactions between amino acids were predicted from wild-type and mutant protein sequences (Figure 3). The 3D structure of wild-type protein was obtained from the AlphaFold database. Wild-type and mutant amino acids are presented, and the predicted interaction with other structura ladjacent amino acid was indicated and connected by the dashed line.The substitution from Arg303 to Trp303 led to the contraction of cavity volume of the protein. In addition, the interaction between Arg303 and Arg1043 was disappeared
when mutant Trp303 was replaced. On the other hand, ATP10B protein is a transmembrane protein in the lysosome, which may be caused by membrane instability by mutation.
Conclusions: To our knowledge, this is the first korean report of ATP10B variant B in parkinson's disease family. We suggest that genetic screening panel for should be provided in Korean PD patients with strong family history, including ATP10B mutation, for appropriate genetic counselling and improve the diagnostic accuracy.

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CHARACTERIZING PERIPHERAL IMMUNE CELLS IN PARKINSON'S DISEASE THROUGH SINGLE-CELL ANALYSIS

Lovatiana Andriamboavonjy[1,2], Sebastien Audet[1,2], Gael Moquin-Beaudry[3], Laura Hamilton[2], Antoine Duquette[1,4], Sylvain Chouinard[1,4], Michel Panisset[1,4], Tetreault Martine[1]
[1]University of Montreal, Neuroscience, Montreal, Canada, [2]CRCHUM, Neuroscience, Montréal, Canada, [3]Gustave Roussy Institute, Paris, France, [4]CHUM, Neurology, Montreal, Canada

Aims: Although Parkinson's disease (PD) research has unsurprisingly focused on the neurodegeneration happening in the brain, mounting evidence suggests the immune system plays an important role in pathogenesis. Suggesting the involvement of the peripheral immune system alteration, we seek to identify specific signatures from blood samples. We aimed to perform the first comprehensive analysis of the complete peripheral blood mononuclear cells (PBMC) compartment in PD patients utilizing the resolution of single-cell sequencing.
Methods: PBMC were isolated from 14 blood samples from individuals with PD diagnosis, and 10 healthy age-matched control samples. Single-cell libraries were obtained with standard 10X Genomics protocols, with each pool of libraries (5-plex samples) being split into two prior to sequencing. Transcriptomic and T cell receptor (TCR) sequencing were run in parallel on the pools to enable the comparison of transcriptomic and immunologic profiles from single cells. Thorough bioinformatics processing and annotations were performed with standard tools such as Seurat.
Results: Broad cluster analysis showed a general increase in activation signaling in PD samples, with the latter exhibiting a slight trend of increased monocytes and decreased lymphocytes. Further analysis of myeloid cells revealed an activated $CD14^{+}/CD83^{+}$ monocyte subpopulation, for which differentially expressed genes suggested a heightened inflammatory state in PD. Lymphoid cells analysis also showed increased pro-inflammatory NK56hi cells in PD samples. TCR clonotyping identified PD-specific sequences, with multiple motifs shared across multiple samples, but none were linked to known causative sequences in current annotation databases.
Conclusions: Overall, we present the first comprehensive single-cell atlas of the PBMC compartment, and provide insights into the peripheral immune mechanisms at play in PD pathogenesis. We believe these data could lead to the definition of prognosis gene signatures, and the identification of new therapeutic targets.

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SIGNIFICANCE OF PGK1 ACTIVITY IN PD MECHANISM

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Aims: To examine the relationship between a glycolytic enzyme of PGK1 and Parkinson's disease.
Methods: We report clinical characteristics of a boy with PGK-1 deficiency and his mother who carries a heterozygous mutation in *PGK-1*. Then, we investigate the phenotypes of drosophila models with the knockdown of the Drosophila PGK-1 homologue, the Pgk gene. Furthermore, to determine significance of PGK activity in sporadic PD, we measure PGK activities of RBCs from 68 of individuals with PD and 34 of controls.
Results: The boy developed parkinsonism at age of 9. His parkinsonism was partially responded to levodopa treatment. MIBG uptake was normal. His mother, whose PGK activity in erythrocytes was normal, developed parkinsonism at age of 36. Her symptoms were undistinguishable from Parkinson's disease, despite her normal uptake of MIBG. In drosophila model, DA neuron-specific Pgk knockdown lead to locomotive defects in both young and aged adult and was accompanied by progressive DA neuron loss with aging. Pgk knockdown in DA neurons decreased dopamine levels in the central nervous system (CNS). Pan-neuron-specific Pgk knockdown induced low ATP levels and the accumulation of reactive oxygen species in the CNS of third instar larvae. PGK activity of the PD group was significantly higher than that of the control group in participants aged sixty-five years or younger. PGK activity was correlated negatively to the specific binding ratio of dopamine transporter scintigraphy in the striatum.
Conclusions: Loss of function of PGK induces dopaminergic neurodegeneration via decreased ATP production and may be related to the PD development. The fact that PGK activity is elevated in relatively younger individuals with PD, suggesting that PGK1 may play a role as a compensatory function for decreased energy production.

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PROTEOMIC ANALYSIS OF SYNUCLEIN SEEDING ASSAY POSITIVITY IN NEURODEGENERATIVE DISORDERS

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Aims: To explore proteomic changes related to alpha synucleinopathy in cerebrospinal fluid (CSF) across different clinical contexts.
Methods: We analyzed Somascan protein assay data to profile proteomic changes linked to CSF SAA positivity in the Parkinson's Progression Markers Initiative (PPMI), focusing on Parkinson's disease (PD). These findings were then compared with similar analyses from the Alzheimer's Disease Neuroimaging Initiative (ADNI), focusing on Alzheimer's disease (AD).
Results: Sixty proteins were associated with SAA status. Five proteins—DLK1, GPI, NEFH, PTPRR, and VEGFA—were common to both the PPMI and ADNI datasets. Forty-one proteins were linked exclusively to the PD context, while seven were unique to the ADNI context.
Conclusions: These findings contribute to a better understanding of disease-specific and non-specific alpha-synuclein pathology and its impact on CSF proteomic profiles.

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Virtual OO - 001

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ASSOCIATION OF GLYOXALASE DOMAIN CONTAINING PROTEIN 4 (GLOD4) WITH ALZHEIMER'S DISEASE IN HUMANS AND MICE

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Aims: Glyoxalase domain containing protein 4 (GLOD4), a protein of an unknown function, is associated with Alzheimer's disease (AD). Three GLOD4 isoforms are known. The mechanism underlying GLOD4's association with AD was unknown. We aimed to assess GLOD4's role in the central nervous system by studying GLOD4 isoforms expression in human frontal cerebral cortical tissues from AD patients and in brains of *Blmh*$^{-/-}$5xFAD mouse AD model of AD. We also assessed effects of Glod4 silencing on the expression of Aβ precursor protein (Aβpp) and autophagy-related proteins in mouse neuroblastoma N2a-APPswe cells.
Methods: GLOD4 protein and mRNA were quantified in human and mouse brains by western blotting and RT-qPCR, respectively. Mouse brain amyloid β (Aβ) was quantified by western blotting. Behavioral assessments of mice were performed by cognitive/neuromotor testing. *Glod4* gene in mouse neuroblastoma N2a-APPswe cells was silenced by RNA interference and the expression of Glod4, Aβpp, Atg5, p62, and Lc3 proteins and mRNAs were quantified by western blotting and RT-qPCR, respectively.
Results: *GLOD4* mRNA and protein isoforms were downregulated in cortical tissues from AD patients compared to non-AD controls. *Glod4* mRNA was downregulated in brains of *Blmh*$^{-/-}$5xFAD mice compared to *Blmh*$^{+/+}$5xFAD sibling controls, but not in *Blmh*$^{-/-}$ mice without the 5xFAD transgene compared to *Blmh*$^{+/+}$ sibling controls. The 5xFAD transgene downregulated Glod4 mRNA in *Blmh*$^{-/-}$ mice of both sexes and in *Blmh*$^{+/+}$ males but not females. Attenuated Glod4 was associated with elevated Aβ and worsened memory/sensorimotor performance in *Blmh*$^{-/-}$5xFAD mice. Glod4 depletion in N2a-APPswe cells upregulated AβPP, and downregulated autophagy-related *Atg5*, *p62*, and *Lc3* genes.
Conclusions: These findings suggest that GLOD4 interacts with AβPP and the autophagy pathway, and that disruption of these interactions leads to Aβ accumulation and cognitive/neurosensory deficits.

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Virtual OO - 003

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MODULATION OF TRNA MODIFYING ENZYME EXPRESSION REVERTS ER STRESS AND PROTEOSTASIS IMPAIRMENTS IN ALZHEIMER'S DISEASE MODELS

Marisa Pereira[1], Julia Lacerda[1], Laura Fernandes[1], Israel Coronel-Morales[2], Stephany Francisco[1], Miguel Moutinho[3], Ana Soares[1]
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Aims: tRNA modifications, that constitute the tRNA epitranscriptome, play a key role in translation. Impairments in tRNA modifications occur in several diseases, including neurological disorders, and are collectively named modopathies. However, little is known about their impact in the context of Alzheimer's disease (AD). We have recently shown that particular tRNA modifications and the corresponding tRNA modifying enzymes are altered in AD. Here we aim to understand the molecular mechanisms underlying these alterations and explore the potential of tRNA modification modulation as a therapeutic approach in AD.
Methods: We performed a combination of tRNA epitranscriptomics, small non-coding RNA-Seq, and molecular biology experiments including western blotting, immunoprecipitation and protein aggregation assays in AD models.
Results: We found that the expression of several tRNA modifying enzymes and the levels of tRNA modifications are impaired in AD patients and the expression of specific tRNA modifying enzymes negatively correlates with the amyloid plaque burden. Additionally, we found that accumulation of beta-amyloid aggregates is the trigger for tRNA modifying enzyme expression disruption and for tRNA epitranscriptome alterations in AD cellular models. Manipulation of the expression of two specific tRNA modifying enzymes that were found disrupted in these models, alleviated the ER stress and inhibited the accumulation of toxic beta-amyloid aggregates.
Conclusions: Our data suggest that correcting tRNA epitranscriptome deficiencies triggered by alterations of tRNA modifying enzymes may represent a valid therapeutic strategy to recover translation efficiency and proteostasis in AD. We are now confirming these findings in mouse models of the disease, as well as in patient derived iPSCs.

Virtual OO - 004

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SYNAPTIC ADAPTATION BY TRANSCRIPT ISOFORMS IN RESPONSE TO AMYLOID PATHOLOGY IN THE APPNL-G-F KNOCK-IN MOUSE MODEL OF ALZHEIMER'S DISEASE DETERMINED USING LONG-READ TRANSCRIPTOME ANALYSIS

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Aims: Genome-wide association studies (GWAS) have identified a transcriptional network of Alzheimer's disease (AD) risk genes that are primarily expressed in microglia and are associated with AD pathology. However, traditional short-read sequencers have limited our ability to fully characterize how GWAS variants exert their effects on gene expression regulation or alternative splicing in response to the pathology, particularly resulting in inaccurate splicing detection.
Methods: Single Cell RNA Sequencing, Bioinformatic analyses.
Results: We show that long-read RNA-seq can recapitulate the expected induction of microglial expressed risk genes such as *Trem2* in response to amyloid-β at 9 months of age reflecting microglial proliferation and activation;associated with an ageing-dependent decrease in spatial short-term memory in the App^{NL-G-F} knock-in mice. Our results not only identified novel splicing events and transcript isoforms abdundance in genes associated with AD, but also revealed the complex regulation of gene expression through splicing in response to amyloid plaques. Surprisingly, the regulation ofalternative splicing (AS) in response to amyloid was seen in genes previously not identified as AD risk genes, expressed in both microglia and neurons, and included genes such as *Syngr1* that modulate synaptic physiology.
Conclusions: Our data suggests a model whereby induction of AD risk gene expression associated with microglial proliferation and activation is concomitant with alternative splicing in a different class of genes expressed by microglia and neurons, which act to adapt or preserve synaptic activity in response to amyloid-β during early stages of the disease. Our study provides new insights into the mechanisms and effects of the regulation of genes associated with amyloid pathology, which may ultimately enable better disease diagnosis, and improved tracking of disease progression. Additionally, our findings identify new therapeutic avenues for the treatment opportunities of AD.

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Virtual OO - 005

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MAPPING EARLY INTERACTION PARTNERS OF AB42 USING METABOLIC LABELLING

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Aims: In Alzheimer's disease (AD), amyloid beta 42 (Aβ42) is the predominant peptide found within amyloid fibrils. Aβ42 is the most extensively studied amyloid-forming protein. Its aggregation serves as a critical factor that triggers downstream changes in the AD-associated pathways. The process of Aβ42-aggregation predominantly occurs as a self-driving phenomenon; however, the influence of other proteins on the early aggregation of Aβ peptides remains poorly understood. Our objective is to identify proteins that interact with Aβ42 at the very early stages of the amyloid aggregation pathway.
Methods: We recently made significant strides in developing a novel biochemical protocol for the purification of amyloid fibrils from mouse and human brain tissues. Our approach utilizes highly pure amyloid fibril cores derived from various sources, including human, mouse, primary rat neurons, and Drosophila. We labeled mouse brain tissues with heavy lysine for three weeks and performed quantitative mass spectrometry analyses (MS3) on purified amyloids. We further performed biochemical and imaging experiments to validate our proteomics data.
Results: Our robust experimental pipeline, including metabolic labeling of brain tissues, biochemical isolation of amyloid fibrils, and MS^3 proteomics successfully identified proteins interacting with Aβ42 at very early stage of amyloid deposition. By analyzing light and heavy protein abundance, we could distinguish early interaction partners from those accumulating later in the amyloid aggregation. We further validated our mass spectrometry findings by multiple biochemical tools and assays.
Conclusions: While Aβ peptides are known to aggregate readily *in vitro*, their oligomerization and aggregation within the human brain are undoubtedly affected by numerous factors. The early protein interaction partners that collaborate with small Aβ peptides may significantly impact the trajectory and profile of amyloid aggregation, leading to the pathological changes associated with Alzheimer's disease.

Virtual OO - 007

Virtual E-Posters and Oral On-Demand
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IMPACT OF PERSISTENT LOW-GRADE GUT INFLAMMATION IN THE CENTRAL AMYLOID-B PROGRESSION AND COGNITIVE DECLINE WITH ADVANCED AGE

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Aims: Alzheimer's disease (AD) is the sixth leading cause of death in the US. The exact cause and origin of AD are still unknown. Recently it was found that bidirectional communication between the gastrointestinal tract and brain through the "Gut-brain axis" has an important role in AD progression. AD progression is associated with imbalance in healthy gut bacteria referred as gut dysbiosis. The extrinsic connections between the gut and brain by the vagus nerve are poorly understood. Therefore, we propose that luminal pathogenic bacterial proteins can cause neuroendocrine activation from the gut to the brain which promotes central Aβ pathology via gut-brain axis signaling in the presence of early gut inflammation.
Methods: 6-9 months (pre-symptomatic) and 15-16 months (symptomatic) Tg2576 of AD mice and aged match WT littermate controls were used in this study. 16sRNA gene sequencing was used to investigate bacterial gut dysbiosis. Preotein/gene detection using IHC and qRT-PCR analysis. Gut inflammation is achieved by DSS (dextran sulphate sodium) administration for 7 days in the drinking water at 3 months of age
Results: AD mice with gut inflammation showed accelerated cognitive decline. We found changes in the gut microbiota composition with significant gut dysbiosis. This was associated with elevated TLR2 ($p<0.05$), and PGP9.5 ($p<0.01$) levels in the small intestine. Elevated TLR2 expression in symptomatic AD mice brains with gut inflammation at pre-symptomatic timepoint. Microglia was significantly activated with pro-inflammatory cytokines analyzed by flow cytometry in AD mice with gut inflammation. All data were compared to age-matched littermate AD mice without gut inflammation.
Conclusions: Our study reveals that early gut inflammation accelerated Aβ pathology in the brain followed by cognitive decline at an age when AD animals without gut inflammation did not show pathology.

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Virtual OO - 008

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SOCS PROTEINS AS NOVEL INFLAMMATORY TARGETS IN ALZHEIMER'S DISEASE

Adriana Gea González[1,2], María De Los Ángeles Cortés-Gómez[1,2,3], Dimitri Budinger[4], Natividad Pérez-Riquelme[5], Víctor Manuel Barberá-Juan[6], Javier Sáez-Valero[2,3,7], Michael Heneka[4], María Salud García-Ayllón[1,2,3]
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Aims: Alterations in the expression of suppressor of cytokine signaling proteins (SOCS) have been demonstrated in a variety of diseases, including cancer and autoimmune disorders. The dysregulation of cytokine signaling pathways may play a critical role in the pathogenesis of Alzheimer's disease (AD), promoting inflammation. However, there is little information regarding regulatory functions of SOCS proteins in the brain. Therefore, understanding the molecular mechanisms of SOCS proteins in immune cells could represent a powerful tool for deciphering their involvement in AD and their anti-inflammatory potential. In this study we will target the most active SOCS proteins in the brain: SOCS1 and SOCS3.
Methods: Levels of SOCS1 and SOCS3 were analyzed in brain samples of control subjects and AD patients via western blot and qPCR. Microglial cells were derived from AD patient-derived induced pluripotent stem cells (iPSCs) and treated with LPS (lipopolysaccharide) and amyloid-beta. SOCS1 and SOCS3 were also knocked out from iPSCs from AD patients and isogenic controls via CRISPR/Cas9.
Results: Different SOCS proteins presented contrasting patterns of expression, as SOCS3 was increased in AD patients' brains, whilst SOCS1 levels remained unchanged. There was a similar pattern in microglia derived from AD patients after its exposure to pro-inflammatory agents as LPS and amyloid-beta peptide. *SOCS1* and *SOCS3* genes were targeted in different iPS cell lines, resulting in the suppression of their expression. The cells were also free from any genomic footprint and demonstrated normal pluripotency.
Conclusions: Our results suggest that the SOCS response could be altered in the AD brain, thus failing to participate correctly in the anti-inflammatory system. This study provides novel insights into the role of anti-inflammatory regulators SOCS proteins in AD pathogenesis, highlighting their potential as therapeutic targets for the disease.

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Virtual OO - 009

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NERVE GROWTH FACTOR RECEPTOR REGULATES IMMUNE FUNCTION OF T CELLS

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Aims: Alzheimer's disease (AD) is an age-associated dementia disorder without a cure with altered metabolism of the neurotrophin NGF in brain. We previously reported that exogenous NGF therapy showed promise in restoring cognitive decline in AD patients. Recently, role of immune system on AD pathology are actively investigated in relation to inflammation. Currently, our understanding of NGF-immune cell interaction is limited. This study intends to expand this avenue by exploring NGF receptor's expression on immune cells.
Methods: Splenic immune cells were isolated from C57BL/6 mice and examined for NGF receptor (Tropomyosin receptor kinase A: TrkA) expression by flowcytometry. Splenocytes were stimulated with PMA-ionomycin ex-vivo and treated with mature-NGF for 48hr. Cells were collected to examine TNF-a cytokine by flow cytometry.
Results: We examined the expression of NGF receptor TrkA in immune cells from innate and adaptive immunity. Dendritic cells (DC) showed higher level of TrkA compared to macrophage and NK cells. B and T cells from adaptive immunity possess comparable expression of TrkA but lower than DC. Among the subsets of T cells i.e. CD4, CD8, follicular-helper T (Tfh) cells and regulatory T (Treg) cells, Tfh cells presented more TrkA than CD4, CD8 and Treg cell. Also, central memory CD4 T cells expressed more TrkA than the effector memory and naïve CD4 T cells. We also checked their biological relevance in T cells at an ex-vivo platform. We observed that exogenous NGF supplementation reduced TNF-a cytokine production from stimulated splenic T cells.
Conclusions: Our results show that most of the immune cells express NGF receptor TrkA, thus possesses the ability to respond to NGF. NGF-TrkA signaling can modulate the immune response in T cells by reducing pro-inflammatory cytokine production.

Virtual OO - 010

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IMPACT OF SARS-COV-2 ON BLOOD-BRAIN BARRIER INTEGRITY AND NEUROLOGICAL HEALTH: COMPARATIVE ANALYSIS USING TRANSCRIPTOMIC STUDIES

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Aims: To investigate the impact of SARS-CoV-2 on blood-brain barrier (BBB) integrity and neurological health, focusing on the molecular mechanisms involved.
Methods: Transcriptomic analysis of BBB endothelial cells, blood vessels, and peripheral blood mononuclear cells (PBMCs) from COVID-19 patients and controls was conducted. Differentially expressed genes were identified and functionally characterized using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses.
Results: The transcriptomic analysis of BBB endothelial cells, blood vessels, and peripheral blood mononuclear cells (PBMCs) revealed significant alterations in gene expression in response to SARS-CoV-2 infection. **1. Inflammation and Immune Response:** Genes associated with the production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), were significantly upregulated in SARS-CoV-2-infected samples.Genes involved in the activation and recruitment of immune cells, including neutrophils, monocytes, and T cells, were also overexpressed. **2. Oxidative Stress and Mitochondrial Dysfunction:** Genes involved in the generation of ROS, such as NADPH oxidase and xanthine oxidase, were upregulated, indicating increased oxidative stress. Genes associated with mitochondrial dysfunction, including those involved in electron transport chain, oxidative phosphorylation, and mitochondrial biogenesis, were downregulated. **3. Blood-Brain Barrier (BBB) Disruption:** Genes encoding tight junction proteins, which are essential for maintaining BBB integrity, were downregulated. This suggests that SARS-CoV-2 infection may disrupt the tight junctions, leading to increased BBB permeability.Genes associated with endothelial cell activation, including those involved in cell adhesion molecules and signaling pathways, were upregulated.
Conclusions: These findings suggest that SARS-CoV-2 infection can induce inflammation, oxidative stress, and disruption of BBB integrity, contributing to neurological complications in COVID-19 patients. Targeting these pathways may offer potential therapeutic strategies to mitigate the long-term effects of the virus on the brain.

Virtual OO - 011

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P53 STABILIZATION MEDIATES AMYLOID-BETA-INDUCED NEUROINFLAMMATION LEADING TO NEURODEGENERATION

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Aims: Amyloid-beta (Aβ) and Tau protein aggregates lead to neuronal loss and cognitive decline in Alzheimer's Disease (AD) patients. We have previously described a key role for p53 in Aβ-induced neurodegeneration. Recently, glia-induced neuroinflammation has emerged as a key factor in AD pathophysiology and p53 has been postulated as a modulator of the immune response in microglia. Here, we evaluated the possible role of p53 as a regulator of the microglial response to Aβ, and its impact on neurodegeneration and cognitive decline.
Methods: Oligomerized $A\beta_{25-35}$ (9 nmol) was intracerebroventricularly injected into wild-type (WT) and p53 knockout (p53KO) mice. Some WT animals were treated intraperitoneally with the p53 transcriptional activity inhibitor, pifithrin-alpha (PFT-α; 2 mg/kg). Also, primary neuronal cultures were incubated with conditioned medium from primary microglia previously treated with Aβ (10 μM). Neuroinflammation and neurodegeneration were assessed *in vivo* and *in vitro*. Cognitive status was tested 5 days post-injection.
Results: We found that oligomerized $A\beta_{25-35}$ caused early p53 accumulation in the hippocampus, leading to rapid microglial activation, astrogliosis and inflammation. Moreover, the early proinflammatory or M1 profile evolved to an anti-inflammatory or M2 profile happened in a p53-dependent manner. Together, these events led to neurodegeneration and memory impairment, which were prevented by genetic and pharmacological inhibition of p53. Furthermore, p53 controlled microglial activation *in vitro*, which regulated neuronal susceptibility to Aβ through neuronal p53 stabilization.
Conclusions: Our results highlight a key role of p53 in the Aβ-induced inflammatory response, which may contribute to neurodegeneration and cognitive impairment in AD. Funded by Instituto de Salud Carlos III (PI21/00727, RD21/0006/0005 and PMP22/00084, cofunded by the European Union); FEDER; Junta de Castilla y León (CSI151P20; 04/18/LE/0017).

Virtual OO - 012

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DESIGNING, DEVELOPMENT , SYNTHESIS AND NEUROPROTECTIVE ACTIVITY ASSESSMENT OF A NOVEL HYBRID CONJUGATE OF L-DOPA AND CURCUMIN AS AN EFFICACIOUS THERAPEUTIC AGENT FOR PARKINSON'S DISEASE

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Aims: The concept of hybrid molecules incorporating pharmacophores of herbal drugs and commercial ones is novel and promising that can effectively target multifactorial diseases . In the present work a hybrid molecule has been prepared containing the pharmacophores of L-Dopa and Curcumin
Methods: We have designed , synthesized and tested a hybrid molecule containing pharmacophores of L-Dopa , the commercial drug for Parkinson,s disease and Curcumin. . Curcumin protects neuronal mitochondria against oxidative/nitrosative stress, induces glutathione synthesis in cell and animal models of Parkinson's disorder. The composition was designed through in silico methods .The hybrid molecule has been synthesized in one step with quantitative yield .In vitro tests on N27 Neuronal cell line and study conducted in neurotoxin 6-hydroxydopamine induced sporadic Parkinson's disease rat model show positive results.
Results: The synthetic hybrid molecule was characterized by IR, H^1, ^{13} C NMR and Mass spectra. *In-silico* studies show that this modified Curcumin - L-DOPA drug can serve as a highly efficient inhibitor of both i.e. Parkin (c-Abl) as well as α-Synuclein, the two neuronal proteins implicated in Parkinson disease. In vitro tests on N27 Neuronal cell line and study conducted in neurotoxin 6-hydroxydopamine induced sporadic Parkinson's disease rat model show enhanced activity vis-a vis L-Dopa.
Conclusions: The Conjugate containing pharmacophores of L-Dopa and Curcumin shows protection of surviving neurons in case of Parkinson's disease. The hybrid approach has potential future in drug discovery.

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AIR POLLUTION AND NOISE EXPOSURE-RELATED PRO-INFLAMMATORY STATES IN DEMENTIA

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Aims: Inflammatory pathways may be a mechanism linking environmental exposures and dementia. We aimed to assess whether air pollution and noise exposure were related to inflammatory states and how this was related to incident cognitive impairment (CIND) and dementia.
Methods: We relied on 1789 participants of the Sacramento Area Latino Study on Aging cohort, followed from 1998 to 2007. IL-6 and TNF-α were measured in serum and air pollution (NO_2, particulate matter) and noise levels were measured with a land-use regression model and the SoundPLAN software. We also estimated traffic-related air pollution using the CALINE4 emissions-based model (TRAP-NO_x). We estimated the influence of the exposures and inflammation markers on dementia and/or CIND with linear regression and Cox proportional hazards models.
Results: Higher TRAP-NO_x (β=0.57 per tertile, SE=0.24, p=0.02) and noise (β=0.48 per tertile, SE=0.23, p=0.04) were associated with higher IL-6. In Cox models, IL-6 (HR=1.07 per IQR, 95% CI=1.01, 1.12), TRAP-NO_x (HR=1.27 per tertile, 95% CI=1.00, 1.62), and noise (HR=1.22 per tertile, 95% CI=1.01, 1.49) were associated with faster time to dementia or CIND. LUR estimated NO_2 was most strongly associated with faster time to incident CIND (HR=1.43 per tertile, 95% CI=1.01, 2.02). Participants at the highest risk for dementia or CIND were those with both high levels of IL-6 (>Q3) and air pollution (>Q3): IL-6 & LUR-NO_2: HR=1.77, 95% CI=1.01, 3.10; IL-6 & noise: HR=2.11, 95% CI=1.26, 3.53. There was only moderate attenuation with noise and air pollution co-pollutant adjustment.
Conclusions: An increasing number of epidemiologic studies are linking air pollution and noise exposures to dementia. Our results suggest air pollution and noise exposure are related to pro-inflammatory states and these exposures may have indirect effects on dementia through inflammatory pathways.

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INFLAMMATORY-DEPENDENT DEFICITS OF SOCIAL MEMORY AND INTERACTION AS EARLY MARKERS OF ALZHEIMER'S DISEASE

Marco Rinaudo[1,2], Chiara D'Amelio[2], Fabiola Paciello[1,2], Domenica Li Puma[1,2], Raimondo Sollazzo[2], Claudio Grassi[1,2]
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Aims: Recent works suggested that alterations in social behavior characterize early phases of Alzheimer's disease (AD). The present study was aimed at investigating the impact of neuroinflammation on ventral striatum functions in a mouse model of sporadic AD we recently established (PMID: 37261502).
Methods: C57Bl/6 wild-type mice were infected through lip inoculation with Herpes Simplex Virus 1 (HSV-1). Following mice exposure to thermal stress, virus reactivates and travels back to the brain, where it induces an inflammatory response, tau protein hyperphosphorylation and accumulation of amyloid-β along with memory deficits. Social behavior was evaluated by the free social interaction test and the 3-chambers social memory test. Behavioral data were analyzed using ANY-mazeTM and KeyPoint-MoSeq software. Inflammatory response was assessed through immunofluorescence analysis of the ventral striatum.
Results: In the free social interaction test, HSV-1-infected animals showed lower interaction with the conspecific than the mock-infected control mice (interaction time with the conspecific: 61.7±3.5 vs. 93±9.1 s, HSV-1 vs. mock, respectively; $p<0.05$, Student's t-test). In the 3-chamber social interaction test, HSV-1 mice showed higher preference for the conspecific, albeit significantly lower than mock-infected mice (preference index for conspecific vs. object: 72.7±5.6% vs. 90.8±4.8%, HSV-1 vs. mock, respectively; $p<0.05$, Student's t-test). Furthermore, HSV-1 infected mice showed social memory deficits, as they failed to discriminate the novel conspecific from the old one (preference index for the new mouse: 49.6±10.1% vs. 70.1±6.7%, HSV-1 vs. mock, respectively; $p<0.05$, Student's t-test). Finally, HSV-1 mice exhibited microglia activation in the ventral striatum, as revealed by higher number Iba1$^+$ cells and their shift to a pro-inflammatory phenotype.
Conclusions: Collectively, our results indicate that early phases of AD are characterized by altered social behavior that is associated with increased inflammatory response in the ventral striatum.

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Virtual OO - 015

Virtual E-Posters and Oral On-Demand
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SHORT-TERM CD8+ T CELLS ABLATION REDUCES MICROGLIOSIS IN THE HIPPOCAMPUS OF AGED APP/PS1 ANIMALS

Marco Zattoni[1], Sabine Bernegger[1], Sophie-Marie Rieder[1], Barbara Altendorfer[1], Heike Mrowetz[1], Ariane Benedetti[2], Jennifer Forster[1], Michael Unger[1], Ludwig Aigner[1]
[1]Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg, Austria, [2]Institute of Experimental Neuroregeneration, Paracelsus Medical University, Salzburg, Austria

Aims: Alzheimer's disease (AD) progression has recently been associated with the infiltration of $CD8^+$ T cells into disease-affected brain parenchyma, where they tightly associate with microglial and neuronal structures. However, the functional role of $CD8^+$ T cells in the AD brain is still elusive. Therefore, we investigated the impact of short-term $CD8^+$ T cell ablation in transgenic AD mice (APP/PS1).
Methods: $CD8^+$ T cell ablation was performed via intraperitoneal injections of anti-CD8 antibody for three days in two-year-old APP/PS1 and wild-type male mice. Control groups received the respective isotype antibody (four animals per group). Heart-collected blood samples underwent flow cytometry analysis. After transcardiac perfusion, the brain tissue was processed for immunohistochemistry staining and RNA isolation for gene expression analysis.
Results: As expected, anti-CD8 injections resulted in a substantial decrease of $CD8^+$ T cells from the blood circulation as well as brain parenchyma. Immunohistochemistry analysis revealed a mild reduction in amyloid plaque pathology upon anti-CD8 treatment and a statistically significant reduction in the percentage area of $Iba1^+$ cells in the hippocampus of APP/PS1 mice injected with anti-CD8 antibody, when compared to isotype-treated mice. Furthermore, we noticed a trend of reduction in the volume of amyloid plaque-associated microglial phagolysosomes. Quantitative PCR analysis did not reveal significant anti-CD8-dependent changes in the disease-associated microglia markers, *Tspo* and *Trem2*.
Conclusions: Short-term $CD8^+$ T cell ablation leads to a consistent reduction of microglial cell staining area in the hippocampus of treated animals. Collectively, our results suggest that short-term $CD8^+$ cell ablation could influence microglia in the brain of APP/PS1 mice.

Virtual OO - 016

Virtual E-Posters and Oral On-Demand
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DELINEATING AB PLAQUE ASSOCIATED LIPID CO-AGGREGATION DYNAMICS USING MASS SPECTROMETRY IMAGING

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Aims: The progressive accumulation of β-amyloid (Aβ) peptide derived from amyloid precursor protein (APP) is one of the hallmarks of Alzheimer's disease (AD). The neuronal lipid has been reported to be implicated in Aβ proteopathy in AD, though the overall molecular processes between neuronal lipids and Aβ remain unclear. It is critical to understand how lipid interacts with Aβ peptide in amyloid plaque pathology over time. The primary aim of this research is therefore to follow spatial lipid and amyloid dynamics in precipitating plaque pathology.
Methods: Herein, we utilized stable isotope labelling along with advanced correlative chemical imaging based on mass spectrometry to monitor Aβ plaque associated lipid-Aβ co-aggregation dynamics in $APP^{NL\text{-}G\text{-}F}$ knock-in mice. We futher expanded these experiments toward steady state imaging of lipid patterns in post mortem human AD brain.
Results: The results show specific incorporation of 15N into ganglioside species that allow to establish ganglioside-amyloid co-aggregation dyncamics . Here, GM1 (d36:1) consistently interacts with Aβ 1-42 throughout the plaque deposition, suggesting a continuous involvement in plaque pathology. In contrast, GM2 (d36:1) and GM3 (d36:1) appear to deposit into plaques at later specific stages, highlighting a more transient interaction. Similarely, GM1 was found to associate with neuritic plaques in post mortem brain and correlate with Aβ 1-40 deposition specific to plaque core formation.
Conclusions: This innovative approach enables the detailed investigation of molecular events in the complex pathology of AD, providing new insights into the temporal and spatial dynamics of lipid-Aβ interactions.

Virtual OO - 017

Virtual E-Posters and Oral On-Demand
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GALECTIN-3 AND TREM2 INTERACT IN MICROGLIA WITH AGE

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Aims: Galectin-3 (gal3) has been identified as a ligand for the microglial innate immune receptor triggering receptor expressed on myeloid cells 2 (TREM2); however, little is known about the cross talk between gal3 and TREM2 in the context of aging or neurodegenerative disease. The main goal of this study was to define interactions of gal3 and TREM2 in microglial responses to pathology.
Methods: Aged wildtype and Trem2-deficient mice were used to examine interactions of gal3 and TREM2 *in vivo*. Primary microglia harvested from these models were used to study the regulation of microglial phenotypes and function.
Results: We found that gal3 and TREM2 expression, along with their interaction, increased with age in B6 mice. This increased interaction was also observed in aging-related white matter pathology and in microglia phagocytosing myelin *in vitro*. To dissect the role of gal3 and TREM2 in microglia function, we used a phagocytosis assay to show that Trem2-deficent microglia shared overlapping functional deficits with microglia treated with a gal-3 inhibitor. The shared deficits included impaired myelin uptake, altered lysosomal function, ER stress and lipid droplet accumulation. Adding recombinant gal3 (rgal3) to Trem2-deficient microglia rescued these deficits. RNA-seq analysis of primary microglia treated with myelin revealed common genes and pathways affected by Trem2-deficiency and galectin-inhibition including alterations in genes associated with the integrated stress response.
Conclusions: These findings show TREM2 and gal3 interact with age in microglia. Gal3 mediates and throttles the TREM2-dependent stress response during microglial myelin phagocytosis. Our data suggest that the gal3/TREM2 interaction is beneficial with age.

Virtual OO - 018

Virtual E-Posters and Oral On-Demand
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APOLIPOPROTEIN E AGGREGATION IN MICROGLIAL LYSOSOMES LEADS TO THE GENERATION OF AMYLOID PLAQUES IN ALZHEIMER'S DISEASE

Seiji Kaji, Stefan Berghoff, Lena Spieth, Mikael Simons
Technical University Munich, Institute Of Neuronal Cell Biology (tum-ncb), Munich, Germany

Aims: The actual interplay of apolipoprotein E (APOE) and amyloid plaques in the pathogenesis of Alzheimer's disease (AD) is poorly understood. Our aim is to clarify how APOE leads to plaque development in AD.
Methods: We created a mouse line expressing endogenous APOE with Halo-tag for improved APOE visualization and purification. Crossbreeding APOE-Halo mice with 5xFAD model allowed us to analyze APOE in the context of amyloid pathology. We analyzed intra/extracellular localization of APOE in relation to β-sheet-positive structures by immunohistochemistry, and biochemically characterized plaque-associated APOE by immunopurification.
Results: Immunohistochemistry of APOE Halo 5xFAD mice showed substantial numbers of extracellular MX04+ plaques which are predominantly enriched with APOE with little Aβ immunoreactivity. In addition, we also detected APOE-enriched MX04+ structures in microglial lysosomes. Using Halo-tag, we purified plaque-associated APOE through Sarkosyl-extraction and immunoprecipitation, which enabled the visualization of wavy APOE aggregates by EM in the absence of Aβ. These findings verified that some plaque-associated APOE exist as Aβ-independent aggregates. Injection of the APOE aggregates to 5xFAD mice led to markedly enhanced plaque pathology in early-stage 5xFAD mice brains, which indicated that APOE aggregates serve as primary seeds for plaque generation. Importantly, we observed the absence of seeding activity of 5xFAD brain lysate in Plexxikon-treated mice suggesting that microglia play a crucial role in APOE-driven plaque generation. Modulation of APOE lipidation status largely affected the plaque generation via altered APOE uptake into microglia, demonstrating the link between lipidated APOE and initiation of plaque pathology.
Conclusions: Our findings suggest that APOE aggregation in microglial lysosomes leads to amyloid plaque generation. Further understanding on the mechanism of APOE aggregation will expand the possibilities for the development of new disease-modifying therapies against AD.

Virtual OO - 019

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UTILIZATION OF FLUORESCENT PROBES TO VISUALIZE CHANGES IN PROTEASOME AND IMMUNOPROTEASOME PROTEOLYTIC ACTIVITY IN MICROGLIAL CELLS UNDER INFLAMMATORY CONDITIONS

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Aims: Proteostasis plays a crucial role in maintaining proper protein synthesis, folding, and degradation within cells. Disruption of this balance can contribute to the development of neurodegenerative conditions characterized by protein inclusions, such as Alzheimer's and Parkinson's diseases. Proteostasis dysregulation may result from changes in the catalytic activity of 20S proteasome and immunoproteasome subunits. The aim of this study was to analyze how inflammation induces activity of 20S proteasome and immunoproteasome subunits in human microglial cell lines.
Methods: Our research included transcriptomic analysis using RT-qPCR, proteomic analysis with western blotting, and activity profiling using chemical probes (abtivity based probes; ABP).
Results: Transcriptome analysis revealed increased expression of β1 and β5 subunits in the presence of LPS, while protein-level analysis showed elevated levels of β1 and β2 and a decrease in β5. Activity profiling indicated higher activity for β1 and β2 subunits and lower activity for β5, consistent with the protein level findings.
Conclusions: These studies shed light on the dynamic changes in proteostasis during inflammation in microglial cells, suggesting that targeting 20S proteasome β subunit activity could be a promising therapeutic approach for neurodegenerative diseases.

Virtual OO - 020

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ABCA7 DEFICIENCY IMPAIRS THE RESPONSE OF MICROGLIA TO AMYLOID PATHOLOGY IN A HUMANIZED MODEL OF AD

Jessie Premereur[1,2], Anika Perdok[1,2], Bob Asselbergh[2], Paula Miquel[2], Lena Duchateau[1,3], Kristel Sleegers[1,3], Renzo Mancuso[2]
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Aims: The ATP-binding cassette transporter, subfamily A member 7 (ABCA7) is one of the most important AD risk genes identified, wherein loss-of-function (LOF) variants are linked to several microglial pathways, including lipid metabolism and endocytosis. However, the contribution of ABCA7 to microglial biology and AD remains largely unknown. Our main objective is to define the role of ABCA7 dysfunction in microglial homeostasis and AD pathology.
Methods: We generated two ABCA7-KO ESC lines and one patient-derived iPSC line (E709fs), together with their isogenic controls, and differentiated all lines into ESC/iPSC-derived microglia using our MIGRATE protocol. To understand the effect of microglial ABCA7 dysfunction on AD pathology *in vivo*, we transplanted them into the brains of AD (AppNL-G-F) and control mice. We investigated the differences in the microglia transcriptome and cellular surface proteins using CITE-sequencing (Cellular Indexing of Transcriptomes and Epitopes), and their response to amyloid pathology with histopathology and phagocytosis assays at late stages of amyloid pathology.
Results: ABCA7 LOF cells display an altered internalization of amyloid β particles *in vitro*, indicating either enhanced phagocytic capacity or diminished degradation. Grafted ABCA7-KO cells displayed a reduced activation in response to amyloid pathology at the level of transcriptomic and histopathology at 6 months, followed by increased homeostasis at 9 months. In contrast to TREM2 variants, ABCA7-KO microglia cluster around plaques similarly to controls but do not engage into a disease associated program, suggesting correct recognition of the AD protein aggregates but failure to engage their endo-lysosomal system and process phagocytic material appropriately, supported by decreased phagocytosis.
Conclusions: Our data suggests that distinct molecular mechanisms operate in microglia to contribute to the risk of AD, where ABCA7 LOF microglia fail to engage in an activated response profile.

Virtual OO - 021

Virtual E-Posters and Oral On-Demand
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MICROGLIA-CONTAINING CEREBRAL ORGANOIDS MODEL APOE4-DRIVEN ALZHEIMER'S DISEASE PATHOLOGIES

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Aims: The APOE ε4 allele (APOE4) is the strongest genetic risk factor for Alzheimer's disease (AD) in the typical population and increases the risk for AD in people with Down syndrome (DS-AD) in comparison to the most common allele, APOE3. Data support the hypothesis that microglial-apoE interactions drive neuroinflammation and contribute to DS-AD progression, highlighting a valuable potential therapeutic target for improving cognition and longevity in people with DS-AD. However, little is known about the mechanisms underlying microglial-apoE interactions and their contributions to neuroinflammation and neurodegeneration in the human brain.
Methods: We developed hiPSC-based microglia-containing cerebral organoids (MCOs), using CRISPR-Cas9 gene editing to convert the genotype from APOE3/3 to APOE4/4 in an hiPSC line derived from a donor with DS, and in an isogenic control hiPSC line disomic for chromosome 21. We then developed MCOs and cerebral organoids without microglia (COs) to investigate how APOE4 affects the microglial contribution to AD pathologies in the DS brain.
Results: In our DS-AD models, we found that the microglia present in the MCOs, which were not present in the COs, expressed markers of microglial maturity, colocalized with amyloid plaques, and modulated plaque deposition and morphology at different stages of disease. APOE4/4 MCOs exhibited neurodevelopmental and/or neurodegenerative phenotypes resulting in reduced organoid size relative to APOE3/3 MCOs. We also performed a high-throughput drug screen of 2,560 compounds and identified 23 hit compounds that decreased apoE4-catalyzed Aβ fibrillization in a ThT-based amyloid assay. Three of the 23 lead drug candidates reduced intracellular Aβ neuropathology in iPSC-derived DS neurons.
Conclusions: These studies help delineate the molecular pathways linking APOE4 to DS-AD and potentially identify a novel set of drugs that may prevent or delay the onset of DS-AD in APOE4 carriers.

Virtual OO - 022

Virtual E-Posters and Oral On-Demand
ON-DEMAND ORAL IN ONLINE GALLERY AND MOBILE APP ONLY

SHARED BIOLOGICAL PATHWAYS ALTERED IN TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE

Mauricio Erazo[1], Iara De Souza[2], Ekaterina Aladyeva[3], Jacqueline Kaczaral[2], Ricardo D'oliveira Albanus[4], Hongjun Fu[5], Celeste Karch[6], Oscar Harari[2]
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Aims: Epidemiological and clinical studies indicate that traumatic brain injury (TBI) significantly elevates the risk of Alzheimer's disease (AD). Moderate to severe TBI is linked with earlier cognitive decline and AD onset, likely due to persistent changes in brain structure and neuroinflammation, tau pathology, and amyloid-beta accumulation. Both conditions share pathological features such as neurofibrillary tangles and amyloid plaques. To explore molecular mechanisms potentially connecting TBI and AD, we analyzed gene expression at the single-cell level between these conditions.
Methods: Using a TBI mouse model (fluid percussion injury) at acute and subacute stages in the hippocampus and frontal cortex, we compared gene expression changes to those in human AD single-cell datasets.
Results: The analysis revealed overrepresented gene sets with similar expression patterns in both conditions. Notably, there was a shared downregulation of energy metabolism genes and an upregulation of immune response genes in astrocytes of both brain regions. Additionally, microglia showed increased proteasome degradation-related genes and decreased RAS signaling. Astrocytes also exhibited downregulation in alcohol metabolism pathways, consistent across TBI and AD samples from the frontal cortex and hippocampus.
Conclusions: These findings suggest shared molecular pathways in TBI and AD, emphasizing altered metabolic and immune responses as key intersections in disease pathology. Future studies will extend these findings to human TBI samples and validate the identified signatures through functional assays, focusing on astrocyte roles in disease progression.

Virtual OO - 023

Virtual E-Posters and Oral On-Demand
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SINGLE CELL RNA-SEQ DATA ANALYSIS OF AD BRAIN SAMPLES

Lilach Soreq
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Aims: Alzheimer's disease (AD) is a devastative late-life disease with no early diagnosis methods/cure. It is the 2nd most frequent neurodegenerative disease worldwide. Single Cell RNASeq analysis allows detailed inspection of gene expression changes (specifically, cell type specific marker genes) as well as molecular pathways. I aimed to detect cell-type specific gene expression changes in AD
Methods: I have applied Chromium Seq machine to computationally analyze samples from 2 AD and 2 control frontal cortex samples. I used statistical tests and classification methods on the data as well as network analysed.
Results: I detected specific changes in Astrocyte marker genes.
Conclusions: My study findings may open new venues for future treatment of AD using Cas9/Crispr genetic interference.

Virtual OO - 024

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LONGITUDINAL ASSESSMENT OF CEREBRAL BLOOD FLOW, AUTOREGULATION AND BAROREFLEX IN ALZHEIMER PATIENTS: CONSEQUENCES FOR ANTIHYPERTENSIVE TREATMENT

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Aims: There is concern that blood pressure lowering with antihypertensive treatment causes cerebral hypoperfusion in Alzheimer patients. Cerebral autoregulation and baroreflex sensitivity (BRS) are key mechanisms that help stabilize blood pressure (BP) and cerebral blood flow. We assessed whether these mechanisms are affected in Alzheimer's disease (AD) in a longitudinal design with 1.5 year follow-up.
Methods: We measured continous BP, heart rate, and cerebral blood velocity at baseline, 0.5 and 1.5 years, in rest, during rapid increases and decreases in BP, and during an orthostatic challenge. Next we studied cerebrovascular reactivity during hypo- and hypercapnia. Cerebral autoregulation was estimated using transfer function analysis and the autoregulatory index. BRS was estimated by calculating the heart rate response to rapid BP changes. Linear mixed models were used to assess changes over time.
Results: 56 patients were included (mean age:73 ± 6 years, 57% female). BRS did not change over time. Autoregulation parameters showed only small changes after 0.5 years, suggestive of a minor reduction in efficiency (e.g. higher gain [linear mixed effect model: B = 0.09, SE = 0.03, *P* = 0.008] and lower phase [B = -9.7, SE= 3.2, *P* = 0.004] in the very low frequency domain, and lower autoregulatory index [B = -0.69, SE = 0.26, *P* = 0.010]). These changes however did not show further progression after 1.5 years of follow-up.
Conclusions: In this longitudinal study of patients with dementia due to AD we found no evidence that autoregulation or BRS become impaired during AD progression. This suggests that patients with AD do not have an increased risk of cerebral hypoperfusion with antihypertensive treatment. This is relevant because BP lowering may reduce the risk of adverse events in AD immunotherapy.

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Virtual OO - 025

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REDUCING CETP ACTIVITY PREVENTS MEMORY DECLINE IN AN ALZHEIMER'S DISEASE MOUSE MODEL

Jasmine Phenix[1], Isabel Sarty[2], Megan Katz[3], Anouar Hafiane[4], Chu Han Nie[3], Anja Kerksiek[5], Dieter Lütjohann[5], Robert Kiss[4], William Pastor[3], Judes Poirier[2], Lisa Marie Munter[1]
[1]McGill Pharmacology and Therapeutics Department, Montreal, Canada, [2]Douglas Mental Health University Institute, Research Center, Montreal, Canada, [3]Department of Biochemistry, Montreal, Canada, [4]McGill Division of Experimental Medicine, Montreal, Canada, [5]Institute of Clinical Chemistry and Clinical Pharmacology, Bonn, Germany

Aims: Genetic studies suggest lipid metabolism perturbation is central to Alzheimer's disease (AD). Elevated plasma cholesterol and cholesteryl ester transfer protein (CETP) activity, which raises low-density lipoprotein cholesterol, are linked to an increased AD risk. CETP is also expressed in endothelial cells, playing a key role in maintaining vascular and brain health. CETP inhibition, like with the drug evacetrapib, has not been studied in the context of AD thus far. We previously found that CETP inhibition preserved memory in an AD mouse-model of amyloidosis. We now found that endothelial function underlies the beneficial effects of CETP inhibition.
Methods: WT, APPtg, CETPtg, and APPtg/CETPtg mice on a high cholesterol diet were injected daily with 30 mg/kg evacetrapib or vehicle from 11 to 21 weeks of age followed by behavioral and biochemical analyses. Human cerebrospinal fluid (CSF) samples came from the PREVENT-AD cohort consisting of individuals at higher AD risk due to family history but cognitively unimpaired at enrollment.
Results: We previously showed that CETP inhibition maintained memory performance in APPtg/CETPtg mice. Improved memory correlated with higher hippocampal free cholesterol. RNA sequencing of brain tissue followed by pathway analysis revealed blood-brain barrier (BBB)-related changes. Using CSF proteomic data of PREVENT-AD subjects, we correlated CETP abundance with cognition, amyloid-beta, vascular and neuronal proteins that we found differentially regulated in mice, and the results from human data reflect results from our mouse model. Thus, CETP expression in mice may affect cerebrovasculature and BBB integrity, reflected in human subjects.
Conclusions: Our findings support the idea that CETP activity may affect endothelial function and that lipid metabolism modulates AD risk. This study offers preclinical evidence that CETP inhibitors like evacetrapib could delay or prevent AD as a novel therapeutic option.

Virtual OO - 026

Virtual E-Posters and Oral On-Demand
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BLOOD-BRAIN BARRIER WATER EXCHANGE ACROSS THE SPECTRUM OF ALZHEIMER'S DISEASE

Jeremy Ford, Raquel Taddei, Meher Juttukonda, Teresa Gomez-Isla, David Salat, Susie Huang
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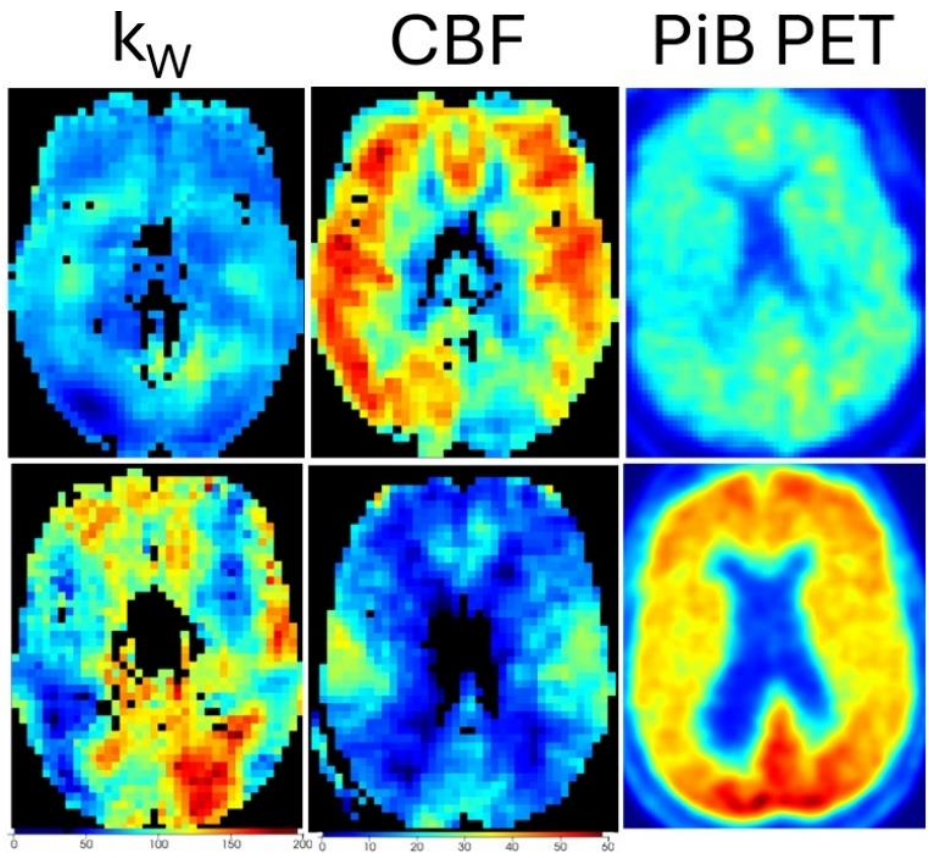
Aims: We aim to explore blood-brain barrier (BBB) water exchange (k_w) across the continuum of Alzheimer's disease (AD). Previous diffusion-prepared arterial spin labeling (DP-ASL) studies indicated a decline in k_w in aging and mild cognitive impairement (MCI), while dynamic contrast-enhanced (DCE) perfusion studies have shown increased BBB permeability as AD advances. Here, we investigate the relationship between k_w, cerebral blood flow (CBF), and AD stage, assessed by Clinical Dementia Rating Scale (CDR) and CDR-Sum of Boxes (CDR-SB).
Methods: 17 healthy controls (HC, CDR 0, amyloid PET-), 17 MCI (CDR 0.5, amyloid PET+), and 9 AD patients (CDR 1.0+, amyloid PET+) were enrolled. Whole brain k_w and CBF were measured using DP-ASL at a 3.5x3.5x8mm. Group differences in k_w , CBF, and k_w /CBF were analyzed using one-way ANOVA and Tukey's multiple comparison test. Linear regression assessed CDR-SB scores and k_w among MCI/AD subjects.
Results: MCI showed lower k_w values compared to HC (adjusted p=0.0047). However, k_w was significantly higher in AD (adjusted p=0.0115 vs. MCI). In contrast, CBF was lower in AD compared to MCI (adjusted p=0.0445). The k_w/CBF ratio was notably higher in AD than in HC and MCI (both adjusted p<0.001). Among MCI and AD, there was a positive linear relationship between CDR-SOB and k_w (R^2=0.1781, p=0.0318)


k_W
CBF
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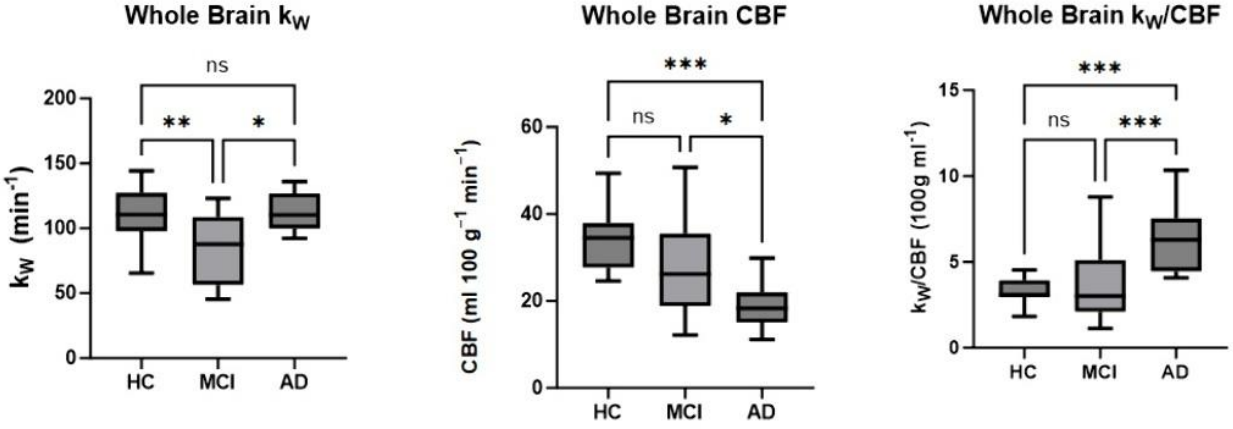
Whole Brain k_W
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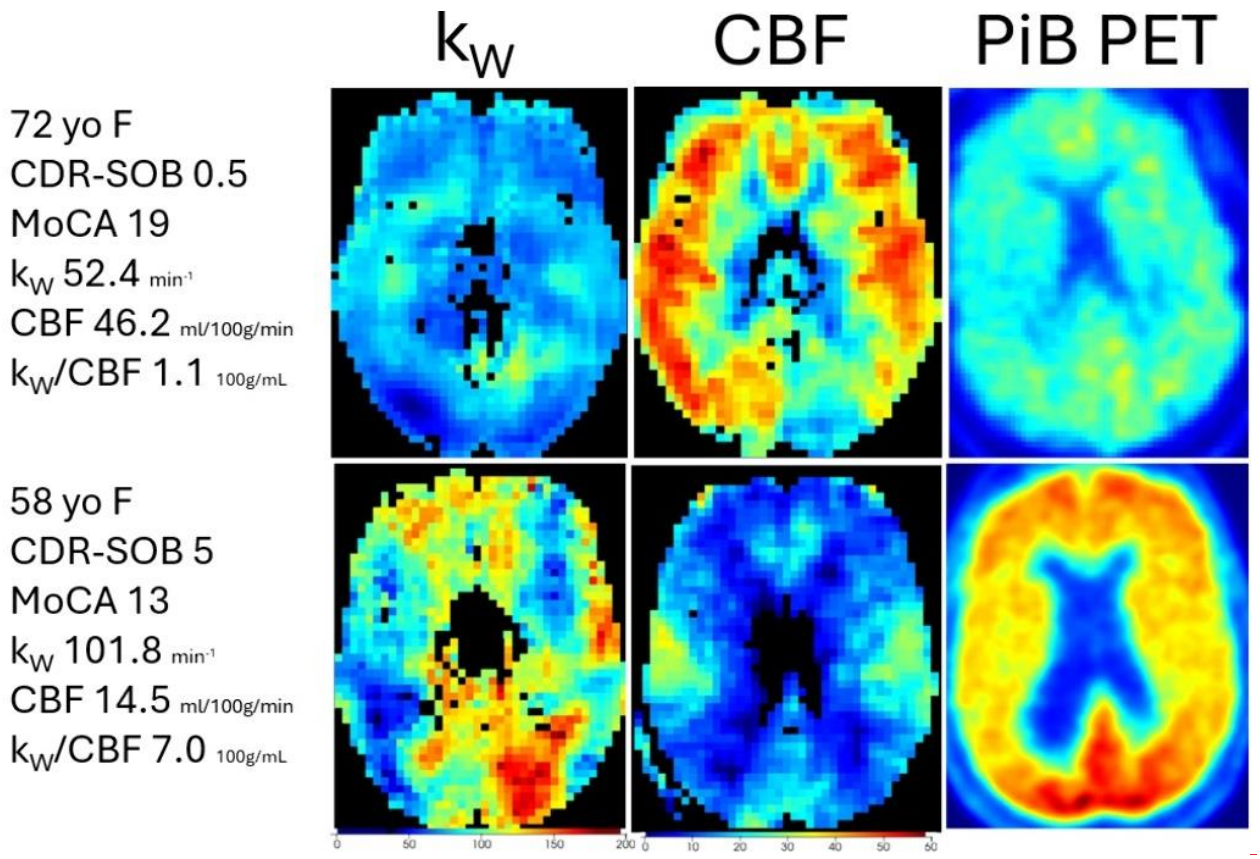

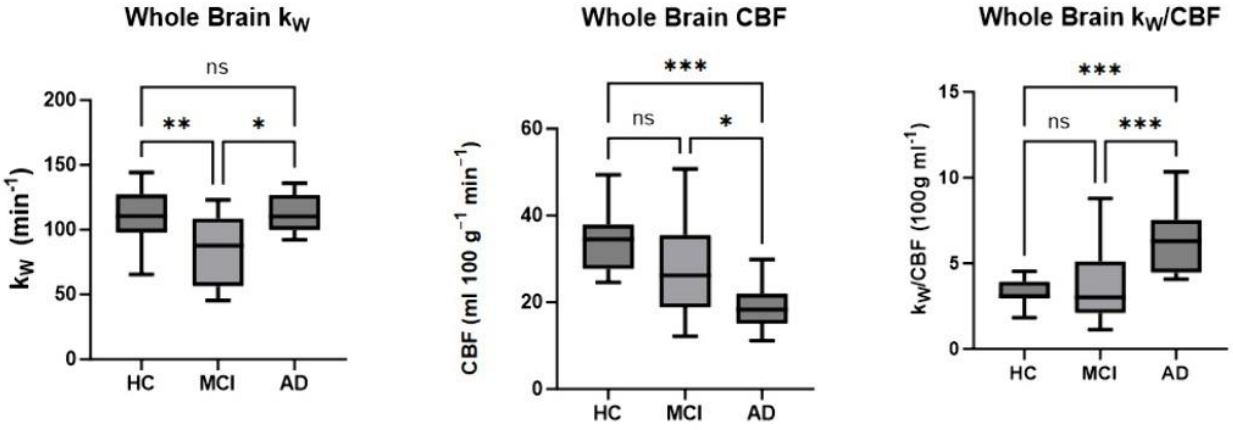

Conclusions: Noninvasive imaging of k_W and CBF may enhance our understanding of AD progression and BBB dynamics. The novel finding that k_W is higher while CBF is lower in more advanced AD may explain previous divergent results from DCE perfusion studies. k_W may serve as a prognostic marker of AD progression, with decreased aquaporin-4 polarization mediating early k_W reductions and increased paracellular leakage driving higher k_W in later stages.

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Virtual OO - 027

Virtual E-Posters and Oral On-Demand
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INVESTIGATING THE ROLE OF CHOROID PLEXUS AND BLOOD-CSF BARRIER IN ALZHEIMER'S DISEASE

Alemeh Zamani, Karolína Jeřábková, Petra Orviská, Parisa Emamiaref, Ahad Zareravasan, Vaclav Brázda, Malahatosadat Dianat, Andrea Joukal
Masaryk University, Alemeh Zamani Research Group, Brno, Czech Republic

Aims: Alzheimer's disease is a progressive neurodegenerative disorder characterized by the gradual worsening of dementia over several years, eventually becoming completely debilitating in its later stages. The three hallmark features of AD are amyloid-beta (Aß) aggregation, tau hyperphosphorylation, and neuroinflammation. However, the precise sequential relationship among these phenomena remains unclear. The Choroid Plexus, which forms the blood-cerebrospinal fluid barrier, plays a crucial role in the clearance of Aß from the brain. In Alzheimer's disease, insufficient Aβ clearance and increased inflammatory changes in the choroid plexus and cerebrospinal fluid are observed. This study investigates the underlying mechanism by which the choroid plexus is altered during Alzheimer's disease.
Methods: We used an *in vitro* model of Alzheimer's disease in Z310 cells developed in our lab. The choroidal epithelial cells, Z310 cells, were incubated with Aß peptide for various time points, and molecular techniques were used to investigate the Z310 cell alterations.
Results: We showed the molecular structure alteration of Z310 cells as early as 1 hour after the Aß treatment. We observed a significant increase in molecular alteration with time. Alzheimer's disease-associated molecules, such as amyloid precursor protein (APP) and inflammatory mediators, were found to be among the molecules that exhibited alterations. Furthermore, proteins responsible for the barrier properties were demonstrated to be influenced by treatment with Aß.
Conclusions: Our results provide valuable insights into the importance of understanding the role of the choroid plexus in the early stages of the disease. This includes its contribution to disease progression as well as its protective functions.

Virtual OO - 028

Virtual E-Posters and Oral On-Demand
ON-DEMAND ORAL IN ONLINE GALLERY AND MOBILE APP ONLY

MALNUTRITION EXACERBATES NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S CONTINUUM BY SUPPRESSING CAMP SIGNALING PATHWAY: HUMAN AND MOUSE STUDIES

Jiwei Jiang, Tianlin Jiang, Min Zhao, Jun Xu
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Aims: This study aimed to investigate the causal relationships between malnutrition and neuropsychiatric symptoms (NPS) in Alzheimer' s disease (AD), and then develop a APP/PS1 mice model to explore the underlying mechanisms of malnutrition's impact on NPS.
Methods: Baseline and longitudinal associations of nutritional status and cerebral blood flow with NPS were analyzed in 374 patients on the AD continuum and 61 healthy controls. Serum biomarkers, behavioral tests, cerebral neurotransmitters, and differential gene expressions were evaluated in Four-month-old APP/PS1 and wild-type mice fed a malnourished or standardized diet for two months. The neurotransmitters levels in the striatum or midbrain of mice were detected by ultra-high-performance liquid chromatography, western blot, immunofluorescence, and immunohistochemistry. Differential gene expressions in the striatum or midbrain of mice were determined using RNA sequencing. KEGG database was used to reveal potential biological functions and signaling pathways enriched in differential neurotransmitters and gene expressions. In vivo experiments were performed to validate the key pathway mediating malnutrition and NPS.
Results: Poor nutritional status and increased cerebral blood flow of midbrain and striatum at baseline worsened the NPS and its subtypes in patients among AD continuum, especially depression, anxiety, and apathy. APP/PS1 mice fed a malnourished diet showed significantly poor nutritional status, and exacerbated depression- and anxiety-like behaviors, along with altered levels of dopamine, acetylcholine, and GABA at both midbrain and striatum; RNA sequencing identified downregulated *c-Fos* expression in the midbrain and striatum of APP/PS1 mice, all of which were enriched in the cAMP/c-Fos signaling pathway, which has also been validated using independent pharmaceutical in vivo validation experiments.
Conclusions: Malnutrition exacerbates NPS altering *c-Fos* expression and neurotransmitter levels in midbrain and striatum via downregulating cAMP pathway, suggesting potential for targeted nutritional interventions to mitigate NPS on the AD continuum.

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Virtual OO - 029

Virtual E-Posters and Oral On-Demand
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18F-FLUORODEOXYGLUCOSE IN CEREBROSPINAL FLUID REFLECTS BOTH BRAIN GLUCOSE DEMAND AND IMPAIRED BLOOD-BRAIN BARRIER TRANSPORT IN ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA

Caterina Motta[1], Agostino Chiaravalloti[2], Chiara Giuseppina Bonomi[1], Alessandro Martorana[1]
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Aims: Glucose delivery to brain requires transport across blood-brain barrier (BBB) via glucose transporters (GLUT). GLUT downregulation may be associated with neuronal deficits in Alzheimer disease (AD), but whether this is due to reduced demand in affected tissues or by primary BBB dysfunction remains unclear. The study investigated the relationships between cerebrospinal fluid (CSF) [18F]Fluorodeoxyglucose (18F-FDG) and cortical glucose metabolism in patients with AD compared to a group of patients with frontotemporal dementia (FTD) and healthy controls.
Methods: 224 biologically defined AD patients and 50 patients with FTD underwent CSF analysis within 4-weeks of an 18F-FDG PET/CT scan. Core AD biomarkers, glycorrhachia, lactate and Albumin Quotient (QAlb) were evaluated. Additionally, 35 age-matched healthy subjects underwent 18F-FDG PET/CT. All images were analyzed using WFUpickatlas toolkit implemented in statistical parametric mapping (SPM12), with normalization of brain areas and ventricles (CSFv) using the pons as reference.
Results: AD patients showed the lowest levels of 18F-FDG in CSFv, followed by FTD patients and controls ($F=23.58$, $p<0.001$). Conversely, lactate levels were significantly higher in AD compared to FTD and controls. Both AD and FTD groups showed reduced correlations between 18F-FDG in CSFv and cortical glucose metabolism (AD: $r=0.37$; $p<0.001$; FTD: $r=0.17$; $p=0.23$; ctrl: $r=0.76$; $p<0.001$). In both AD and FTD groups, increased BBB permeability (Qalb) was associated with lower cortical glucose uptake (AD: $r=-0.16$; $p=0.018$) and 18F-FDG in CSFv (AD: $r=-0.16$; $p=0.018$).
Conclusions: 18F-FDG levels in CSF reflect glucose delivery to the brain. Patients with AD and FTD showed reduced glucose supply, not solely due to decreased demand, as indicated by the weakened correlation with cortical glucose metabolism compared to healthy individuals. These findings point to an impairment in glucose transport associated with non-specific neurodegenerative changes, including BBB dysfunction.

Virtual OO - 030

Virtual E-Posters and Oral On-Demand
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STRUCTURAL CONNECTIVITY OF THE MEDIAL TEMPORAL LOBE: ASSOCIATIONS WITH AMYLOID LOAD AND FUNCTIONAL CONNECTIVITY

Elise Saul, Jade Lasserve, Léa Chauveau, Brigitte Landeau, Géraldine Poisnel, Gaël Chetelat, Robin De Flores
Normandy University Unicaen, Inserm, U1237, Phind "physiopathology And Imaging Of Neurological Disorders", Neuropresage Team, Caen, France

Aims: Two networks within the medial temporal lobe (MTL)—the anterior-temporal (AT) and posterior-medial (PM)—are known to be functionally impaired in aging and Alzheimer's disease (AD). While our previous work suggested that AT hyperconnectivity is a pivotal mechanism in AD, and PM hypoconnectivity is canonical to aging, their structural connectivity is not fully understood. This study leverages longitudinal data to (i) identify the white matter fibers supporting the AT and PM networks, (ii) explore the effects of amyloid-β (Aβ) accumulation on these fibers, and (iii) examine the link between fiber integrity and functional connectivity.
Methods: Eighty-nine cognitively healthy older adults (68.96 ± 3.89 years) were included. Structural and functional connectivity within the AT and PM networks were assessed using resting-state fMRI and DKI, respectively, using the perirhinal and parahippocampal cortices as seeds for correlation or tractography analyses. Amyloid-β deposition was quantified with Florbetapir-PET imaging.
Results: The hippocampal cingulum and inferior longitudinal fasciculus were identified as independent components of both networks. Additionally, the AT network is supported by the thalamic radiations and corpus callosum, while the PM network is underpinned by the cingulum and inferior fronto-occipital fasciculus. An inverted U-shaped relationship was found between Aβ burden and white matter fiber integrity. Although no direct association was observed between fiber integrity and AT or PM functional connectivity, significant interactions with Aβ load were found: individuals with high Aβ levels showed a negative association between AT structural and functional connectivity, while those with low Aβ levels showed a positive correlation.

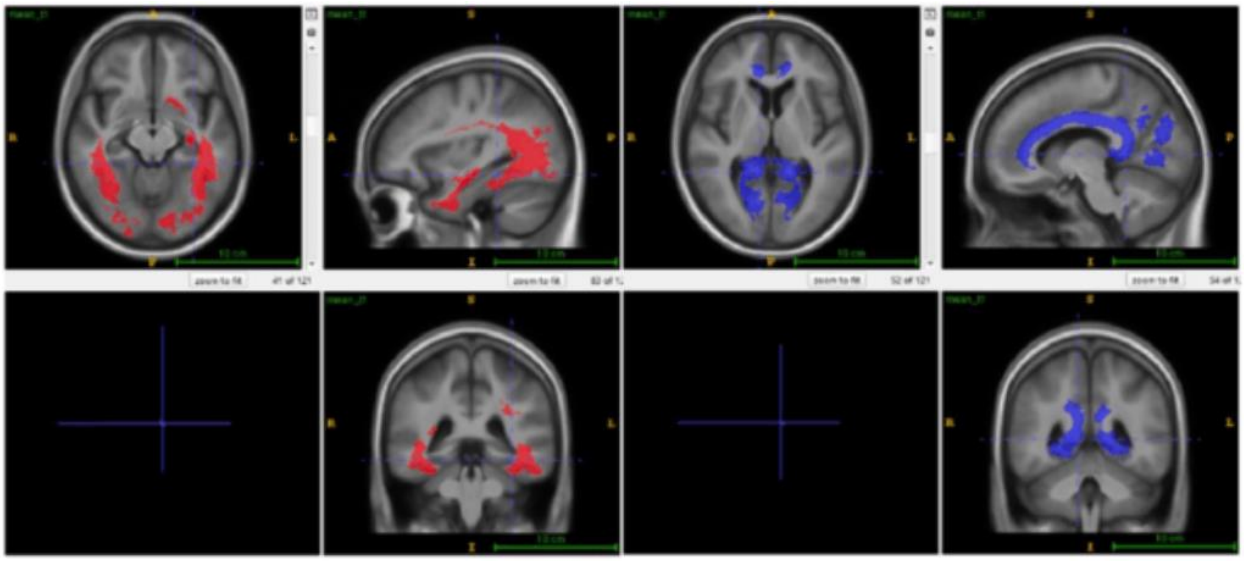

Figure 1: Fibers supporting the AT and PM networks. Red corresponds to fibers supporting the AT network and blue corresponds to fibers supporting the PM network.

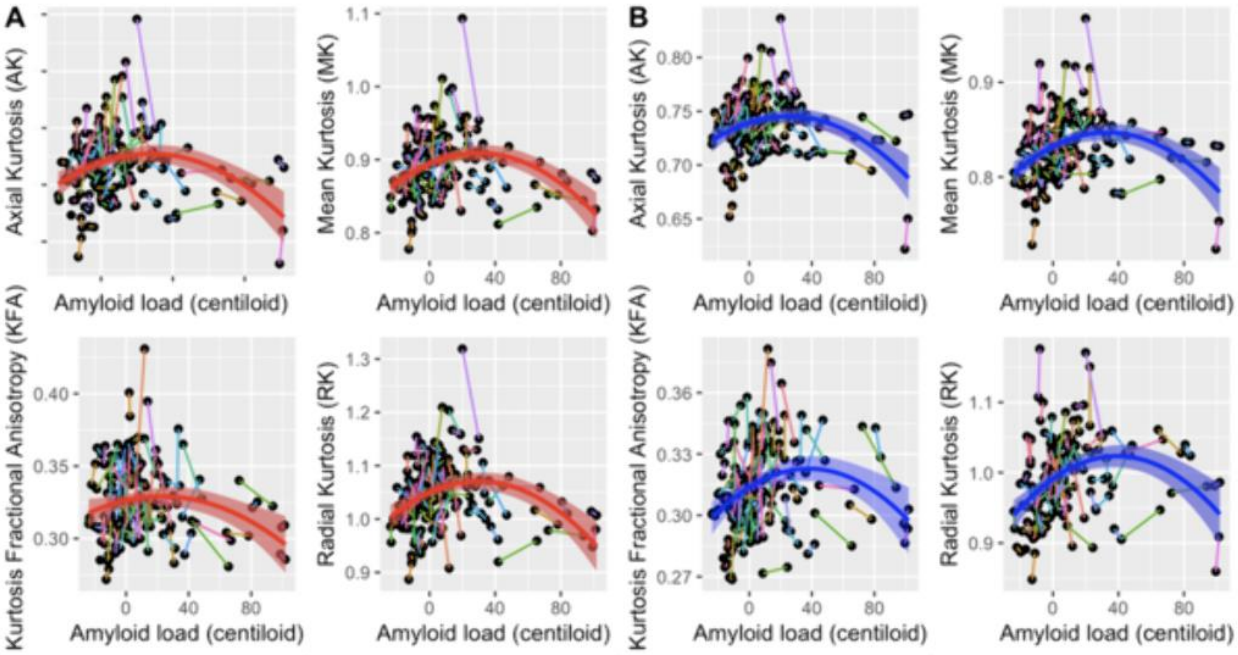

Figure 2: **Evolution of fiber integrity as a function of Aβ load** (centiloid), **following a non-linear model.** A) Graphs of measurements within fibers passing through the PRC (perirhinal cortex) B) Graphs of measurements within fibers passing through the PHC (parahippocampal cortex).

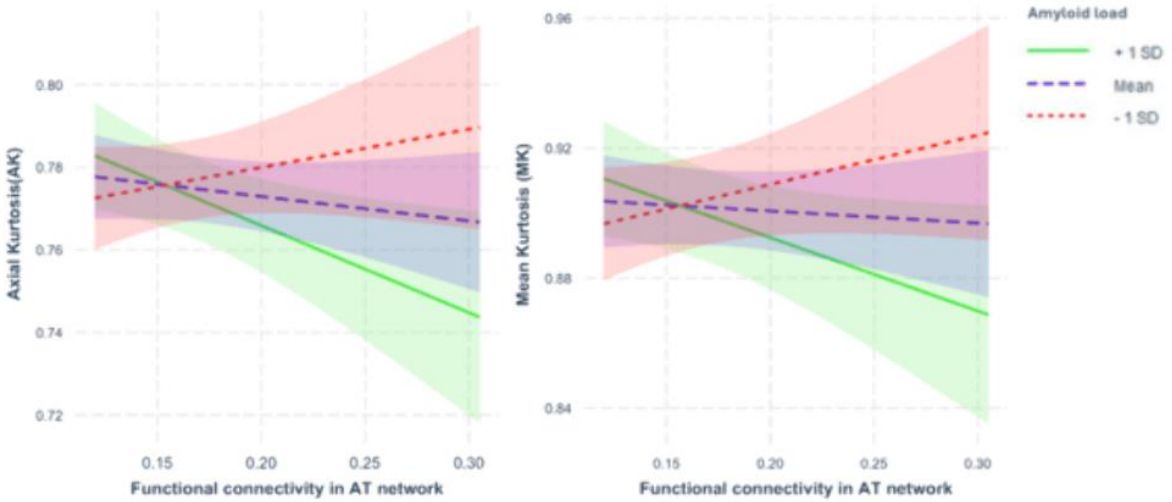

Figure 3: Evolution of fiber integrity measurements as a function of functional connectivity, in interaction with Aβ load (centiloid).

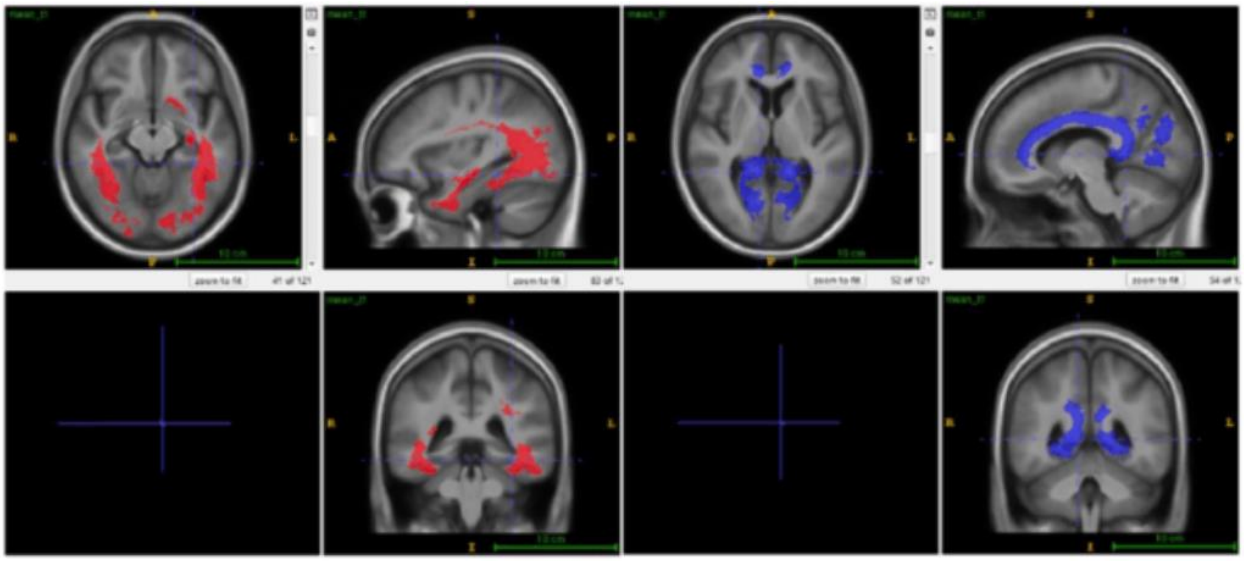

Figure 1: Fibers supporting the AT and PM networks. Red corresponds to fibers supporting the AT network and blue corresponds to fibers supporting the PM network.

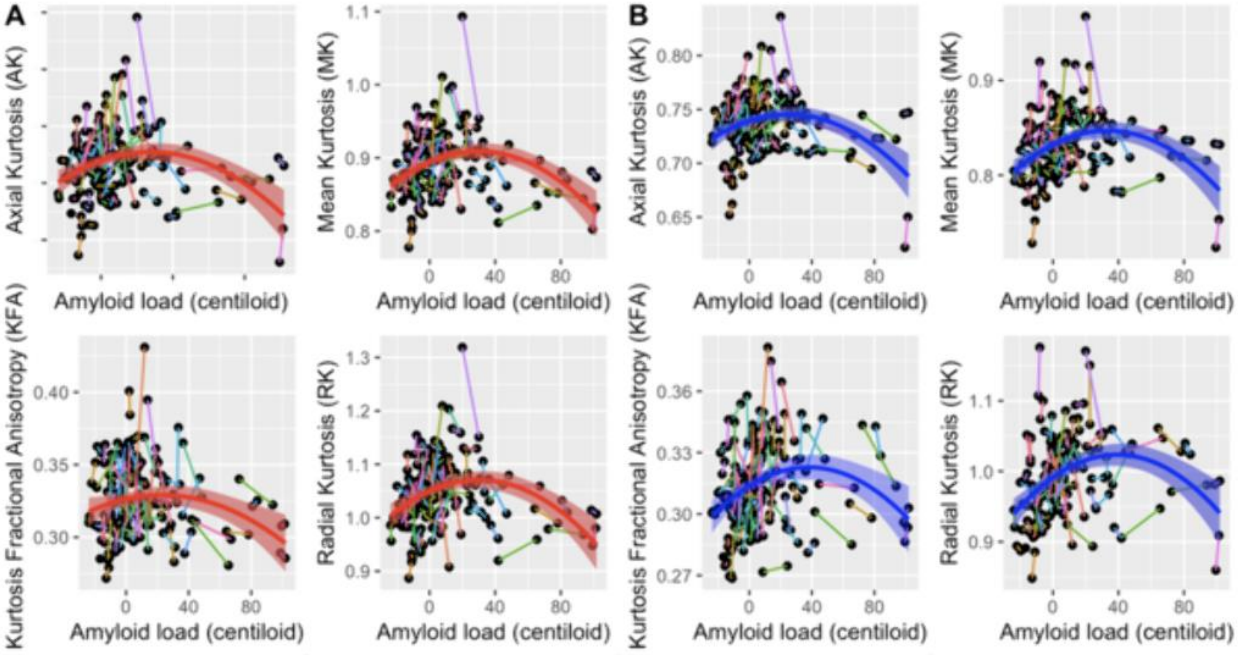

Figure 2: Evolution of fiber integrity as a function of Aβ load (centiloid), **following a non-linear model.** A) Graphs of measurements within fibers passing through the PRC (perirhinal cortex) B) Graphs of measurements within fibers passing through the PHC (parahippocampal cortex).

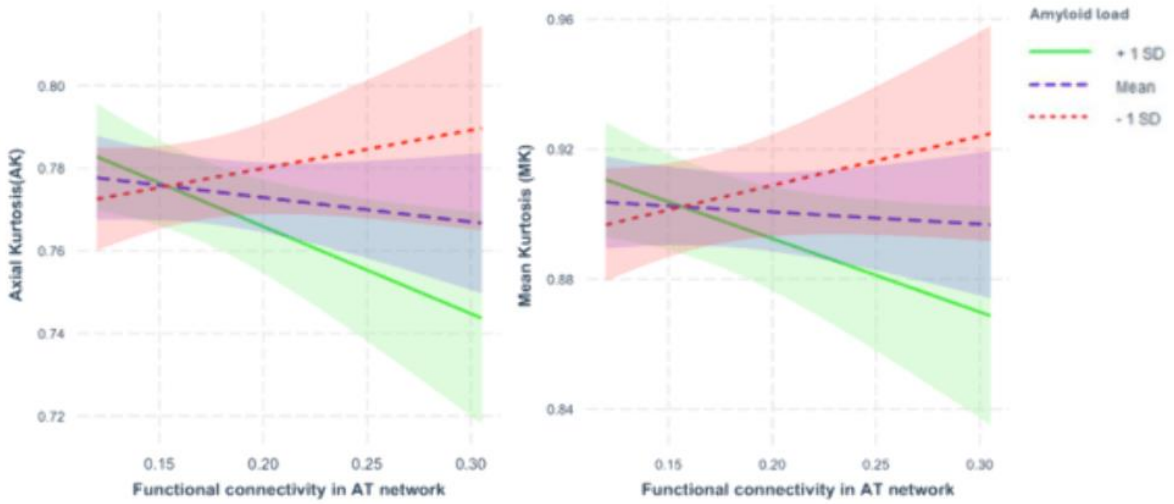

Figure 3: Evolution of fiber integrity measurements as a function of functional connectivity, in interaction with Aβ load (centiloid).

Conclusions: These findings underscore the impact of Aβ on MTL structural connectivity and its association with increased AT functional connectivity, providing new insights into the complex relationship between connectivity and Aβ.

Virtual OO - 031

Virtual E-Posters and Oral On-Demand
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ASSESSING BIOMARKER PATTERNS FOR SUBTYPE ASSOCIATIONS

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Aims: Late-onset Alzheimer disease (AD) is a complex and heterogeneous disease. Various plasma/CSF tests based on ratios of amyloid-beta and p-tau species are valuable for diagnosing brain amyloid pathology, but fall short of identifying AD subtypes. Assessment of a biomarker pattern with an AD subtype is commonly conducted by fitting a regression model and calculating the AUC. We recently demonstrated the inability of AUC to discriminate associations when the subtype comprises less than half of the AD cases in the sample. We introduce a customized metric and present a pattern of 63 genes that is significant for both discovery data and independent validation data.
Methods: Existing gene expression dataset GSE15222 was downloaded from GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE15222). The AD cases and normal controls were divided into 60% Discovery and 40% Validation sets. We utilized the Duo correlation metric on the Discovery data and created a network with the 1000 highest weight edges. Breadth-first search (BFS) was employed to identify all of the separated components and each component was tested using our new method. The four largest components were tested for associations.
Results: The Duo network included edges with weights >= 0.798. BFS revealed four components with node cardinalities ranging from 4 to 131. There were 31 smaller components and 48,395 singleton nodes. The component with 63 nodes exhibited odds ratio of 4.83 with 95% CI of (2.66,8.78), Youden J value of 0.349 and p-value < 0.0001 for the Discovery data. It exhibited odds ratio of 3.85 with 95% CI of (1.93,7.67), Youden J value of 0.325 and Bonferroni-corrected p-value of 0.0064 for the Validation data.
Conclusions: Our new metric revealed a promising genetic pattern and holds potential for future AD precision medicine research.

Virtual OO - 032

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MACULAR DEGENERATION, ALZHEIMER'S, PARKINSON'S AND MULTIPLE SCLEROSIS THE CAUSE AND TREATMENT

Jeremy Mcmeen
Superior Vision, P.C., Optometric Physician, Superior, United States of America

Aims: Macular degeneration, Alzheimer's, Parkinson's and Multiple Sclerosis are caused by a virus, bacteria and odontoblast cells. The key to these diseases is the virus-bacteria interactions and how the odontoblast cells affect the human body. In simple terms, periodontitis and gum disease cause these neurodegenerative diseases.
Methods: Clinical evaluation and treatment of patients.
Results: Macular degeneration, Alzheimer's, Parkinson's and Multiple Sclerosis are caused by periodontal bacteria, herpes viruses and odontoblast cells.
Conclusions: Macular degeneration, Alzheimer's, Parkinson's and Multiple Sclerosis are caused by periodontal bacteria, herpes viruses and odontoblast cells.

Virtual OO - 033

Virtual E-Posters and Oral On-Demand
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IMPAIRED BETA AMYLOID HOMEOSTASIS AND ELEVATED LEVELS OF FSH AND LH IN WOMEN AS AN INDEPENDENT RISK FACTOR

Milena Jovicic[1], Svetlana Jovicic Pavlovic[2], Natalija Pavlovic[3], Svetlana Vujovic[4]
[1]Institute for virusology, vaccine and sera torlak, Department For Laboratory Diagnostic, belgrade, Serbia, [2]ukcs, Clinic For Nephrology, Beograd, Serbia, [3]ukcs, National Center For Infetility And Ebdocrinology Of Gender, Clinic For Endocrinology, Diabetes And Diseases Of Metabolisam, Beograd, Serbia, [4]ukcs, Head Of Clinical For Endocrinology And Metabolic Disease, Beograd, Serbia

Aims: Although aging is the main risk factor for the development of neurodegenerative diseases such as AD. The aim of our study was to demonstrate that elevated levels of FSH and LH can be an independent risk factor for disruption of amyloid beta homeostasis.
Methods: We compared literature data on neuroendocrine changes in the menopausal transition of neuroendocrine changes in patients with premature ovarian failure that we published earlier.
Results: Literature data indicate that women are at a higher risk than men for developing Alzheimer's disease during their lifetime. The results we previously published indicate a positive correlation between elevated levels of FSH and LH and amyloid beta in patients with POI.
Conclusions: Impaired amyloid beta homeostasis caused by elevated FSHand LH levels in both menopausal women and POI patients. These data open new avenues for future preventive treatments in the early stages.

Virtual OO - 034

Virtual E-Posters and Oral On-Demand
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REVEALING GLIAL DIVERSITY AND MOLECULAR CLOCKS ACROSS HUMAN HIPPOCAMPAL POSTNATAL LIFESPAN AND IN ALZHEIMER'S DISEASE USING SINGLE-CELL RNA-SEQ TECHNOLOGY

Yijing Su
University of Pennsylvania, Department Of Oral Medicine, Philadelphia, United States of America

Aims: To reveal the molecular diversity of glial cells in the human hippocampus and their temporal dynamics over the lifespan.
Methods: We performed single-nucleus RNA sequencing to generate a transcriptome atlas of the human hippocampus across the postnatal lifespan.
Results: Detailed analyses of astrocytes, oligodendrocyte lineages, and microglia identified subpopulations with distinct molecular signatures and revealed their association with specific physiological functions, age-dependent changes in abundance, and disease relevance. We further characterized spatiotemporal heterogeneity of GFAP-enriched astrocyte subpopulations in the hippocampal formation using immunohistology. Leveraging glia subpopulation classifications as a reference map, we revealed diversity of glial cells differentiated from human pluripotent stem cells, and identified dysregulated genes and pathological processes in specific glia subpopulations in Alzheimer's disease (AD).
Conclusions: Our study significantly extends our understanding of human glial cell diversity, population dynamics across the postnatal lifespan, and dysregulation in AD, and provides a reference atlas for stem cell-based glia differentiation.

Virtual OO - 035

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ALZHEIMER'S DISEASE-DERIVED BACTEROIDES DOREI CONTRIBUTES TO COGNITIVE DECLINE IN A STRAIN-SPECIFIC MANNER

Leah Beauchamp, Lily Palumbo, Shuqi Li, Christine Chen, Caroline Wasen, Seth Gale, Howard Weiner, Laura Cox
Harvard Medical School, Brigham & Women's Hospital, Neurology, Boston, United States of America

Aims: The gut microbiota changes in aging and in Alzheimer's disease (AD) and can contribute to cognitive decline by modulating immunity. We previously found that *Bacteroides fragilis* increases amyloid-beta (Ab) plaques by impairing microglial Ab phagocytosis. Because Bacteroides strains are functionally diverse and have either beneficial or detrimental roles, we investigated Bacteroides from AD vs. healthy controls (HC).
Methods: We isolated *Bacteroides* species from AD and HC subjects and investigated their ability to modulate Ab uptake by myeloid cells in vitro and their effects on cognition and immune responses in APP/PS1 mice in vivo.
Results: We found that a *Bacteroides dorei* strain isolated from a healthy control stimulated Ab uptake more than the *B. dorei* strain isolated from the AD subject. We then administered HC- or AD-derived *B. dorei* live bacteria to APP/PS1 and WT mice from 4 months of age to 7 months of age. We found that AD-derived *B. dorei* impaired spatial memory, and cognitive deficits were only observed in female mice. AD-derived *B. dorei* stimulated the release of pro-inflammatory cytokines TNFa and IFNg, whereas HC-derived *B. dorei* reduced the levels of pro-inflammatory cytokines Grzb and IL-17. Finally, microglia were analyzed by bulk RNA sequencing and pathway analysis revealed an increase in metabolic processing stimulated by AD-derived *B. dorei* compared to HC.
Conclusions: These data suggest that *B. dorei* may have important strain-specific and sex-specific effects on cognition in AD by triggering an inflammatory response that effects microglia. Understanding immunologic, metabolomic, and bacterial genomic differences will provide novel insight into mechanisms by which the microbiome can contribute to AD pathogenesis.

Virtual OO - 036

Virtual E-Posters and Oral On-Demand
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SYNTHESIS AND STUDY OF SOME COUMARIN-OXADIAZOLE CONJUGATES AS POTENTIAL CANDIDATES FOR THE TREATMENT OF COGNITIVE DECLINE

Poonam Piplani, Ajay Kumar, Geetakshi Arora
Panjab university, University Institute Of Pharmaceutical Sciences, chandigarh, India

Aims: Novel *4-((5-substrituted phenyl-1,3,4-oxadiazole-2-yl)methoxy)-2H-chromen-2-one* derivatives were designed, synthesized and evaluated against scopolamine induced deficit cholinergic transmission and oxidative stress serving as promising leads for treatment of cognitive dysfunction.
Methods: A series of 8 compounds have been synthesised and evaluated against behavioural alterations using step down passive avoidance protocol at a dose of 2 mg/kg using reference standard rivastigmine. All the synthesised compounds were evaluated for their *in vitro* acetylcholinesterase (AChE) inhibition at five different concentrations using mice brain homogenate as the source of the enzyme. Biochemical estimation of markers of oxidative stress (lipid peroxidation, superoxide dismutase, glutathione, catalase) has also been carried out to assess the role of synthesised compounds on oxidative stress induced by scopolamine
Results: Compound **PP-389** showed better AChE inhibitory activity with percentage inhibition of 51.83±7.29 as compared to the standard (48.00±3.28). The resulting compound also displayed appreciable results in combating scopolamine induced oxidative stress, thus serving as promising lead for the amelioration of oxidative stress induced in cognitive decline. In molecular docking studies against active site of acetylcholinesterase **(PDB ID: 4EY7)** , compound **PP-389** established hydrogen bond and pie-pie interactions with the prominent amino acid residues.
Conclusions: Thus, **PP-389** compound could be a promising lead structure that can be used for further development of agents with potential for cognition improvement.

Virtual OO - 037

Virtual E-Posters and Oral On-Demand
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INHIBITION OF PI3K AND MTOR BY GSK1059615 AS A THERAPEUTIC CONTENDER AGAINST AB AGGREGATION IN EARLY-ONSET ALZHEIMER'S DISEASE

Bill Chan, Shaohua Qi, Michael Chan, Li Yang, Zheng Yin, Hong Zhao, Stephen Wong
Houston Methodist, T. T. & W. F. Chao Center For Brain, Houston, United States of America

Aims: Alzheimer's disease (AD) is marked by an array of pathologies, including the accumulation of β-amyloid (Aβ) plaques and hyperphosphorylated tau (p-Tau) proteins, neuroinflammation, and neuronal loss. While the FDA has approved promising therapies, identifying high-confidence mechanistic targets of cognitive decline persists as a challenge. We aim to investigate the therapeutic potential of drugs and bioactive compounds in restoring AD-impaired memory, executive function, and physiology.
Methods: High-content screening through a systematic AD drug repositioning framework with 4,600 known agents yielded GSK1059615, a PI3K/mTOR inhibitor that diminishes AD pathology in 3D human AD cell culture and mice models. Cell-free *in vitro* aggregation assays validated effects on Aβ oligomerization. *In vivo* testing employed three-month-old 5xFAD and PS19 mice, injected intraperitoneally every other day for a month with vehicle (0.1 % DMSO) or treatment (GSK1059615, 10mg/kg BW). To assess memory-related alterations, we conducted the Y-Maze, Open Field Test, Novel Object Recognition Task, and Morris Water Maze. Organs were harvested for neuropathological and toxicological appraisal, with downstream effects of Aβ formation evaluated by Western blot, ELISA, and RT-qPCR. Single-cell mRNA sequencing and spatial transcriptomics elucidated cellular interaction networks.
Results: The 3D human AD cell model and cell-free Aβ aggregation assay established that GSK1059615 dose-dependently inhibits Aβ accumulation. Treated mice exhibited behavioral improvements in recognition and spatial memory compared to vehicle controls. Morphological analyses confirmed declines in Aβ deposition and neuron loss within hippocampus and cortex regions of treated mice.
Conclusions: Pharmacological inhibition of PI3K/mTOR by GSK1059615 improved cognitive performance and neuronal health in AD mice models without adverse effects. GSK1059615 administration yielded key reductions beyond Aβ plaque deposition, displaying neuroprotective effects on early-onset AD. Further investigations are warranted to explore our findings' clinical translatability.

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Virtual E-Posters and Oral On-Demand
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TRANSCRIPTIONAL RESPONSES OF MICROGLIA AND ENDOTHELIAL CELLS TO ANTI-ABETA TREATMENT IN MICE WITH ARIA

Praveen Bathini[1,2], Maria Tzousi Papavergi[3,4], Stephan Schilling[5], Jens Rahfeld[5], David Holtzman[6], Cynthia Lemere[1,2]
[1]Brigham and Womens Hospital, Boston, United States of America, [2]Harvard Medical School, Boston, United States of America, [3]Maastricht University, Maastricht, Netherlands, [4]Neurology, Brigham and Womens Hospital, Boston, United States of America, [5]Fraunhofer Institute for Cell Therapy and Immunology, Halle (Saale), Germany, [6]washington university, st. louis, st. louis, United States of America

Aims: Anti-Aβ antibodies are linked to amyloid-related imaging abnormalities (ARIA), including vasogenic edema and microhemorrhages, particularly in ApoE4 carriers. This study aimed to compare 3D6-L mAb, a murine version of bapineuzumab, with IgG2a, an isotype control, to explore cell-specific transcriptional changes in the brain following passive immunization.
Methods: Plaque-rich 16.5-mo-old APP/PS1dE9; hApoE4 mice were treated weekly (i.p.) for 7- weeks with 15 mg/kg 3D6-L or IgG2a. Amyloid-beta (Aβ) plaque load, C1q, fibrillar amyloid-associated C1q immunostaining, and Prussian blue staining for microhemorrhages were quantified. Microglia cells were FACS sorted, followed by RNAseq to evaluate differentially expressed genes (DEGs). Additionally, 20-month-old APP/PS1dE9;hApoE4 mice underwent 7-week passive immunization with 15 mg/kg 3D6-L or IgG2a followed by FACS sorting of CD31+ vascular endothelial cells and RNAseq to evaluate differentially expressed genes (DEGs). In the current experiments, we are working on CDC-mutant 3D6 mAb to inhibit complement activation in a CAA-rich 5xFAD;E4 mouse model.
Results: Passive immunization in 16.5-month-old mice with 3D6-L reduced the plaque burden, increased C1q levels in the brain and plaques-associated C1q colocalization. Prussian blue staining revealed a significant increase in microhemorrhages. Microglial RNAseq identified 3D6-L treatment-dependent DEGs, including elevation of complement *Cfp*, *C4b* gene expression, and pathways related to innate immune response, and cytokine-mediated signaling. Endothelial cell transcriptome in 20-mo-old mice that underwent 7-weeks of passive immunization revealed increased expression of genes involved in inflammation and lipid metabolism including *IL1r1, Cxcl12, Lcn2, Abca1, CH25H, vWf*, and *Cfh*.
Conclusions: In summary, 3D6-L reduced plaque burden and increased C1q levels but caused more microhemorrhages. Microglia showed increased complement and immune-related gene expression, while endothelial cells exhibited increased inflammation and lipid metabolism genes, indicating potential therapeutic targets to mitigate ARIA.

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Virtual OO - 039

Virtual E-Posters and Oral On-Demand
ON-DEMAND ORAL IN ONLINE GALLERY AND MOBILE APP ONLY

RATIONAL DESIGN OF ALZHEIMER'S VACCINE TO MAXIMIZE SELECTIVE TARGETING OF TOXIC AMYLOID-BETA OLIGOMERS

Johanne Kaplan[1], Ebrima Gibbs[2], Scott Napper[3], Erin Scruten[3], Juliane Coutts[2], Neil Cashman[1]
[1]ProMIS Neurosciences, Cambridge, United States of America, [2]University of British Columbia, Vancouver, Canada, [3]University of Saskatchewan, Saskatchewan, Canada

Aims: A large body of evidence indicates that soluble toxic oligomers of amyloid-beta (Abeta) are a primary driver of Alzheimer's disease (AD). Through computational modeling, 4 different conformational B cell epitopes of Abeta oligomers were identified. The objective was to select an optimal vaccine composition amongst 15 possible combinations of 1 to 4 epitopes to provide maximal binding to a toxic oligomer-enriched low molecular weight (LMW) fraction of soluble AD brain extract.
Methods: Mice were vaccinated with the 4 different conformational B cell epitopes conjugated to KLH to provide T cell help and formulated with QS-21 adjuvant. Serum IgG titers against the peptide epitopes were measured by ELISA and T helper cell responses by ELISPOT. The reactivity of serum antibodies with Abeta oligomers versus monomers was evaluated by SPR, and plaque binding by immunohistochemistry.
Results: All 4 epitopes elicited robust antibody responses. ELISPOT analysis showed a T cell response to KLH only, and not the oligomer epitopes. Serum antibodies elicited by the 4 epitopes all showed the desired selective reactivity with oligomers, not monomers nor plaque. Comparison of the SPR binding responses to the LMW fraction of AD brain extract by equivalent amounts of IgG from immune serum of monovalent vaccines vs mixtures of 2, 3 or 4 sera was used to rank vaccine compositions. Maximal reactivity was observed with immune IgG against a single epitope (peptide 301), the target of PMN310, our clinical-stage monoclonal antibody. There was no advantage of additional epitopes.
Conclusions: Vaccination with oligomer-restricted conformational B cell epitopes conjugated to KLH produced strong antibody responses with no measurable pro-inflammatory T cell responses against Abeta. Immunization with epitope 301 alone was sufficient to produce maximal reactivity against brain oligomers.

Virtual OO - 040

Virtual E-Posters and Oral On-Demand
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ELEVATED CSF AB42/TOTAL TAU INDEX PREDICTS ARIA RISK IN ALZHEIMER'S PATIENTS TREATED WITH LECANEMAB

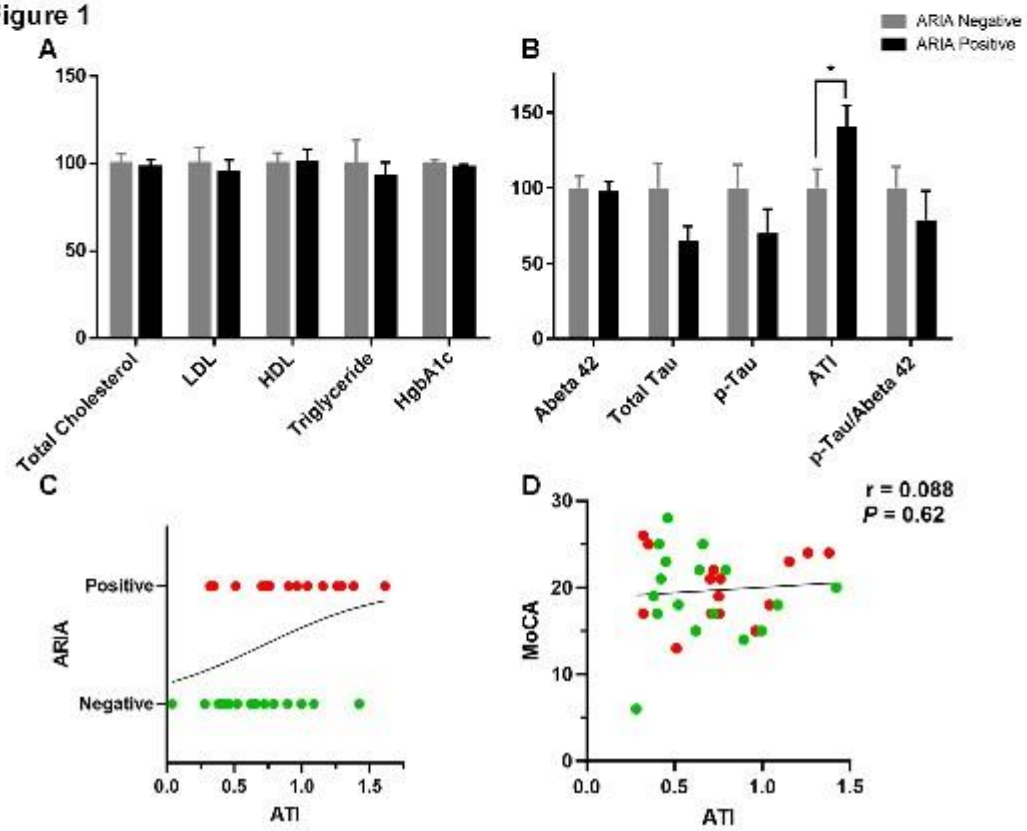
Shenghua Zhu, Saurabh Rohatgi, Jeremy Ford, Esteban Calle Cadavid, Odette Ganem Chagui, Benjamin Kozak, Maryam Vejdani-Jahromi, Jarrel Seah, Hana Farzaneh, Nim Omid-Fard, Harry Griffin, Javier Romero
Massachusetts General Hospital, Radiology, Boston, United States of America

Aims: Anti-amyloid immunotherapies (AAIs) effectively treat Alzheimer's disease (AD) but are often associated with amyloid-related imaging abnormalities (ARIA). Identifying biomarkers to predict ARIA risk is crucial. While cerebrospinal fluid (CSF) biomarkers aid in AD diagnosis, their predictive value for ARIA development remains underexplored. This study investigates whether CSF biomarkers can predict ARIA in AD patients treated with lecanemab.
Methods: In this single-center retrospective study, 54 AD patients treated with lecanemab were identified, with 27 developing ARIA post-treatment. Baseline clinical and CSF data were compared between patients with and without ARIA. Logistic regression analyzed associations between CSF biomarkers and ARIA development, while linear regression evaluated the relationship between CSF biomarkers and cognition, assessed by the Montreal Cognitive Assessment (MoCA).
Results: Baseline characteristics were comparable between ARIA-positive and ARIA-negative groups. No significant differences were observed in lipid profiles, HbA1c levels, CSF Aβ42, phosphorylated tau levels, or p-tau/Aβ42 ratio. Total tau levels were lower in ARIA-positive patients (408.6 vs. 626.6 pg/mL; $p = 0.067$), but this did not reach statistical significance. However, Aβ42/total tau index (ATI) was significantly higher in patients who developed ARIA (0.8760 vs. 0.6217; $p = 0.0337$). Logistic regression showed that a higher ATI was associated with increased ARIA risk (odds ratio 8.741; 95% CI: 1.242–92.19; $p = 0.0284$), with an area under the ROC curve of 0.696 ($p = 0.042$). No significant association was found between MoCA scores and ATI ($p = 0.626$).

Table 1

	ARIA Positive	ARIA Negative	*p* values
Total patients included	27	27	
Female	14 (51.8%)	13 (48.1%)	1.0
Age (in years)			
Mean	69.2	70.1	
Median	68	69	0.717
Range	56-84	56-88	
Baseline Cognition			
MoCA	20.4	19.1	0.304
MMSE	24.8	22.9	0.076
Genetic profile			
APOE ε4 carrier status	19 (70.4%)	14 (51.8%)	0.264
Comorbidities			
Hypertension	13 (48.1%)	14 (51.8%)	1.0
Diabetes	2 (7.41%)	3 (11.1%)	1.0
Dyslipidemia	19 (70.4%)	20 (74.1%)	1.0
Anticoagulation			
Aspirin use	6 (22.2%)	5 (18.5%)	1.0

Figure 1



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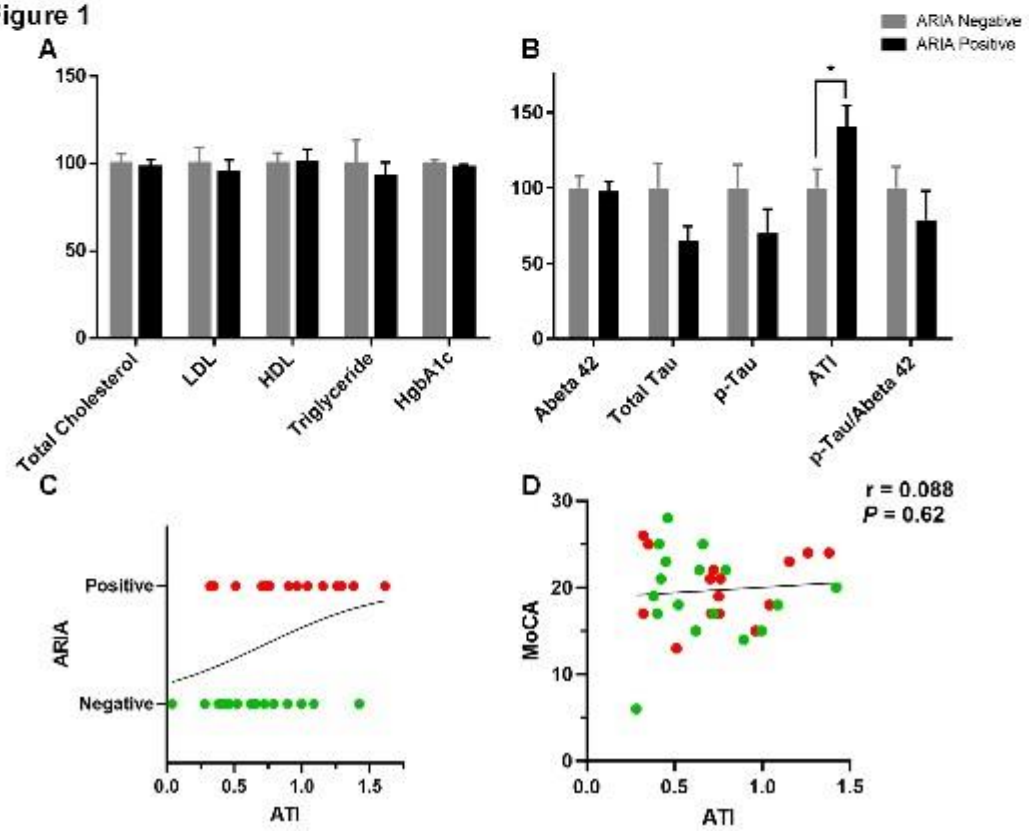

Conclusions: A higher ATI is significantly associated with an increased risk of developing ARIA in AD patients treated with lecanemab. The lack of association between ATI and cognitive function suggests that ATI may reflect underlying mechanisms independent of cognitive status. Therefore, ATI may serve as a candidate CSF biomarker for predicting ARIA risk, potentially enhancing patient selection and monitoring during therapy.

Virtual OO - 041

Virtual E-Posters and Oral On-Demand
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DEVELOPMENT, CHARACTERISATION AND NEUROPROTECTIVE EFFECTS OF NOVEL POLYMER-DRUG CONJUGATE NANO-POLYPLEX: TOWARDS A MULTI-TARGET TREATMENT FOR NEURODEGENERATIVE DISEASES

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Aims: This study aimed to develop a multifunctional polymer-drug conjugate nano-polyplex combining antioxidant and anticholinesterase polymers, to explore its potential for enhancing therapeutic effects in neurodegenerative diseases (NDs).
Methods: A nano-polyplex was formulated by mixing cationic antioxidant-polymer and anionic anticholinesterase-polymer conjugates. Particle size was measured using a Zetasizer and confirmed by cryogenic transmission electron microscopy (Cryo-TEM). The antioxidant activity was evaluated using the oxygen radical absorbance capacity (ORAC) assay, while cholinesterase inhibition was assessed *via* Ellman's assay. Cytotoxicity, neuroprotective, and anti-inflammatory effects were studied in undifferentiated SH-SY5Y human neuroblastoma and BV-2 murine microglial cell lines using the MTT assay. The Thioflavin T (ThT) assay and TEM were used to analyze amyloid beta (Aβ) aggregation in a cell-free assay, and western blotting was conducted to evaluate tau protein expression in undifferentiated SH-SY5Y cells induced with okadaic acid.
Results: The nano-polyplex formed uniform nanoparticles of 30.5±7.9 nm. Significantly enhanced antioxidant activity ($p \leq 0.01$) and cholinesterase inhibition ($p \leq 0.01$) were exhibited with the nano-polyplex compared to parent drugs alone. The nano-polyplex was non-toxic to undifferentiated SH-SY5Y cells (cell viability >80%) but showed significant toxicity in BV-2 cells (cell viability 75%, $^{***}p \leq 0.001$). The nano-polyplex significantly protected undifferentiated SH-SY5Y cells against hydrogen peroxide-induced oxidative stress (45% protection, $p \leq 0.0001$), reduced lipopolysaccharide-induced inflammation in BV-2 cells by more than 20% ($p \leq 0.01$), and reduced Aβ aggregation by over 10% ($p \leq 0.01$) in a cell-free assay. Additionally, the nano-polyplex decreased okadaic acid-induced tau hyperphosphorylation by 50% ($p \leq 0.0001$) and reduced total tau protein expression ($p \leq 0.01$) in undifferentiated SH-SY5Y cells.
Conclusions: This study demonstrates nano-polyplex's potential to be a multi-target treatment option for NDs.

Virtual OO - 042

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ASSESSING THE IMPACT OF STEM CELL CONDITIONED MEDIUM AND PLATELET-RICH PLASMA ON THE HIPPOCAMPUS IN AN STZ-INDUCED ALZHEIMER'S RAT MODEL

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Larestan university of medical sciences, Anatomy, Larestan, Iran

Aims: Alzheimer's disease (AD) is marked by progressive cognitive decline and memory loss. This study explores the combined effects of conditioned medium from human umbilical cord mesenchymal stem cells (CM) and platelet-rich plasma (PRP) on rats modeled with AD.
Methods: Methods Forty-eight male Sprague Dawley rats were divided into six groups: Control, Sham, AD, and three treatment groups. AD was induced using streptozotocin (STZ; 3 mg/kg, intracerebroventricular (ICV)). The treatment groups received injections of CM (200 µl, intraperitoneally (i.p.)) and/or PRP (100 µl, intravenously (i.v.)) for eight days. Behavioral tests, including the Morris water maze and novel object recognition, were conducted to assess learning and memory. After the tests, the rats were sacrificed, and their brains were removed, sectioned, and stained with cresyl violet. The hippocampus volume and neuron count were evaluated using stereological techniques.
Results: Results In the AD group, the discrimination ratio, time spent in the target zone, volume of Cornu Ammonis1 (CA1) and Dentate Gyrus (DG), and the number of pyramidal and granular cells significantly decreased compared to the Sham group. These parameters increased in the CM and CM+PRP groups compared to the AD group ($p < 0.01$). PRP alone did not show any significant effect on the examined parameters.
Conclusions: Conclusions CM appears to be beneficial in treating AD, as it improved STZ-induced learning and memory impairments and the structure of the hippocampus.

Virtual OO - 043

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ON-DEMAND ORAL IN ONLINE GALLERY AND MOBILE APP ONLY

PGK1 ACTIVATORS MAY AS A POTENTIAL STRATEGY FOR TREATING VARIOUS NEURODEGENERATIVE DISEASES

Rong Cai
Beihang University, School Of Engineering Medcine, Beijing, China

Aims: The impaired energy production in PD, together with the ability of TZ to increase PGK1 activity, led us to hypothesize that increasing glycolysis in vivo might slow or prevent the apoptotic neurodegeneration of PD.
Methods: To test this hypothesis, we used models of PD in flies, mice, rats, and human cells, and we interrogated patient databases to learn whether TZ altered the course of disease.
Results: Our results indicate that in both toxin-induced and genetic models of PD in multiple animal species, enhancement of PGK1 activity slows or prevents neurodegeneration in vivo, thereby increasing dopamine levels and improving motor performance. Enhancement of PGK1 activity showed beneficial effects, even when begun after the onset of neurodegeneration. Moreover, interrogation of 2 independent databases suggested that TZ and related quinazoline agents slowed disease progression, reduced PD-related complications in individuals with PD, and reduced the risk of receiving a PD diagnosis.
Conclusions: Evidence from our present and earlier experiments indicates that TZ elicits its beneficial effects in PD by enhancing the activity of PGK1 and not by inhibiting the α1 -adrenergic receptor.

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Virtual OO - 044

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NOVEL AAV-BASED TOOLKIT FOR GENE EDITING PERTURBATIONS FOR THE TREATMENT OF PARKINSON'S AND ALZHEIMER'S DISEASES.

Boris Kantor[1], Bernadette O'Donovan[2], Joseph Rittnier[3], Dellila Hodgson[2], Nicholas Lindner[1], Sophia Guerrero[1], Ornit Chiba-Falek[4]
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Aims: Epigenome-editors packaged into adeno-associated (AAV) vector are attractive therapeutic modalities for neurogenerative diseases. The main caveat of the AAV delivery system, however, remains to be its small packaging capacity mainly not suitable for the delivery of bulky and complex CRISPR interference (CRISPR*i*) tools. To circumvent this limitation, here we aim to develop a compact dCas9-repressor vector packaged within a single, optimized AAV backbone. We thought to validate the developed system in the experimental models related to Alzheimer's and Parkinson's diseases *in vitro* and *in vivo*.
Methods: To circumvent a small packaging capacity of adeno-associated vectors, here we applied a reporter-based, single- virion's resolution screening procedure to devise and select for a compact dCas9-based repressor system. The lead construct that has been evolved uses a smaller dCas9 variant derived from Staphylococcus aureus (*Sa*) fused with a synthetic, bipartite small transcription repression domain (TRD) from MeCP2 protein and KRAB peptides. The final dSaCas9-KRAB-MeCP2(TRD) construct can be efficiently packaged, along with a gRNA, into AAV particles.
Results: The epigenome editing construct developed in this study was found to be suitable for packaging into an all-in-one AAV particles. In fact, the resulting viral titers were in the range sufficient for most gene therapy applications in humans. Furthermore, the engineered vector generated in the cGMP-like concentrated format could induce a long-term and sustainable repression of the GFP/Luciferase reporter system, as well as downregulate the expressions of ApoE and alpha-synuclein genes related to Alzheimer's and Parkinson's diseases, respectively, in vitro and in vivo.
Conclusions: Here, we engineered novel AAV-based epigenome-editing vector capable to efficiently silence *APOE4* and SNCA genes, involved in LOAD and PD, respectively. This new platform will broaden the CRISPR/dCas9 toolset available for transcriptional manipulation of gene expression in research and therapeutic settings.

Virtual OO - 046

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XENON GAS TREATMENT: FROM ALZHEIMER'S MOUSE MODELS TO CLINICAL TRIAL

Wesley Brandão[1], Nimansha Jain[2], Zhuoran Yin[3], Kilian L Kleemann[4], Madison Carpenter[1], Ana Durao[1], Mathew Blurton Jones[5], Ilya Ilin[6], Howard Weiner[1], David Holtzman[2], Oleg Butovsky[1]
[1]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital - Harvard Medical School, Boston, United States of America, [2]Department of Neurology, Washington University School of Medicine, St. Louis, United States of America, [3]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, United States of America, [4]Institute for Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Bonn, Germany, [5]Department of Neurobiology and Behavior at the University of California, Irvine, United States of America, [6]General Biophysics, LLC, Wayland, United States of America

Aims: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, with emerging evidence suggesting that dysregulation of the brain's immune system, particularly microglia, plays a critical role in its onset and progression by increasing neuroinflammation and oxidative stress. A key question is how to modulate microglia to treat AD. Xenon gas (Xe), a noble gas used in anesthesia and neuroprotection, crosses the blood-brain barrier, making it a potential therapeutic.

Our goal is to translate Xe's pre-clinical results into human trials, focusing on the safety of Xe inhalation in AD patients.
Methods: In pre-clinical models (APP/PS1, 5xFAD, P301S), weekly 30% Xe treatments for 2-3 months were followed by pathological analysis. Clinically, Xe will be administered to healthy volunteers at increasing exposure durations (10, 20, 30, and 45 minutes).
Results: Xe inhalation polarizes microglia towards an intermediate activation state termed "pre-MGnD," enhancing amyloid plaque compaction, reducing dystrophic neurites, brain atrophy, and neuroinflammation, while improving nest-building behavior in APOE4 mice. Additionally, Xe modulated the inflammatory profile of human monocytes in vitro and microglia *in vivo*. In collaboration with General Biophysics, we developed a human Xe inhalation system with a sensor. Importantly, the FDA has approved the start of our Phase I safety clinical trial.
Conclusions: These findings support the translation of Xe inhalation as a novel therapy, with our first human clinical trial aiming to establish safety in healthy subjects as a precursor to testing Xe in AD patients.

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SYNERGISTIC ROLE OF GAMMA-AA PEPTIDES TARGETING PATHOLOGICAL MECHANISMS AS A NOVEL STRATEGY FOR ALZHEIMER'S DISEASE

Ning Shen[1], Haiqiang Yang[1], Xiaoyang Lin[2], Jianfeng Cai[1], Chuanhai Cao[3]
[1]University of South Florida, Chemistry, Tampa, United States of America, [2]Taneja College of Pharmacy of University of South Florida, Tampa, United States of America, [3]Taneja College of Pharmacy of University of South Florida, Pharmaceutical Sciences, Tampa, United States of America

Aims: Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) aggregation and neuronal degeneration. This study aimed to evaluate the therapeutic potential of two novel gamma-AApeptides, HW-C9 and 125-6b, for AD treatment. HW-C9 was designed to inhibit Aβ aggregation, while 125-6b was developed to promote neuronal growth. The efficacy of the combined treatment was assessed both in vitro and in vivo.
Methods: In vitro studies initially focused on determining HWC9's effect in inhibiting Aβ aggregation using biochemical assays. Cytotoxicity and neurogenic effects were tested using N2a, N2a/APPswe cells, and primary mouse neurons. In vivo, aged Human APP transgenic mice received intranasal administration of the combined peptide-mimics for three months. Cognitive function was assessed using the Radial Arm Water Maze (RAWM) to evaluate memory performance.
Results: In vitro studies revealed that HWC9 effectively inhibited Aβ aggregation, and 125-6b enhanced neuronal growth. In vivo, the combination therapy showed a positive trend in memory function enhancement in APP transgenic mice, as demonstrated by improved performance in the RAWM test.
Conclusions: Combining AApeptides with different roles exhibits a synergistic effect in the cell culture model and APP mouse model. Our findings strongly imply that future treatment for AD should focus on multi-functional approaches.

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PRECISE QUANTITATIVE ASSESSMENT OF HIPPOCAMPAL SUBREGIONAL STRUCTURAL CHANGES ASSOCIATED WITH COGNITIVE-MOTOR IMPAIRMENT IN CEREBRAL SMALL VESSEL DISEASE

Boyao Chen[1], Yajie Fu[2], Lingfei Guo[1], Changhu Liang[1], Chaofan Sui[1], Yian Gao[1], Na Wang[1], Xinyue Zhang[1], Zhenyu Cheng[1], Yiwen Chen[1], Pengcheng Liang[1], Xinxin Huo[1], Fushuai Zhang[1]
[1]Shandong Provincial Hospital Affiliated to Shandong First Medical University, Department Of Radiology, Jinan, China, [2]The First Affiliated Hospital of Shandong First Medical University, Department Of Medical Ultrasound, Jinan, China

Aims: This study focuses on exploring the differences in the volume of the hippocampal (Hippocampus, HP) subregions in patients with different loads of cerebral small vessel disease (CSVD), and the correlation between HP volume changes and cognitive-motor function impairment in CSVD patients.
Methods: A German Siemens Healthcare MAGNETOM Skyra 3.0T MR scanner was used to collect three-dimensional T1-weighted (3D-T1WI) structural images and other routine sequences from 157 subjects. Subjects were divided into three groups based on the total load score of CSVD: 46 severe CSVD load patients, 45 mild CSVD load patients , and 66 healthy controls. Image segmentation was performed using FreeSurfer image analysis software, and the HP was divided into 19 symmetrical subregions. All subjects underwent psychological scale assessment, cognitive-motor function testing. ANCOVA or chi-square tests were used to analyze the differences in HP subregion volumes among the three groups, and multiple linear regression was used to explore whether the severity of CSVD is independently related to HP subregion volume changes, and to analyze the Pearson correlation between the differences in groups and cognitive-motor function.
Results: The volume reduction of the granular cell layer-molecular layer-dentate gyrus-head (GC-ML-DG-head) subregion of the HP was related to CSVD load (β=-36.52, p<0.001). The reduction in GC-ML-DG-head subregion volume was correlated with MoCA (β=0.19, p=0.02) and TUG (β=-0.1, p=0.004), and the change in GC-ML-DG-head volume played a partial mediating role in motor function (TUG) impairment caused by CSVD (mediation proportion = 27.80%).

Table1 Clinical characteristics of the participants.

General characteristics	Total Sample	HC	CSVD-m	CSVD-s	F/χ^2	*p*
Number of cases (n)	157	66	45	46		
Gender (Male, n (%))	80 (51.0%)	30 (45.5%)	24 (53.3%)	26 (56.5%)	1.47	0.479[χ]
Age (Years)	60.64±7.17	57.56±7.09	60.60±6.14	65.09±5.91	18.21	<0.001[F]
Height (m)	1.66 ±0.07	1.66 ±0.07	1.66 ±0.08	1.66 ±0.07	0.07	0.930[F]
Hypertension，n (%)	64 (40.8 %)	25 (37.9%)	11 (24.4%)	28 (60.9%)	12.89	0.002[χ]
Diabetes，n (%)	82 (52.2%)	34 (51.5%)	23 (51.1%)	25 (54.3%)	0.12	0.942[χ]
Hyperlipidemia，n (%)	80 (51.0%)	36 (54.5%)	22 (48.9%)	22 (47.8%)	0.6	0.742[χ]
Smoking，n (%)	40 (25.5%)	15 (22.7%)	14 (31.1%)	11 (23.9%)	1.07	0.584[χ]
Alcohol Consumption (%)	54 (34.4%)	20 (30.3%)	15 (33.3%)	19 (41.3%)	1.49	0.476[χ]
Glycosylated hemoglobin (mmol/L)	7.45±2.02	7.11±1.92	7.92±2.22	7.48±1.89	2.03	0.118[F]
FBG(fasting blood-glucose) (mmol/L)	7.11±2.39	6.98±2.45	6.97±1.95	7.44±2.70	0.62	0.539[F]
Cholesterol (mmol/L)	5.05±1.09	5.08±1.02	5.18±1.05	4.90±1.22	0.78	0.461[F]
Triglyceride (mmol/L)	1.59±0.92	1.58±1.09	1.59±0.81	1.59±0.75	0	0.999[F]
High-density lipoprotein (mmol/L)	1.39±0.37	1.43±0.45	1.40±0.30	1.33±0.32	1.06	0.378[F]
Low density lipoprotein (mmol/L)	3.10±0.78	3.06±0.79	3.30±0.63	2.96±0.87	2.3	0.103[F]
Degree of educationn (%)					17.5	0.002[χ]
High	64 (40.8%)	35 (53.0%)	17 (37.8%)	12 (26.1%)		
Low	45 (28.7%)	12 (18.2%)	10 (22.2%)	23 (50.0%)		
Middle	48 (30.6%)	19 (28.8%)	18 (40.0%)	11 (23.9%)		
HAMA	3.64±3.23	3.86±3.51	3.11±2.99	3.83±3.03	0.84	0.435[F]
HAMD	3.60±3.15	3.21±3.03	3.80±3.41	3.96±3.05	0.89	0.414[F]
MoCA	23.79±3.46	24.91±2.76	24.04±3.80	21.93±3.32	11.55	<0.001[F]
AVLT	55.31±13.37	58.41±12.47	54.93±15.25	51.22±11.66	4.1	0.018[F]
SDMT	33.22±13.13	37.88±11.70	34.69±12.85	25.11±11.73	15.7	<0.001[F]
SCWT	150.51±52.73	145.64±53.31	139.76±51.04	168.02±50.24	3.89	0.022[F]
TMT (s)	272.66±160.65	225.47±119.52	276.80±208.14	336.33±138.00	6.97	0.001[F]
FTSST (s)	3.58±0.75	3.76±0.53	3.51±0.76	3.39±0.95	2.35	0.030[F]
3-Meter Walk Speed (m/s)	0.94±0.16	0.98±0.17	0.92±0.13	0.91±0.15	3.53	0.032[F]
TUG (s)	8.84±1.54	8.16±1.34	8.88±1.33	9.79±1.52	18.43	<0.001[F]
APOE n (%)					6.14	0.189[χ]
E3	106 (67.5%)	43 (65.2%)	26 (57.8%)	37 (80.4%)		
E4	26 (16.6%)	13 (19.7%)	9 (20.0%)	4 (8.7%)		
E2	25 (15.9%)	10 (15.2%)	10 (22.2%)	5 (10.9%)		

Continuous data is expressed as mean ± standard deviation and discrete data is expressed as n (%); F: ANOVA test; χ^2: Chi-square test; HC：healthy control；CSVD-M：mild CSVD load group；CSVD-S：severe CSVD load group. MoCA：Montreal Cognitive Assessment；AVLT：Rey Auditory Verbal Learning Test；SDMT：Symbol Digit Modalities Test；SCWT：Stroop Color and Word Test; TMT: Trail Making Test; TUG: Timed up and go test; FTSST：Five-Times-Sit-to-Stand Test. Degree of education: junior high school and below is low, senior high school is middle, and senior high school is high.

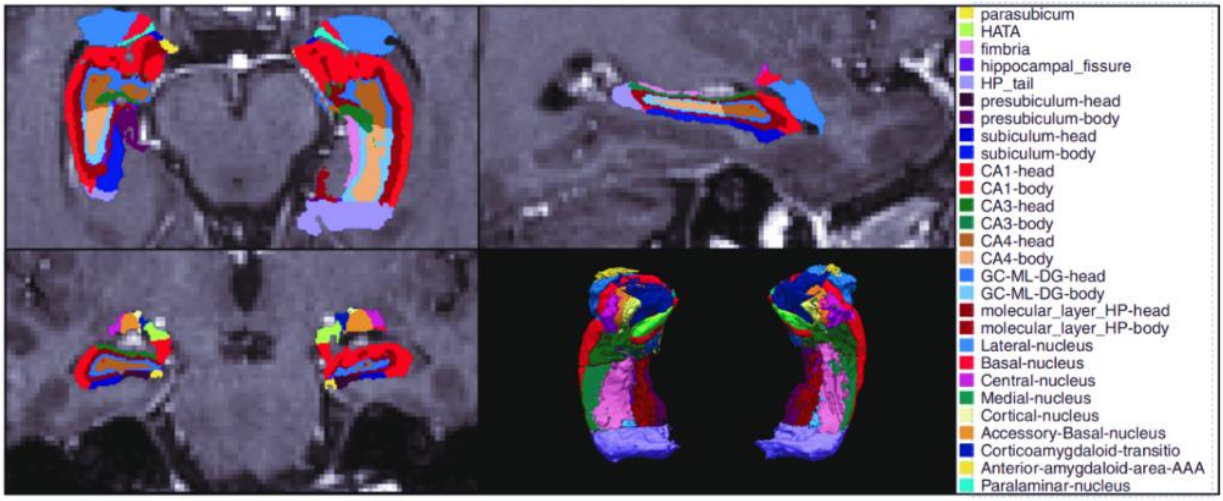

Figure1 Visual 3D rendering of hippocampal subregion segmentation

Table3 Comparison of Volume Differences in 19 Hippocampal Subregions Among Healthy Control Group, Mild CSVD Load Group, and Severe CSVD Load Group

Volume of Hippocampal Subregions (mm^3)	Total Sample	HC	CSVD-m	CSVD-s	*p*	Bonferroni.*P*
	n=157	n=66	n=45	n=46		
Hippocampal_tail	1118.44±138.02	1147.28±136.48	1109.67 ±138.37	1085.64 ±134.20	0.058	1
Hippocampal_tail	546.01±70.11	555.05±62.56	540.00 ±71.08	538.91±78.98	0.389	1
Subiculum-body	286.64±41.20	292.30±41.14	285.22 ±43.84	279.89±38.27	0.283	1
Subiculum-head	439.83±60.58	446.21±52.62	434.42 ±55.85	435.95 ±74.62	0.530	1
Hippocampal-fissure	408.82±50.19	408.16±46.10	402.19±51.96	416.25 ±54.04	0.408	1
Presubiculum-head	306.11±38.41	310.86±31.57	304.29 ±37.82	301.07±47.05	0.388	1
CA1-head	1162.37±124.05	1181.28 ±111.86	1153.59 ±122.05	1143.82 ±140.54	0.250	1
Presubiculum-body	336.35±55.73	345.00±45.25	336.96±70.80	323.33±51.25	0.128	1
Parasubiculum	127.70±24.07	128.17±21.11	123.40±25.04	131.24±26.81	0.295	1
Molecular _layer_HP-head	349.19±44.91	345.08±42.82	343.14±37.98	360.98±52.25	0.103	1
Molecular _layer_HP-body	288.65±46.46	289.25±45.22	291.31±46.29	285.19±49.13	0.815	1
GC-ML-DG-head	346.73±39.21	364.20±32.09	344.12±35.91	324.21±40.12	<0.001	<0.001
CA3-body	194.33±36.27	192.04±39.74	190.8 ±30.61	201.03±36.02	0.327	1
GC-ML-DG-body	300.62±33.33	306.79±31.35	299.25±30.71	293.11±37.34	0.096	1
CA4-head	292.87±34.36	300.90±29.97	290.36±33.95	283.82±38.53	0.029	0.571
CA4-body	272.95±31.51	278.35±30.70	269.92±28.73	268.17±34.62	0.182	1
Fimbria	161.23±37.01	169.78±25.05	161.72±38.56	148.4 ±45.99	0.010	0.207
CA3-head	262.88±34.87	266.26±32.23	260.86±33.84	260.00±39.57	0.584	1
HATA	116.30±16.53	119.21±16.45	115.54±15.58	112.88±17.17	0.128	1
Total volume of hippocampal	6907.40±668.25	7029.38±590.06	6853.28 ±650.39	6785.33 ±769.12	0.133	1

Continuous data is expressed as mean ± standard deviation; CSVD-s: severe CSVD load group; CSVD-m: mild CSVD load group; HC: healthy control group; GC-ML-DG: Granular cell layer-Molecular layer-Dentate gyrus; HATA: hippocampus - amygdala transition area.

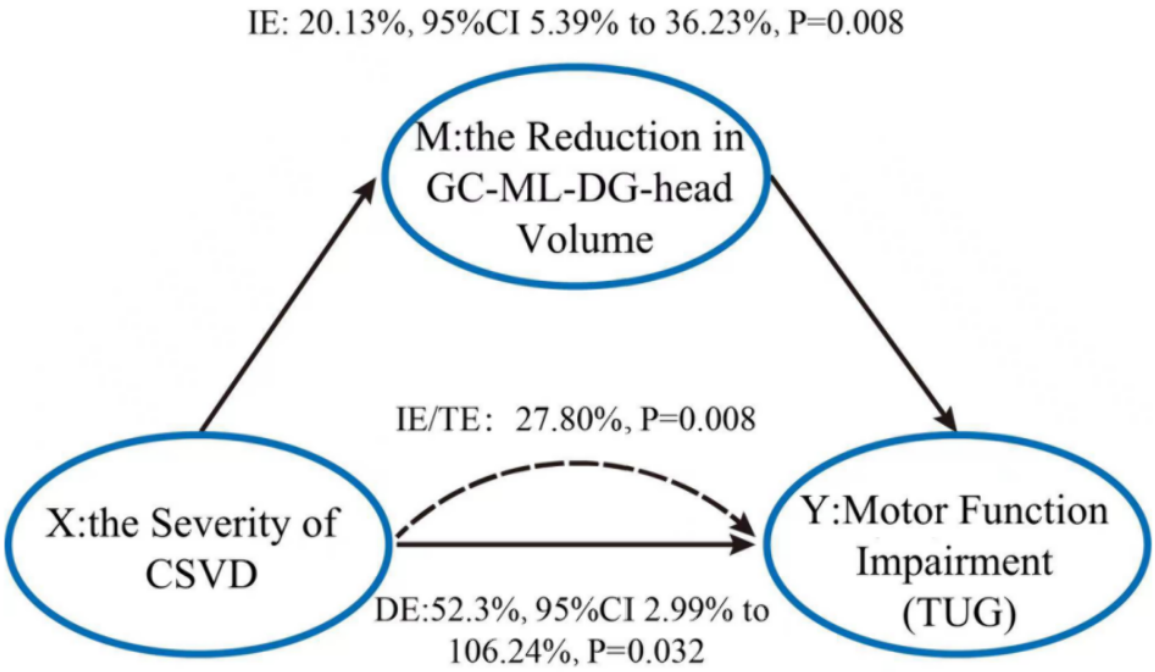

Figure3 Mediating effect of GC-ML-DG-head volume change on the impairment of CSVD motor function

DE: Direct effect; IE: Indirect effect; TE=DE+IE: Total effect; IE/T: mediation proportion

Table1 Clinical characteristics of the participants.

General characteristics	Total Sample	HC	CSVD-m	CSVD-s	F/χ^2	*p*
Number of cases (n)	157	66	45	46		
Gender (Male, n (%))	80 (51.0%)	30 (45.5%)	24 (53.3%)	26 (56.5%)	1.47	0.479[χ]
Age (Years)	60.64±7.17	57.56±7.09	60.60±6.14	65.09±5.91	18.21	<0.001[F]
Height (m)	1.66 ±0.07	1.66 ±0.07	1.66 ±0.08	1.66 ±0.07	0.07	0.930[F]
Hypertension，n (%)	64 (40.8 %)	25 (37.9%)	11 (24.4%)	28 (60.9%)	12.89	0.002[χ]
Diabetes，n (%)	82 (52.2%)	34 (51.5%)	23 (51.1%)	25 (54.3%)	0.12	0.942[χ]
Hyperlipidemia，n (%)	80 (51.0%)	36 (54.5%)	22 (48.9%)	22 (47.8%)	0.6	0.742[χ]
Smoking，n (%)	40 (25.5%)	15 (22.7%)	14 (31.1%)	11 (23.9%)	1.07	0.584[χ]
Alcohol Consumption (%)	54 (34.4%)	20 (30.3%)	15 (33.3%)	19 (41.3%)	1.49	0.476[χ]
Glycosylated hemoglobin (mmol/L)	7.45±2.02	7.11±1.92	7.92±2.22	7.48±1.89	2.03	0.118[F]
FBG(fasting blood-glucose) (mmol/L)	7.11±2.39	6.98±2.45	6.97±1.95	7.44±2.70	0.62	0.539[F]
Cholesterol (mmol/L)	5.05±1.09	5.08±1.02	5.18±1.05	4.90±1.22	0.78	0.461[F]
Triglyceride (mmol/L)	1.59±0.92	1.58±1.09	1.59±0.81	1.59±0.75	0	0.999[F]
High-density lipoprotein (mmol/L)	1.39±0.37	1.43±0.45	1.40±0.30	1.33±0.32	1.06	0.378[F]
Low density lipoprotein (mmol/L)	3.10±0.78	3.06±0.79	3.30±0.63	2.96±0.87	2.3	0.103[F]
Degree of educationn (%)					17.5	0.002[χ]
High	64 (40.8%)	35 (53.0%)	17 (37.8%)	12 (26.1%)		
Low	45 (28.7%)	12 (18.2%)	10 (22.2%)	23 (50.0%)		
Middle	48 (30.6%)	19 (28.8%)	18 (40.0%)	11 (23.9%)		
HAMA	3.64±3.23	3.86±3.51	3.11±2.99	3.83±3.03	0.84	0.435[F]
HAMD	3.60±3.15	3.21±3.03	3.80±3.41	3.96±3.05	0.89	0.414[F]
MoCA	23.79±3.46	24.91±2.76	24.04±3.80	21.93±3.32	11.55	<0.001[F]
AVLT	55.31±13.37	58.41±12.47	54.93±15.25	51.22±11.66	4.1	0.018[F]
SDMT	33.22±13.13	37.88±11.70	34.69±12.85	25.11±11.73	15.7	<0.001[F]
SCWT	150.51±52.73	145.64±53.31	139.76±51.04	168.02±50.24	3.89	0.022[F]
TMT (s)	272.66±160.65	225.47±119.52	276.80±208.14	336.33±138.00	6.97	0.001[F]
FTSST (s)	3.58±0.75	3.76±0.53	3.51±0.76	3.39±0.95	2.35	0.030[F]
3-Meter Walk Speed (m/s)	0.94±0.16	0.98±0.17	0.92±0.13	0.91±0.15	3.53	0.032[F]
TUG (s)	8.84±1.54	8.16±1.34	8.88±1.33	9.79±1.52	18.43	<0.001[F]
APOE n (%)					6.14	0.189[χ]
E3	106 (67.5%)	43 (65.2%)	26 (57.8%)	37 (80.4%)		
E4	26 (16.6%)	13 (19.7%)	9 (20.0%)	4 (8.7%)		
E2	25 (15.9%)	10 (15.2%)	10 (22.2%)	5 (10.9%)		

Continuous data is expressed as mean ± standard deviation and discrete data is expressed as n (%); F: ANOVA test; χ^2: Chi-square test; HC：healthy control；CSVD-M：mild CSVD load group；CSVD-S：severe CSVD load group. MoCA：Montreal Cognitive Assessment；AVLT：Rey Auditory Verbal Learning Test；SDMT：Symbol Digit Modalities Test；SCWT：Stroop Color and Word Test; TMT: Trail Making Test; TUG: Timed up and go test; FTSST：Five-Times-Sit-to-Stand Test. Degree of education: junior high school and below is low, senior high school is middle, and senior high school is high.

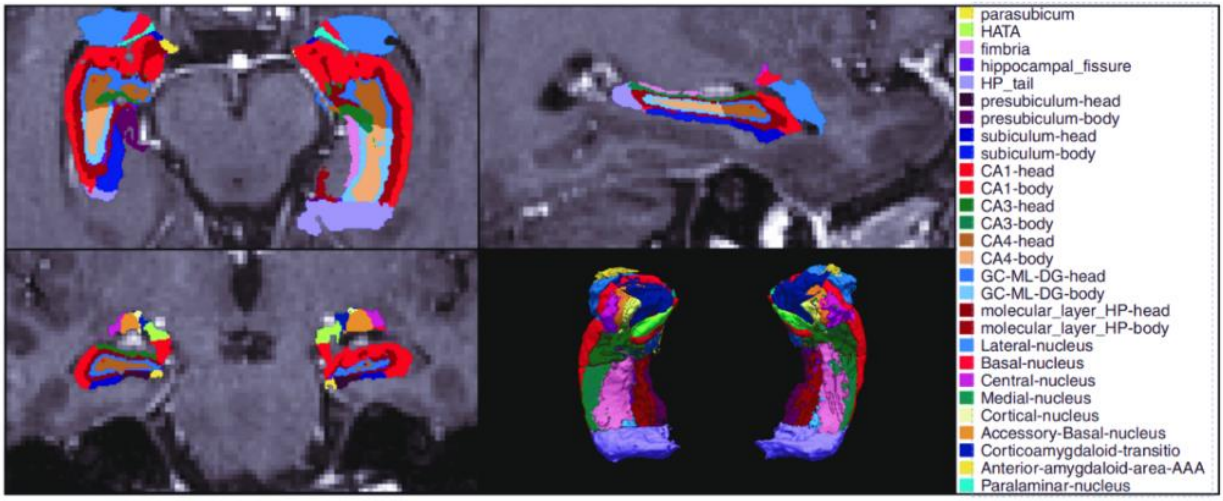

Figure1 Visual 3D rendering of hippocampal subregion segmentation

Table3 Comparison of Volume Differences in 19 Hippocampal Subregions Among Healthy Control Group, Mild CSVD Load Group, and Severe CSVD Load Group

Volume of Hippocampal Subregions (mm^3)	Total Sample	HC	CSVD-m	CSVD-s	*p*	Bonferroni.*P*
	n=157	n=66	n=45	n=46		
Hippocampal_tail	1118.44±138.02	1147.28±136.48	1109.67 ±138.37	1085.64 ±134.20	0.058	1
Hippocampal_tail	546.01±70.11	555.05±62.56	540.00 ±71.08	538.91±78.98	0.389	1
Subiculum-body	286.64±41.20	292.30±41.14	285.22 ±43.84	279.89±38.27	0.283	1
Subiculum-head	439.83±60.58	446.21±52.62	434.42 ±55.85	435.95 ±74.62	0.530	1
Hippocampal-fissure	408.82±50.19	408.16±46.10	402.19±51.96	416.25 ±54.04	0.408	1
Presubiculum-head	306.11±38.41	310.86±31.57	304.29 ±37.82	301.07±47.05	0.388	1
CA1-head	1162.37±124.05	1181.28 ±111.86	1153.59 ±122.05	1143.82 ±140.54	0.250	1
Presubiculum-body	336.35±55.73	345.00±45.25	336.96±70.80	323.33±51.25	0.128	1
Parasubiculum	127.70±24.07	128.17±21.11	123.40±25.04	131.24±26.81	0.295	1
Molecular _layer_HP-head	349.19±44.91	345.08±42.82	343.14±37.98	360.98±52.25	0.103	1
Molecular _layer_HP-body	288.65±46.46	289.25±45.22	291.31±46.29	285.19±49.13	0.815	1
GC-ML-DG-head	346.73±39.21	364.20±32.09	344.12±35.91	324.21±40.12	<0.001	<0.001
CA3-body	194.33±36.27	192.04±39.74	190.8 ±30.61	201.03±36.02	0.327	1
GC-ML-DG-body	300.62±33.33	306.79±31.35	299.25±30.71	293.11±37.34	0.096	1
CA4-head	292.87±34.36	300.90±29.97	290.36±33.95	283.82±38.53	0.029	0.571
CA4-body	272.95±31.51	278.35±30.70	269.92±28.73	268.17±34.62	0.182	1
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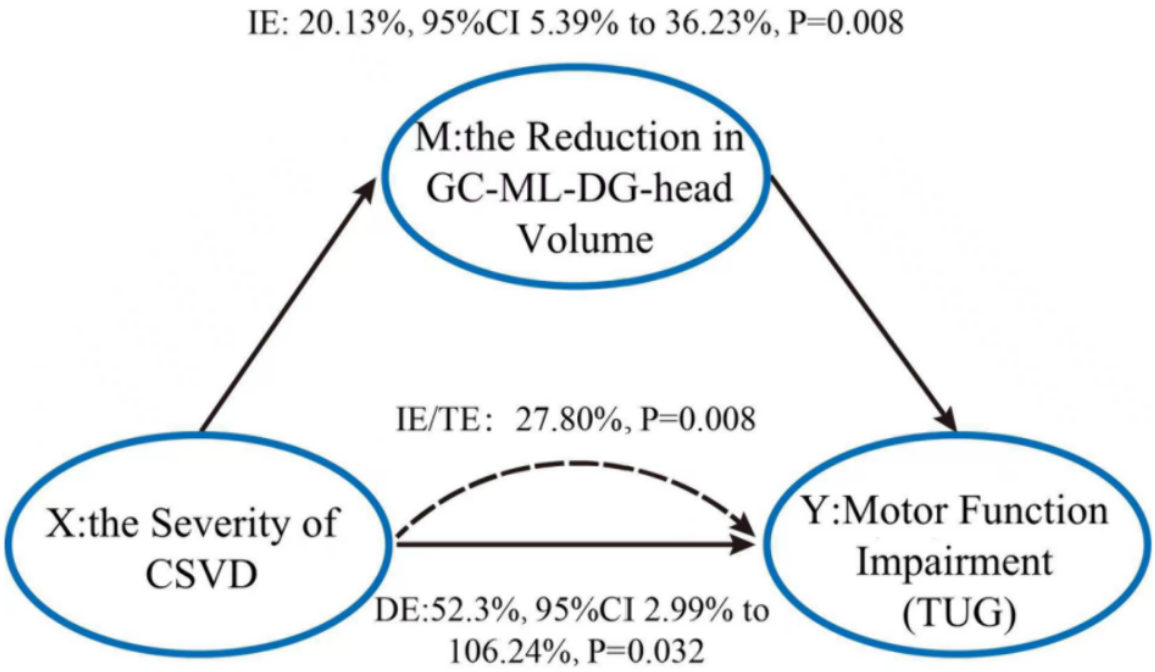

Figure3 Mediating effect of GC-ML-DG-head volume change on the impairment of CSVD motor function

DE: Direct effect; IE: Indirect effect; TE=DE+IE: Total effect; IE/T: mediation proportion

Conclusions: This study provides data on HP subregion volume changes related to CSVD load and their correlation analysis with cognitive-motor function, providing evidence for the mechanism of cognitive-motor function impairment in CSVD.

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HIPPOCAMPAL-TO-VENTRICLE RATIO IS A VIABLE NEURODEGENERATION BIOMARKER FOR EVALUATING THE LONGITUDINAL PROGRESSION OF COGNITIVE DECLINE IN THE CONTEXT OF ALZHEIMER'S DISEASE

Sofia Fernandez-Lozano[1,2], Madeleine Sharp[2], Vladimir Fonov[1,2], D Louis Collins[1,2,3]
[1]Montreal Neurological Institute-Hospital, Mcconnell Brain Imaging Centre, Montréal, Canada, [2]McGill University, Dept. Neurology And Neurosurgery, Montréal, Canada, [3]McGill University, Dept. Biomedical Engineering, Montréal, Canada

Aims: To determine if the Hippocampus-to-Ventricle Ratio (HVR), a more sensitive measure than HC volume, is effective as a neurodegeneration biomarker for the evolution of cognitive decline in Alzheimer's disease.
Methods: From the ADNI cohort[c] (625 cognitively unimpaired (CH) on 2843 visits; 800 mild cognitively-impaired on 3646 visits; and, 325 AD dementia patients on 1796 visits) we segmented the HC and surrounding temporal horns of the lateral ventricles (VC) with a Convolutional Neural Network and calculated the HVR [HC / (HC + VC)]. We fit two longitudinal mixed-effect models (MLM) predicting neurodegeneration using HC volume and HVR when controlling for diagnosis, sex, APOE4 alleles and age, and compared their model fit. From the 5969 visits with valid neuropsychological scores, we fit a multilevel confirmatory factor analysis to create a latent variable of cognitive decline using ADAS delayed word recall, CDR-SB and MMSE. Lastly, we fit a MLM to predict cognitive decline from HVR controlling for age, sex, and APOE4 alleles.
Results: The neurodegeneration MLM using HVR showed a stronger model fit than using HC volume (791 vs 580 Log Likelihood; -1,525 vs -1,103 Akaike Information Criterion; and, -1,329 vs -906 Bayesian Information Criterion, Table 1 & Figure 1). In the cognition MLM (Table 2) we found significant baseline main effects for HVR, sex, APOE4, and age. Longitudinal non-linear effects were significant for HVR and age. There were significant interactions between HVR and sex, APOE4, and (centered) age. See Figure 2. All reported β are for standardized coefficients. Table 1

MLM (random slopes: VISIT|ID)

	Hippocampal integrity	
	HC volume (1)	HVR (2)
Intercept	-0.112*** (0.037)	0.107*** (0.035)
Time	-0.154*** (0.003)	-0.174*** (0.003)
Dx	0.004 (0.022)	-0.006 (0.021)
Dx (Quad.)	0.037*** (0.014)	0.003 (0.013)
Sex (Male)	-0.084* (0.043)	-0.364*** (0.041)
APOE4	-0.563*** (0.054)	-0.387*** (0.051)
APOE4 (Quad.)	-0.031 (0.042)	-0.005 (0.040)
Age (baseline)	-0.056*** (0.003)	-0.066*** (0.003)
Time (Quad.)	0.002*** (0.0003)	0.003*** (0.0003)
Time:Dx	-0.093*** (0.005)	-0.101*** (0.005)
Time:Dx(Q)	-0.026*** (0.004)	-0.029*** (0.004)
Time:Sex(M)	-0.009*** (0.003)	0.00000 (0.003)
Time:A4	-0.055*** (0.005)	-0.065*** (0.005)
Time:A4(Q)	0.0001 (0.003)	-0.001 (0.003)
Time:Age(bl)	-0.004*** (0.0003)	-0.004*** (0.0004)
Dx:Sex(M)	0.044** (0.020)	0.057*** (0.020)
Dx(Q):Sex(M)	-0.004 (0.012)	0.035*** (0.012)
Dx:A4	-0.034 (0.033)	-0.024 (0.032)
Dx(Q):A4	0.028 (0.019)	-0.003 (0.018)
Dx:A4(Q)	0.007 (0.023)	0.026 (0.023)
Dx(Q):A4(Q)	-0.036*** (0.014)	-0.046*** (0.013)
Time(Q):Dx	0.005*** (0.0005)	0.005*** (0.0005)
Time(Q):Dx(Q)	0.002*** (0.0004)	0.001*** (0.0004)
Time(Q):Age(bl)	0.0001*** (0.00003)	0.0001*** (0.00003)
Observations	8,285	8,285
Log Likelihood	579.611	790.719
Akaike Inf. Crit.	-1,103.221	-1,525.438
Bayesian Inf. Crit.	-906.600	-1,328.817

Note: *p<0.1; **p<0.05; ***p<0.01

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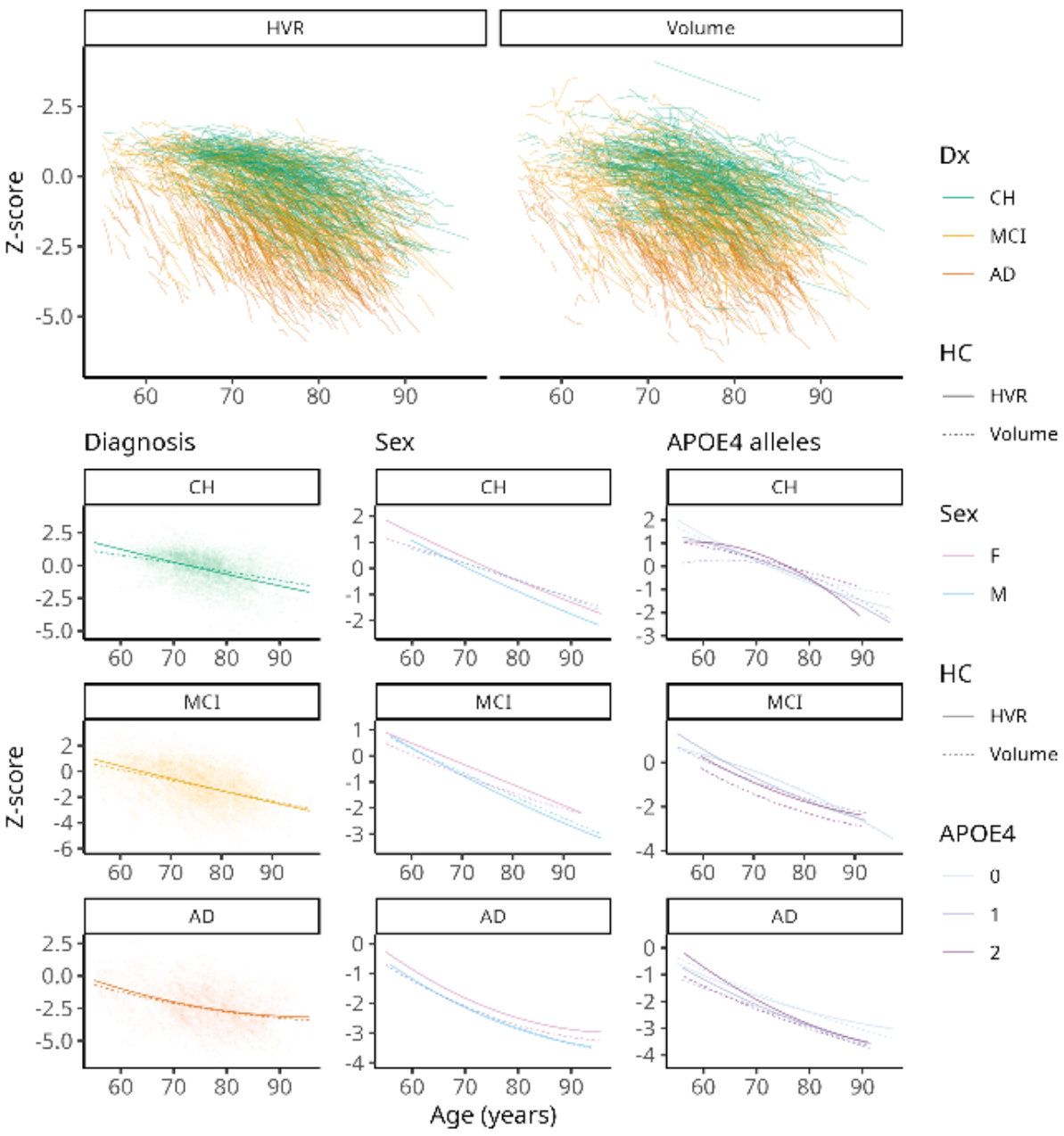
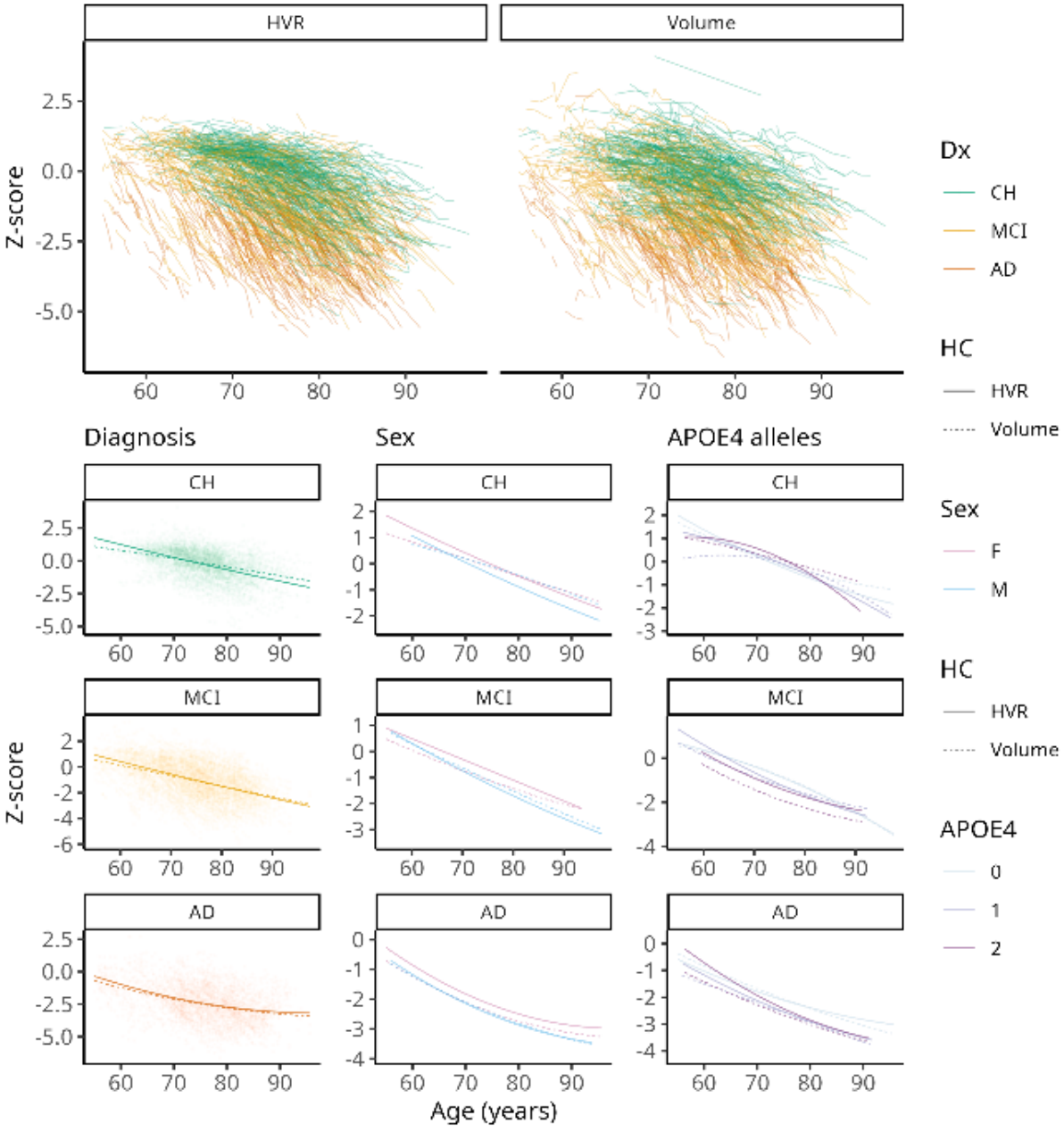


The cognitively healthy group was used as reference for Z scoring

Figure 1.

Neurodegeneration Trajectories

Mixed-effect regressions: Hippocampal volume & HVR; random intercepts and slopes



The cognitively healthy group was used as reference for Z scoring

MLM (random slopes: VISIT|ID)	
	Cognition (latent variable)
Intercept	0.153*** (0.032)
Time	0.084*** (0.014)
HVR	-0.679*** (0.030)
Sex (Male)	-0.112*** (0.038)
APOE4	0.383*** (0.046)
APOE4 (Quad.)	-0.009 (0.036)
Age (baseline)	-0.016*** (0.003)
Time (Quad.)	-0.004** (0.002)
Time:HVR	-0.121*** (0.007)
Time:Sex(M)	-0.003 (0.009)
Time:A4	0.047* (0.026)
Time:A4(Q)	0.004 (0.019)
Time:Age(bl)	-0.006*** (0.001)
HVR:Sex(M)	0.130*** (0.034)
HVR:A4	-0.158*** (0.041)
HVR:A4(Q)	0.058* (0.032)
HVR:Age(bl)	-0.005** (0.002)
Time(Q):HVR	0.004*** (0.001)
Time(Q):A4	0.003 (0.003)
Time(Q):A4(Q)	0.005** (0.002)
Time(Q):Age(bl)	0.0003** (0.0001)
Observations	5,942
Log Likelihood	-4,316.785
Akaike Inf. Crit.	8,683.569
Bayesian Inf. Crit.	8,850.814
Note:	*p<0.1; **p<0.05; ***p<0.01

Table 2.

MLM (random slopes: VISIT|ID)

	Cognition (latent variable)
Intercept	0.153*** (0.032)
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HVR	-0.679*** (0.030)
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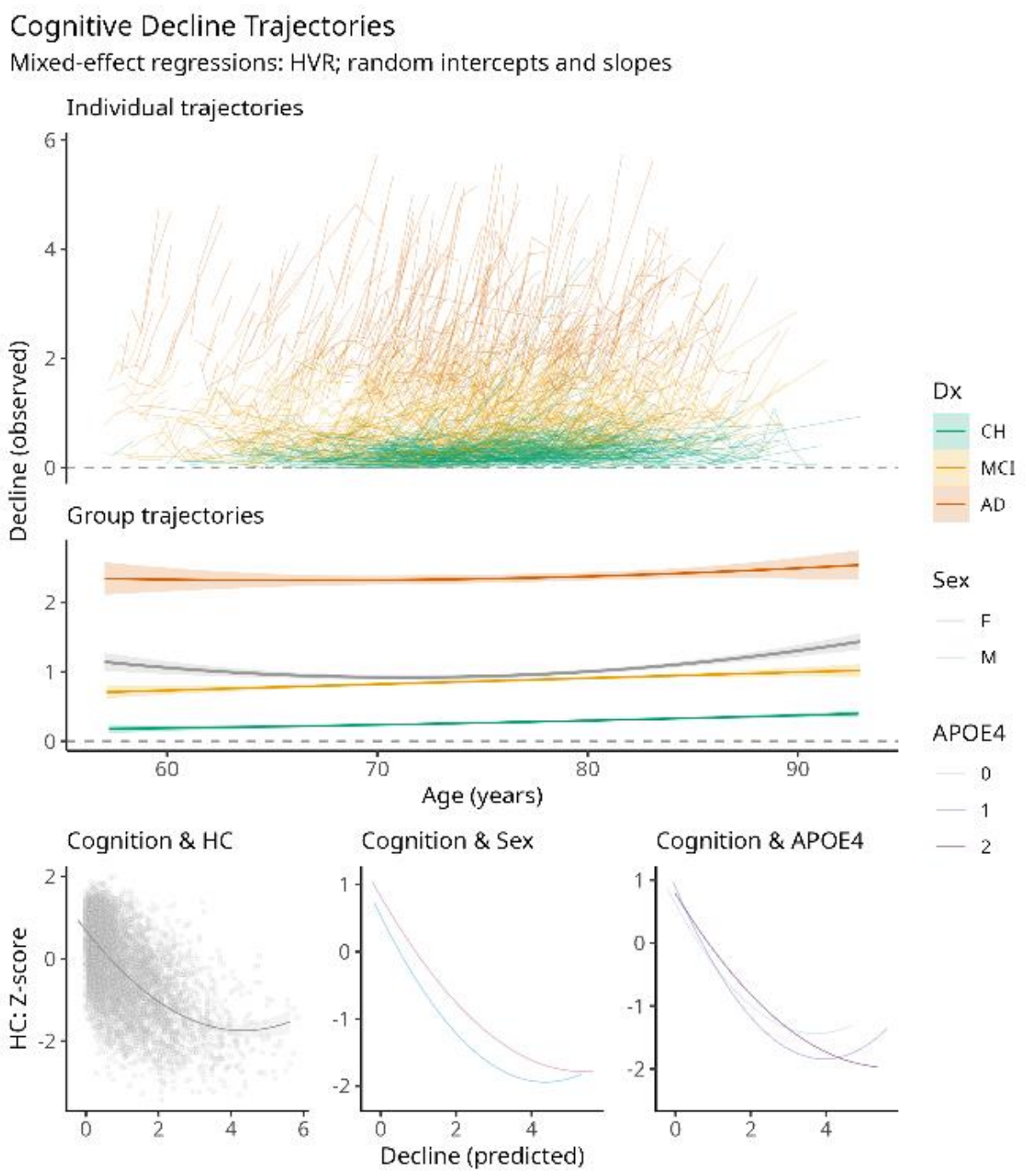
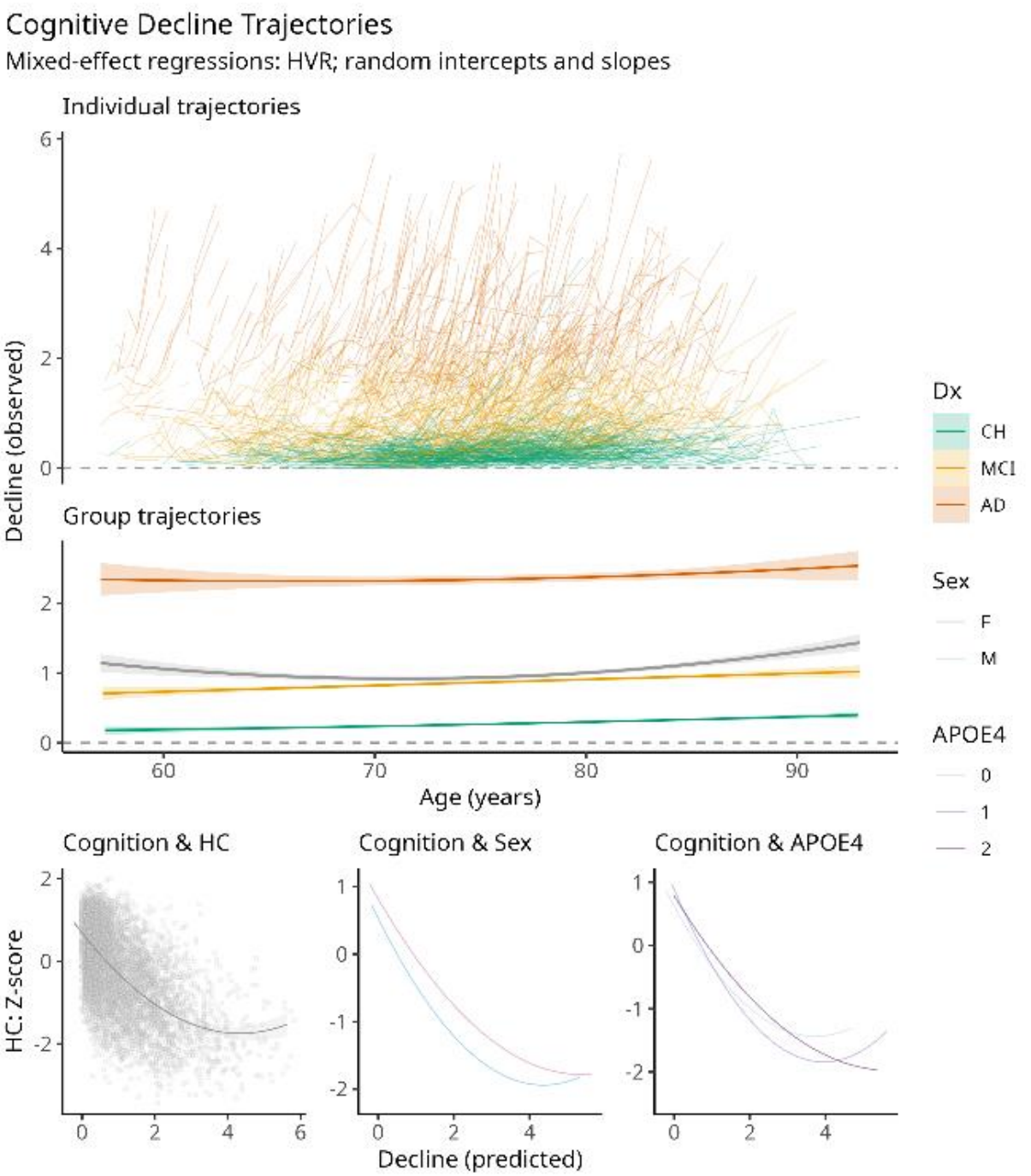


Cognitive decline was measured as a latent variable obtained from: ADASQ4, MMSE & CDRSB

Figure 2.



Cognitive decline was measured as a latent variable obtained from: ADASQ4, MMSE & CDRSB

Conclusions: Our results support that HVR is a more sensible measure of neurodegeneration than conventional HC volume, and it can be a viable biomarker for cognitive decline.

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BRAINAGEGAP IN ALZHEIMER'S DISEASE: SENSITIVITY TO CLINICAL AND BIOLOGICAL STAGES, AND PREDICTIVE VALUE FOR COGNITIVE DECLINE AND BRAIN HEALTH.

Elizabeth Kuhn[1,2], Georgios Antonopoulos[3,4], Luca Kleineidam[1,2], Melina Stark[1,2], Sandra Roeske[1], Oliver Peters[5,6], Julian Hellmann-Regen[5,7,8], Josef Priller[5,6,9,10], Anja Schneider[1,2], Jens Wiltfang[11,12,13], Frank Jessen[1,14,15], Emrah Düzel[16,17], Katharina Buerger[18,19], Robert Perneczky[19,20,21,22], Stefan Teipel[23,24], Christoph Laske[25,26], Annika Spottke[1,27], Frederic Brosseron[1], Michael Ewers[18,19], Peter Dechent[28], Stefan Hetzer[29], Klaus Scheffler[30], Matthias Schmid[1,31], Matthis Synofzik[25,32], Simon Eickhoff[3,4], Kaustubh Patil[3,4], Michael Wagner[1,2]
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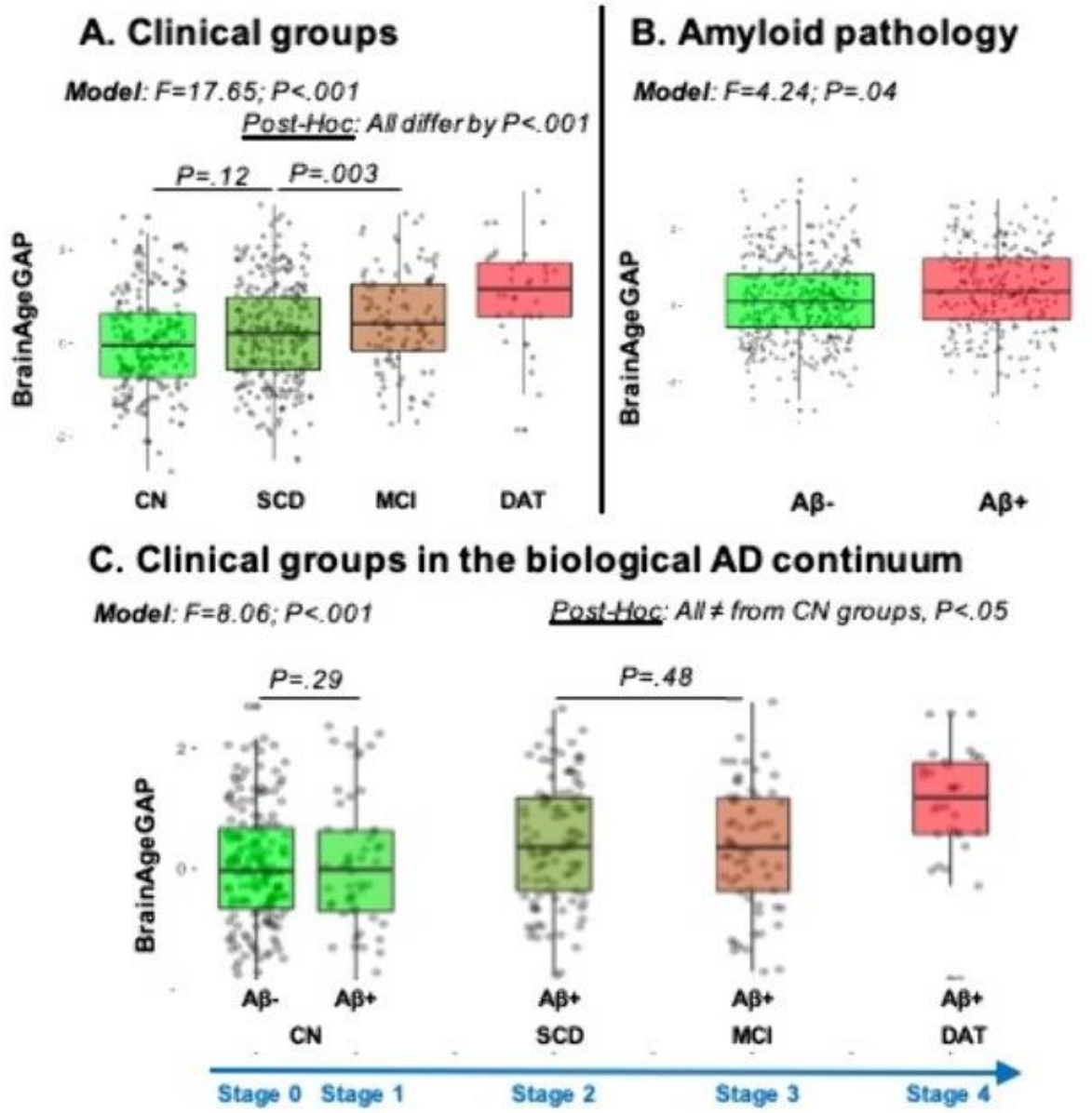
Neurology, Goettingen, Germany, [29]University of Tübingen, Department For Biomedical Magnetic Resonance, Tübingen, Germany, [30]Berlin Center for Advanced Neuroimaging, Charité – Universitätsmedizin Berlin, Berlin, Germany, [31]Institute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany, [32]Hertie Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Division Of Translational Genomics Of Neurodegenerative Diseases, Tübingen, Germany

Aims: To investigate whether BrainAgeGAP (machine-learning-based age predictions from structural MRI) is sensitive to early Alzheimer's disease (AD) stages and underlying pathology. Although BrainAgeGAP is linked to mortality risk (Cole et al., 2018) and dementia progression in patients with mild cognitive impairment (MCI, Franke & Gaser, 2019), its sensitivity to early clinical stages and AD pathology remains unclear.
Methods: Data from 630 DELCODE participants were analyzed: 216 cognitively normal (CN) older adults, 273 patients with subjective cognitive decline (SCD), 105 with MCI, and 36 with Alzheimer's type dementia (DAT). Participants underwent cognitive testing, structural MRI scanning, had amyloid and tau biomarkers, and LIBRA scores. BrainAgeGAP was calculated as MRI-predicted *minus* chronological age using BrainAgeR models. Linear regressions examined BrainAgeGAP in relation to clinical groups, AD pathology, and LIBRA scores. Mixed-effect models and Cox regressions assessed its predictive value for cognitive decline (PACC scores) and clinical progression to MCI/dementia. Analyses were adjusted for chronological age, sex, and education.
Results: BrainAgeGAP increased across clinical stages (Fig.1A, significantly from MCI), and was higher in amyloid-positive participants overall, but did not differ between CN amyloid-negative and amyloid-positive groups (Fig.1B-

Fig.1. Baseline differences in BrainAgeGAP levels (z-scores, with CN-Aβ- as reference) across clinical and biological stages of Alzheimer's Disease



Legend. Aβ-, amyloid-negative; Aβ+, amyloid-positive

C).

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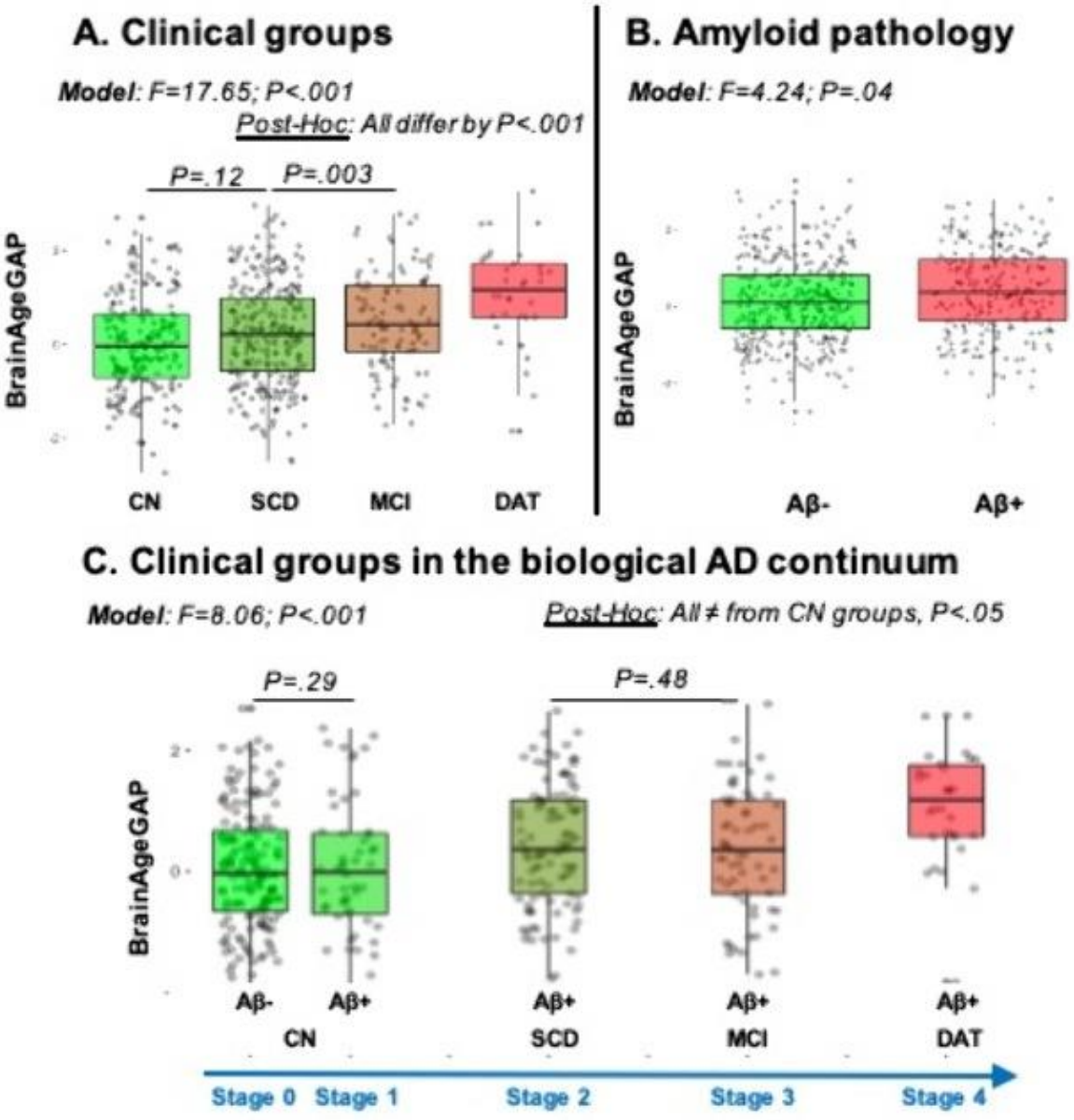
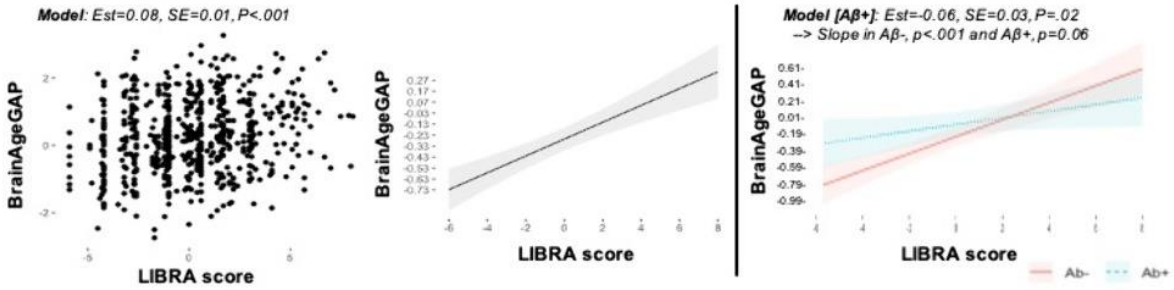


Legend. Aβ-, amyloid-negative; Aβ+, amyloid-positive

BrainAgeGAP was significantly associated with higher LIBRA scores in amyloid-negative participants only

Fig.2. Baseline associations between BrainAgeGAP levels (z-scores, with CN-Aβ- as reference) and LIBRA scores according to the amyloid status in the entire sample (N=630)



(Fig.2).

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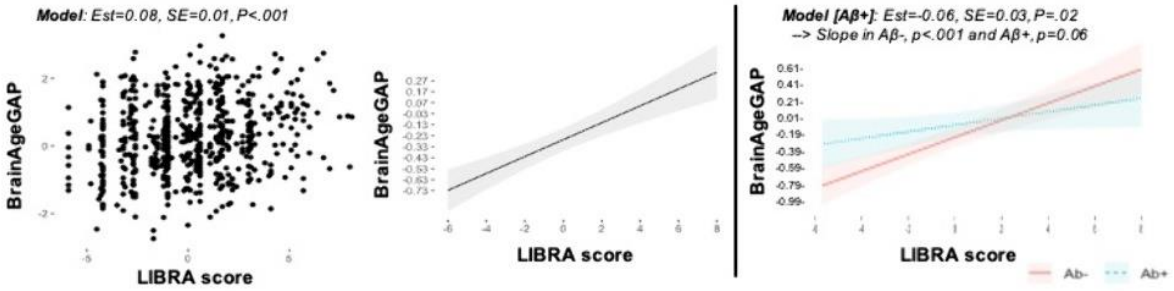
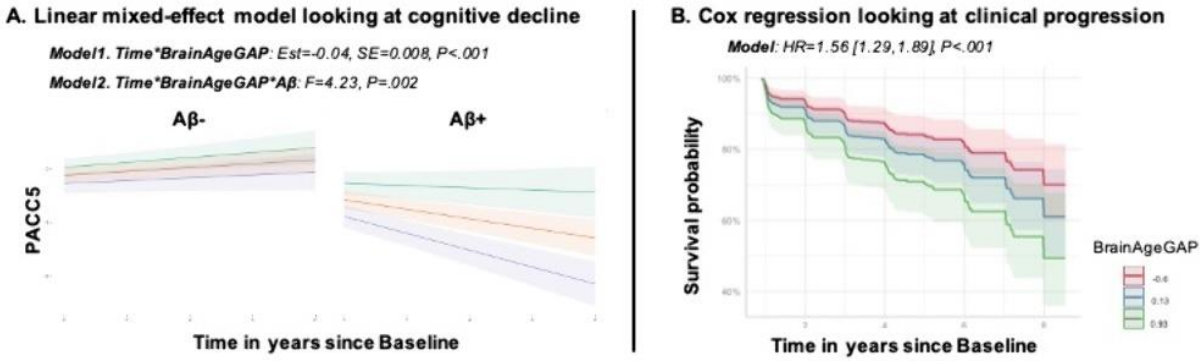


Importantly, it predicted greater cognitive decline, particularly in amyloid-positive participants, and higher risk of clinical progression, even when controlling for amyloid status

Fig.3. Testing the predictive value of baseline BrainAgeGAP levels for cognitive decline (A) and clinical progression to MCI/Dementia (B) over 8 years



(Fig.3).

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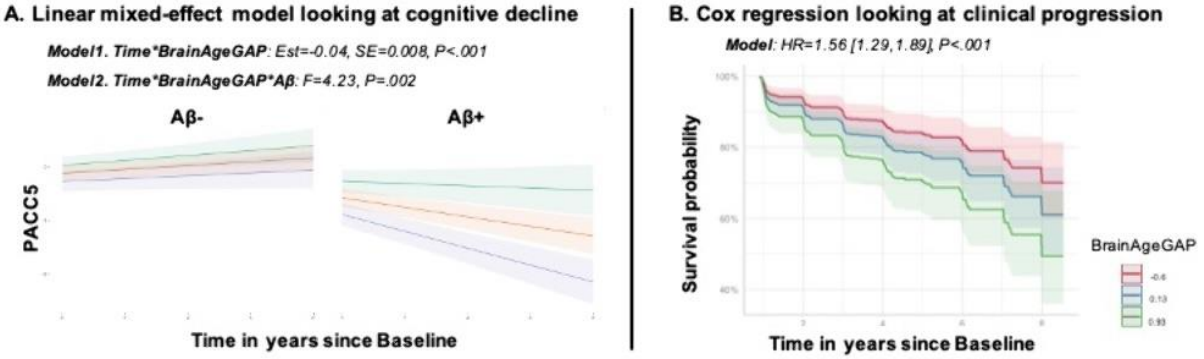

These findings were mainly replicated in a subsample of cognitively unimpaired participants.

Conclusions: Advanced brain aging was observed across clinical and biological AD stages, notably from clinical stage 2 (SCD amyloid-positive patients), and predicted cognitive decline and clinical progression from early stages. Modifiable risk factors may impact brain aging before AD pathology, while later brain changes seem driven by AD pathology.

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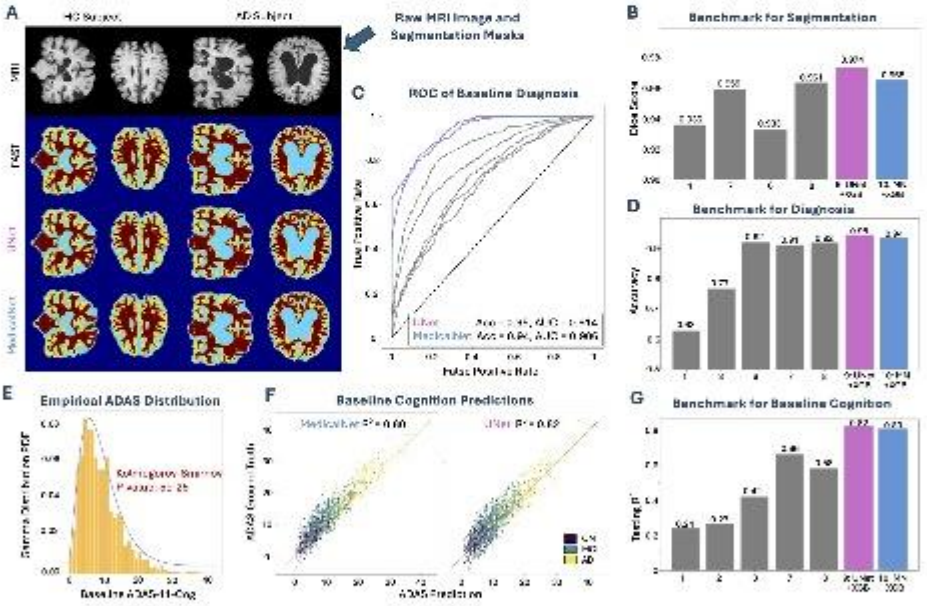
PREDICTING CATEGORICAL AND CONTINUOUS OUTCOMES OF SUBJECTS ON THE ALZHEIMER'S DISEASE SPECTRUM USING A SINGLE MRI WITHOUT PET, COGNITIVE OR FLUID BIOMARKERS

Daren Ma[1], Christabelle Pabalan[2], Abhejit Rajagopal[1], Akanksha Akanksha[2], Yannet Interian[2], Yang Yang[1], Ashish Raj[1]
[1]University of California San Francisco, San Francisco, United States of America, [2]University of San Francisco, San Francisco, United States of America

Aims: Alzheimer's disease (AD) poses a significant global health challenge, affecting millions worldwide, yet our ability to predict its progression, particularly in terms of cognitive decline, remains limited. While advancements in machine learning (ML) and deep learning (DL) techniques have shown promise in classification tasks related to AD, such as early detection and diagnosis, predicting continuous measures of cognitive impairment has proven elusive. Additionally, the incremental value of neuroimaging, particularly MRI, in these tasks has been questioned, and existing models often rely on time-consuming preprocessing and feature selection methods. We address these critical gaps by proposing novel AI strategies aimed at simultaneously segmenting brain MRI, predicting diagnosis, and forecasting continuous measures of disease severity, specifically cognitive scores. This approach is driven by the need for clinical translational relevance, particularly in settings where only structural MRI may be available, such as community clinics. Very few existing methods have succeeded in all 3 prediction tasks (cognition, segmentation, diagnosis) using the same model, and none has achieved them using a single baseline MRI.
Methods: We present two contrasting yet complementary approaches: one leveraging transfer learning and domain adaptation techniques on a pre-trained ResNet50 architecture, and the other relying on domain knowledge-driven custom input features and a 3D UNet module for segmentation.**Results:**

Table 1 Set-aside testing results following 10-fold cross-validation for all 3 tasks and all benchmark models implemented in this study. After evaluating an initial set of models (rows 1-4) we focus on the UNet and MedicalNet models (rows 5-10) with matching model settings between them. The last two rows represent our best models, highlighted by boldface. Our best models achieve field-leading performance for all three tasks, with segmentation Dice measure above 0.96, R^2 of cognition task above 0.8 and diagnosis accuracy above 93%.

#	Model	Input		Segmentation	Cognition (ADAS-Cog-11)			Diagnosis
		Demog.	MRI	Dice Score	Loss	CV R^2 Range	Testing R^2	Accuracy
1	XGB (Standard MSE)	Yes	No	-	86.39	0.19 - 0.30	0.24	-
2	XGB (Gamma Loss)	Yes	No	-	72.3	0.21 - 0.38	0.27	-
3	Single-Task CNN	No	ADNI	-	66.64	0.37 - 0.50	0.42	-
4	Multitask UNet	No	ADNI	0.9856	59.92	0.54 - 0.64	0.60	92.33%
5	UNet	No	ADNI +HCP	0.9361	52.05	0.57 - 0.71	0.66	92.13%
6	MedicalNet	No	ADNI +HCP	0.9825	58.77	0.51 - 0.65	0.58	91.25%
7	UNet	Yes	ADNI +HCP	0.9389	54.40	0.61 - 0.75	0.68	91.70%
8	MedicalNet	Yes	ADNI +HCP	0.9619	46.21	0.65 - 0.73	0.70	92.05%
9	**Ensemble(UNet +XGB)**	**Yes**	**ADNI +HCP**	**0.9740**	**37.96**	**0.78 - 0.87**	**0.82**	**94.56%**
10	**Ensemble(MedicalNet +XGB)**	**Yes**	**ADNI +HCP**	**0.9654**	**40.88**	**0.77 - 0.87**	**0.80**	**93.64%**



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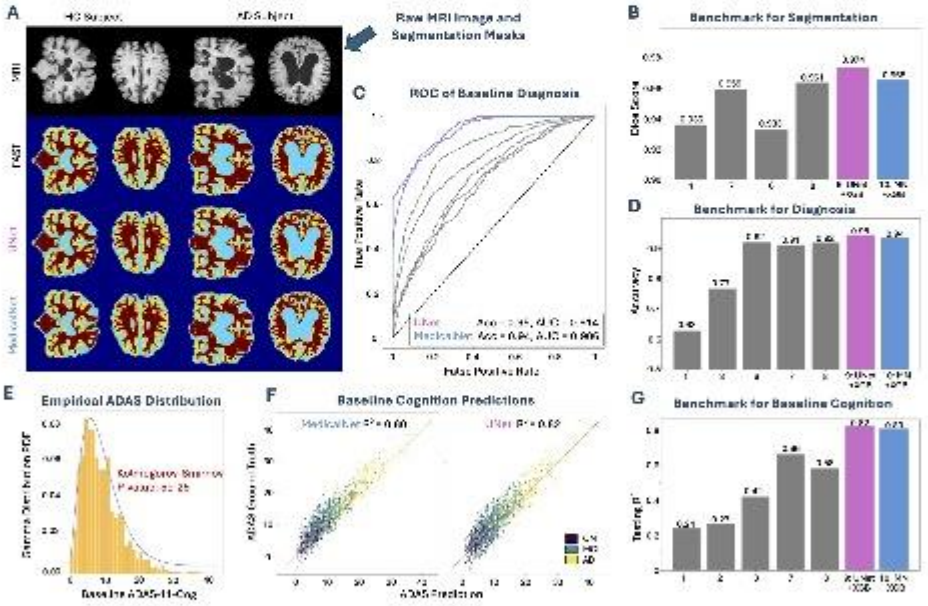

Our multitask framework, combined via an ensemble model, achieves highly effective outcomes across all three tasks, surpassing state-of-the-art performance in segmentation and diagnosis while vastly improving predictions of cognitive scores, up to 36 months in advance.

Conclusions: We believe that our results represent the very top level amongst all currently available approaches based on comparably large sample size. It addresses a pressing need in neurodegenerative disease research and offers innovative solutions with significant clinical relevance.

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AN AMYGDALA-SUPERIOR FRONTAL FUNCTIONAL NETWORK INVOLVED IN COGNITION REGULATION IN FEMALE ADULTS AT RISK OF ALZHEIMER'S DISEASE

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The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China

Aims: Alterations in brain functional connectivity have been linked to cognitive impairment. However, the impact of changes in visual functional circuits on cognition remains unclear.
Methods: In this study, we administered 500nm blue-green light therapy to 14 female adults at risk of Alzheimer's Disease over four weeks. We then examined the enhanced resting-state functional connectivity (FC) within three retinal circuits associated with cognition, emotion, and sleep: the suprachiasmatic nucleus (SCN), lateral geniculate nucleus (LGN) and amygdala.
Results: The results indicated that increased FC between the right amygdala and the right middle temporal gyrus was associated with reduced depression and anxiety. Additionally, decreased FC between the left LGN and the right occipital superior gyrus was linked to reduced depression, while decreased FC between the right amygdala and the right superior frontal gyrus was associated with reduced depression and improved cognitive function.
Conclusions: These findings suggest that the retinal-right amygdala-right superior frontal circuitry may affect cognitive regulation.

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SEX DIFFERENCES IN PLASMA AB42 LEVELS OF HEALTHY SUBJECTS OR PATIENTS WITH ALZHEIMER'S DISEASE RISK FACTORS: A BIOMARKER ANALYSIS.

Sara Serafini[1], Antonella Angiolillo[2], Gabriella Ferretti[1], Laura Sarno[3], Maurizio Guida[3], Alfonso Di Costanzo[2], Carmela Matrone[1]
[1]University of Naples Federico II, Neuroscience, Naples, Italy, [2]University of Molise, Campobasso, Italy, [3]University of Naples Federico II, Neuroscience And Reproductive Medicine, Naples, Italy

Aims: Research on the sporadic form of Alzheimer's disease (AD) has identified three categories of risk factors: age, genetics, and sex. Notably, females constitute an estimated 60% of individuals diagnosed with AD, and while increased life expectancy may account for this overrepresentation, additional biological factors may contribute to these sex differences. This study aimed to examine the correlation between sex and plasma Aβ42 levels in young-to late-life individuals without a diagnosis of dementia.
Methods: We recruited 150 females and 110 males with a mean age of 55+/-0.30 years and we assessed Aβ42 levels using a commercially available ELISA kit.
Results: We observed that male participants exhibited elevated plasma Aβ42 levels, potentially indicating less cortical deposition than their age-matched female counterparts. No significant correlation was observed between Aβ42 levels and age in healthy individuals; however, Aβ42 levels were higher in elderly patients diagnosed with AD or those with risk factors for AD.
Conclusions: These findings align with the higher prevalence of AD among females and reinforce the potential of Aβ42 as a biomarker for AD rather than as a natural aging process, underscoring the importance of considering sex-specific factors in AD research to inform future strategies for early detection and intervention in at-risk populations.

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LONGITUDINAL EVOLUTION OF BRAIN HYPOMETABOLISM PATTERNS IN AUTOPSY-CONFIRMED AD AND LATE

Miguel Ángel Labrador Espinosa[1], Jesús Silva-Rodríguez[2,3], Alexis Moscoso Rial[1], Pascual Sanchez-Juan[4], Michael Schöll[1], Michel Grothe[5,6]
[1]Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden, [2]Fundacion CIEN, Neuroimaging, Madrid, Spain, [3]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIIII, Neuroimaging, Madrid, Spain, [4]Reina Sofia Alzheimer Center. CIEN Foundation, ISCIII,, Madrid, Spain, [5]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIIII, Madrid, Spain, [6]Fundación CIEN (Centro de Investigación de Enfermedades Neurológicas), Neuroimaging, MADRID, Spain

Aims: Limbic-predominant age-related TDP-43 encephalopathy (LATE) can underlie clinical presentations mimicking Alzheimer's disease (AD). Recent imaging-pathological studies have shown that LATE associates with a specific temporo-limbic FDG-PET signature that differs from the typical temporo-parietal pattern of hypometabolism in AD and may be of clinical utility for differential dementia diagnosis. We investigated the temporal evolution of LATE- and AD-specific hypometabolism patterns using longitudinal ante-mortem FDG-PET data from autopsy-confirmed cases.
Methods: Serial ante-mortem FDG-PET scans acquired in an interval of -11 to 0 years before death (mean: -4.8±2.9 years; median of 3 scans/subject) were analysed from 30 autopsy-confirmed AD patients and 10 LATE patients enrolled in ADNI. FDG-PET images were spatially normalized to MNI space and SUVR were calculated across 52 brain regions defined in the Harvard-Oxford atlas. Region-wise z-scores were calculated to quantify hypometabolism relative to a healthy control group (N=179). Group-wise longitudinal metabolic decline of brain regions was calculated using linear mixed-effects models. Moreover, we evaluated the longitudinal evolution of the inferior-to-medial temporal ratio (IMTr) as a previously proposed differential diagnostic imaging marker.
Results: In AD, first pronounced hypometabolism (z>1) was observed in the posterior cingulate cortex and precuneus, approximately 6 years before death and progressively affecting additional temporal and lateral parietal brain regions(Fig-1a). By contrast, first hypometabolism in LATE was observed in the hippocampus/parahippocampal cortex as early as 10 years before death and progressively including anterior temporal and frontal brain regions (Fig-1b). Interestingly, the IMT ratio showed a constant difference between AD and LATE patients across the entire observation period, including earliest disease stages (t=3.04,p=0.005)(Figure-

Figure 1. Longitudinal hypometabolism patterns estimated for AD and LATE groups.

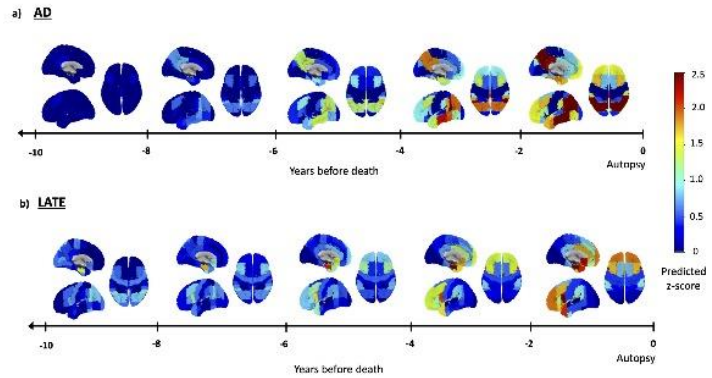
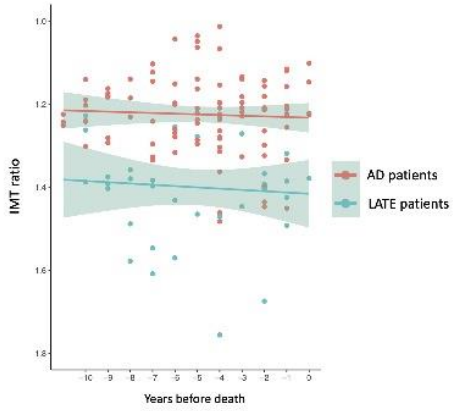


Figure 2. Longitudinal differences in IMT ratio between AD and LATE patients.



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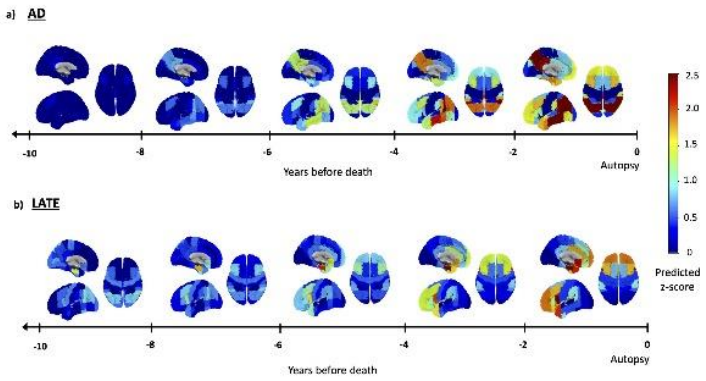

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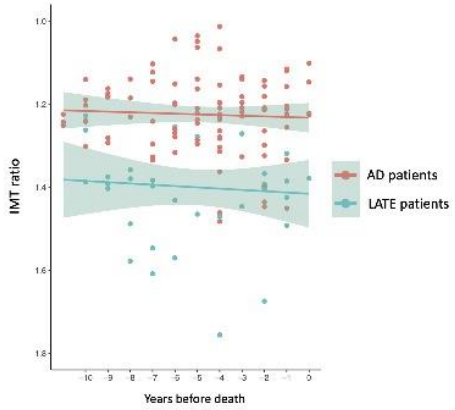

Conclusions: LATE and AD show markedly different origins and temporal trajectories of regional brain hypometabolism, indicating that FDG-PET may differentiate between these pathologies even at early disease stages.

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INCREASED EXTRA-SYNAPTIC LOCALISATION OF THE PRESYNAPTIC PROTEIN, SV2A, IN THE HUMAN ALZHEIMER'S DISEASE BRAIN

Stanley Williams[1], Samrah Siddiqi[1], Sulin Liu[1], Rutvi Patel[1], Leire Melgosa-Ecenarro[1], Carola Radulescu[1], Samuel Barnes[1], Paul Matthews[2], Johanna Jackson[1]
[1]UK Dementia Research Institute at Imperial, LONDON, United Kingdom, [2]UK Dementia Research Institute, London, United Kingdom

Aims: OBJECTIVES: Synapse loss is a key component of Alzheimer's Disease (AD) and correlates with cognitive impairment. PET tracer, UCB-J, binds to pre-synaptic protein SV2a and is a potential biomarker of synapse density. SV2a is reportedly ubiquitously expressed at synapses but has been found in other locations making the origin of the PET signal difficult to interpret. Here, we determined the cellular and sub-cellular distribution of SV2a.
Methods: METHODS: Prefrontal and mid-temporal gyral non-diseased control (n=14, Braak 0-II) and AD (n=14, Braak III-VI) human *post-mortem* tissue sections were stained with SV2a, synaptophysin, VGLUT1, VGAT, PSD-95 and gephyrin to determine synaptic colocalisation. Further staining used MAP2, NfL, Iba1 and GFAP to map the distribution at non-synaptic sites. Confocal imaging and Imaris were used for all analyses.
Results: RESULTS: ~18% SV2a puncta colocalised with synaptophysin with no regional or disease-state differences but a greater propensity to colocalise with VGLUT1 excitatory protein (~11%) vs VGAT inhibitory protein (~8%), similar to mouse models. The proportion of inhibitory and excitatory synapses with SV2a was ~45% and 58% respectively. SV2a was found in axons (~23%), and in somato-dendritic compartments (~7%) which was positively correlated with amyloid pathology. SV2a was observed in astrocytes and significantly increased in AD cortical layer 1 (~24-25%) vs controls (~10-16%) however only ~2% was found in microglia throughout.
Conclusions: CONCLUSIONS: We show that SV2a is not expressed at all synapses, with a substantial proportion found elsewhere in neurons and glia. Therefore, SV2a as a biomarker may not reveal the true extent of synapse loss in AD.

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CROSS-SECTIONAL, TEST-RETEST, AND LONGITUDINAL CHANGES OF R1 MEASURED WITH [18F]FE-PE2I PET, WITH DISTINCT PATTERNS OF RELATIVE CHANGES IN PARKINSON´S DISEASE

Minyoung Oh[1,2], My Jonasson[3], Andrea Varrone[1]
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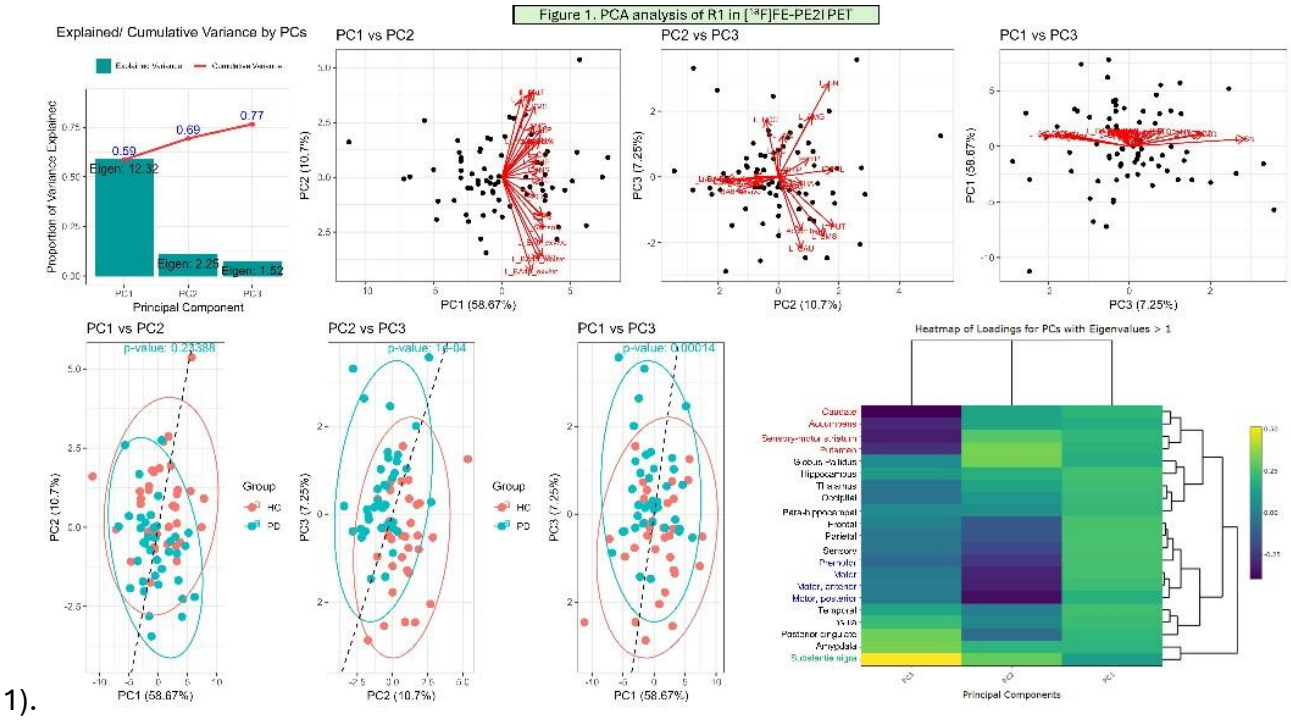
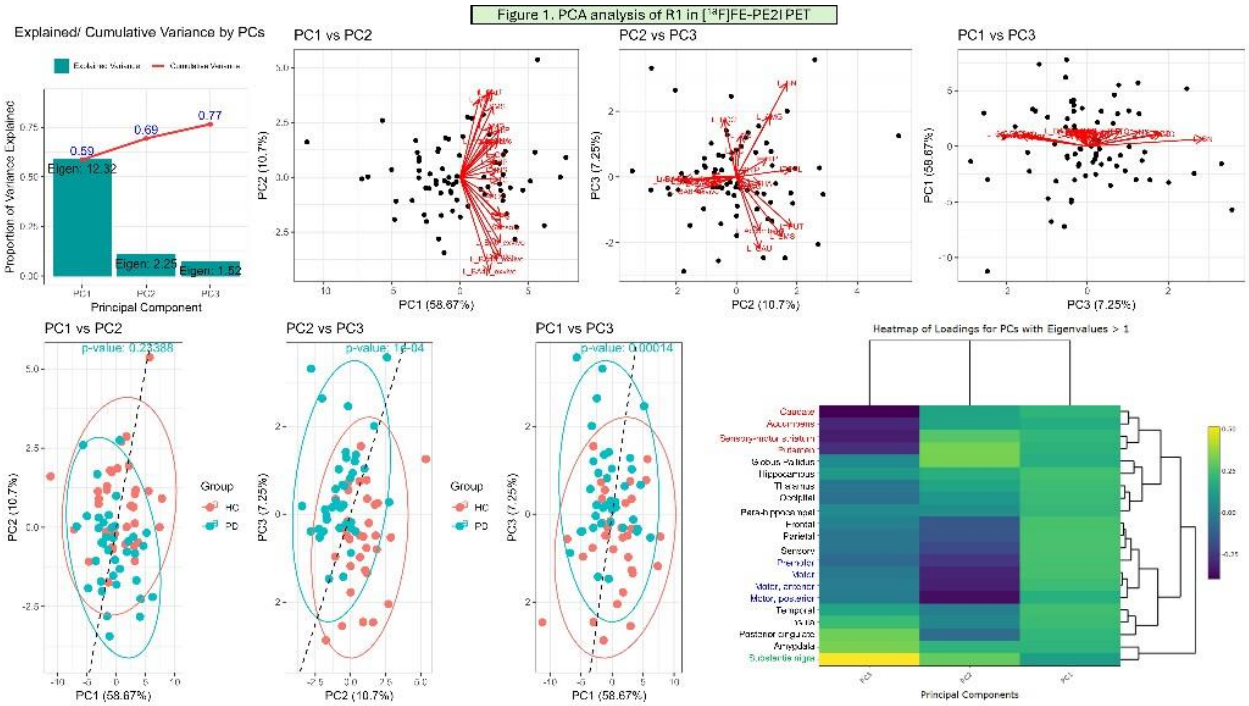
Aims: This study aimed at measuring relative cerebral blood flow (rCBF, R1) and dopamine transporter (DAT) availability in patients with Parkinson's disease (PD) using [^{18}F]FE-PE2I positron emission tomography (PET) in cross-sectional (38 PD, 35 controls), test-retest (9 PD) and longitudinal cohorts (19 PD).
Methods: Binding potential (BP_{ND}) and R1 values were estimated in the striatum (STR), substantia nigra (SN) and cortical regions. Test-retest variability [TRV, abs(T-R)/0.5(T+R)*100(%)], and annual longitudinal changes [ALC, (PET1-PET2) /(PET1*interval)*100(%)] over 2 years were calculated. We assessed the relationship between R1 and DAT availability and performed principal component analysis (PCA) to identify patterns of R1 changes between groups.
Results: PD group showed statistically significant lower R1 in the STR (0.94±0.08 vs. 1.05±0.11, $p<0.001$) and occipital cortex (0.99±0.07 vs. 1.04±0.07, $p=0.006$) compared to controls. R1 and DAT availability in the STR and SN showed low-moderate positive correlation in PD ($r^2 = 0.41$ and 0.3, $p<0.001$) and controls ($r^2 = 0.28$ and 0.42, $p<0.001$). TRV in STR was 5.06 [4.06;6.82], in SN was 5.41 [4.38;9.33] and across cortical regions it ranged from 1.47 [0.85;3.72] to 2.80 [1.23;4.42]. ALC in the STR, SN and across cortical regions were 1.95 [0.48;4.21], -0.47 [-2.42;4.60] and ranged from 0.92 [-0.37;1.35] to 1.17 [0.41;3.46]. Three PCs were identified, explaining 77% of the variance. Negative loadings were observed for striatum (PC1) and motor cortex (PC2), whereas positive loading was observed for the SN (PC1) (Figure

1).





Conclusions: These findings suggest that R1 assessed using [^{18}F]FE-PE2I PET is associated with DAT availability and could serve as a reliable proxy for rCBF. PCA identified brain regions that are known to be functionally altered in PD.

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MULTIOMICS REVEALS BIOLOGICAL MECHANISMS LINKING MACROSCALE STRUCTURAL COVARIANCE NETWORK DYSFUNCTION WITH NEUROPSYCHIATRIC SYMPTOMS ACROSS THE ALZHEIMER'S DISEASE CONTINUUM

Jiwei Jiang[1], Kun Zhao[2], Yong Liu[2], Jun Xu[1]
[1]Beijing Tiantan Hospital, Capital Medical University, Neurology, Beijing, China, [2]School of Artificial Intelligence, Beijing University of Posts and Telecommunications, Beijing, China

Aims: The highly heterogeneity of neuropsychiatric symptoms (NPSs) hinder further exploration of their role in neurobiological mechanisms and Alzheimer's disease (AD). We aimed to delineate NPS patterns based on brain macroscale connectomics to understand the biological mechanisms of NPSs on the AD continuum.
Methods: We constructed Regional Radiomics Similarity Networks (R2SN) for 550 participants (AD with NPSs [AD-NPS, n=376], AD without NPSs [AD-nNPS, n=111], and normal controls [n=63]) from CIBL study. We identified R2SN connections associated with NPSs, and then cluster distinct subtypes of AD-NPS. An independent dataset (n=189) and internal validation were performed to assess the robustness of the NPS subtypes. Subsequent multiomics analysis were performed to assess the distinct clinical phenotype and biological mechanisms in each NPS subtype.
Results: AD-NPS patients were clustered into severe (n=187), moderate (n=87), and mild NPS (n=102) subtypes, each exhibiting distinct brain network dysfunction patterns. A high level of consistency in clustering NPS was internally and externally validated. Severe and moderate NPSs showed significant cognitive impairment, increased plasma p-Tau_{181} levels, extensive decreased brain volume and cortical thickness, and accelerated cognitive decline. Gene set enrichment analysis (GSEA) revealed enrichment of differentially expressed genes in ion transport and synaptic transmission with variations for each NPS subtype. Genome-wide association studies (GWAS) analysis defined the specific gene loci for each subtype of AD-NPS (i.e, logical memory), aligning with clinical manifestations and progression patterns.
Conclusions: This study systematically identified and validated three distinct subtypes of NPSs on the AD continuum using a data-driven methodology, which helped address their subjectivity and heterogeneity of clinical measurements. We underscored the role of NPSs in neurobiological mechanisms and progression of the AD continuum, which could promote the development of tailored treatment approaches for patients with NPSs.

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BRAIN-NOSE INTERFACE – A WINDOW TO THE BRAIN

Marion San Nicolo[1], Roxana Carare[2], Rami Salib[2], Daniel Michalik[2], Nour Gharaibeh[2], Riaz Fazal[2], Sabine Mertzig[1], Richard Metzler[1], Harald Waltenberger[3], Hilary Wunderlich[1]
[1]Noselab, Munich, Germany, [2]Southampton General Hospital, South Hampton, United Kingdom, [3]Microcoat, Bernried, Germany

Aims: The brain-nose interface (BNI) connects the central nervous system (CNS) to the nasal cavity through sensory neurons that pass into the nasal mucosa via the cribriform plate, enabling physiological and pathological interactions beyond olfactory sensing. Experimental studies in different species demonstrate the drainage of cerebrospinal fluid (CSF) into the nasal mucosa. There is evidence from radiological studies in humans that PET tracers reach the nasal mucosa from the CSF and their detection in the nasal mucosa decreases in Alzheimer's disease. Objective: Elucidate the anatomical pathways for transfer of proteins from CSF into nasal mucosa and confirm the presence of biomarkers of neurodegeneration in nasal secretion.
Methods: Cribriform plates with intact olfactory nerves were formalin-fixed and paraffin-embedded. Meningeal and axon specific markers were stained and visualized by confocal microscopy. For biomarker detection in nasal secretion, samples were taken with a proprietary collection method *nosecollect* from the olfactory cleft and measured via immunoassay.
Results: We provide evidence for the anatomical connections between the cerebral subarachnoid space and the nasal mucosa by demonstrating markers for leptomeningeal sheets around the olfactory nerves that penetrate the cribriform plate. Through non-invasive nasal secretion sampling, we have detected multiple neurodegenerative biomarkers including amyloid beta, pTau181, pTau217, tTau, GFAP and NFL which show promising results of distinguishing between healthy and diseased individuals.
Conclusions: Conclusion: Establishing the mechanism of CSF drainage into the nasal cavity deepens the understanding of how CNS biomarkers enter nasal secretion. This is paving the way for the non-invasive, specific and sensitive detection and enabling the early diagnosis and monitoring of neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease.

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A COMPARISON OF DIFFERENT P-TAU ASSAYS FOR DETECTING BRAIN CHANGES IN ALZHEIMER'S DISEASE VERSUS CHANGES IN PERIPHERAL NERVES IN AMYOTROPHIC LATERAL SCLEROSIS

Shorena Janelidze[1], Ulrika Nordström[2], Anna Orduña Dolado[1], Divya Bali[1], Karin Forsberg[2], Peter Andersen[2], Oskar Hansson[1,3]
[1]Lund University, Clinical Memory Research Unit, Department Of Clinical Sciences, Lund, Sweden, [2]Umeå University, Department Of Clinical Sciences, Neurosciences, Umeå, Sweden, [3]Skåne University Hospital, Memory Clinic, Malmö, Malmö, Sweden

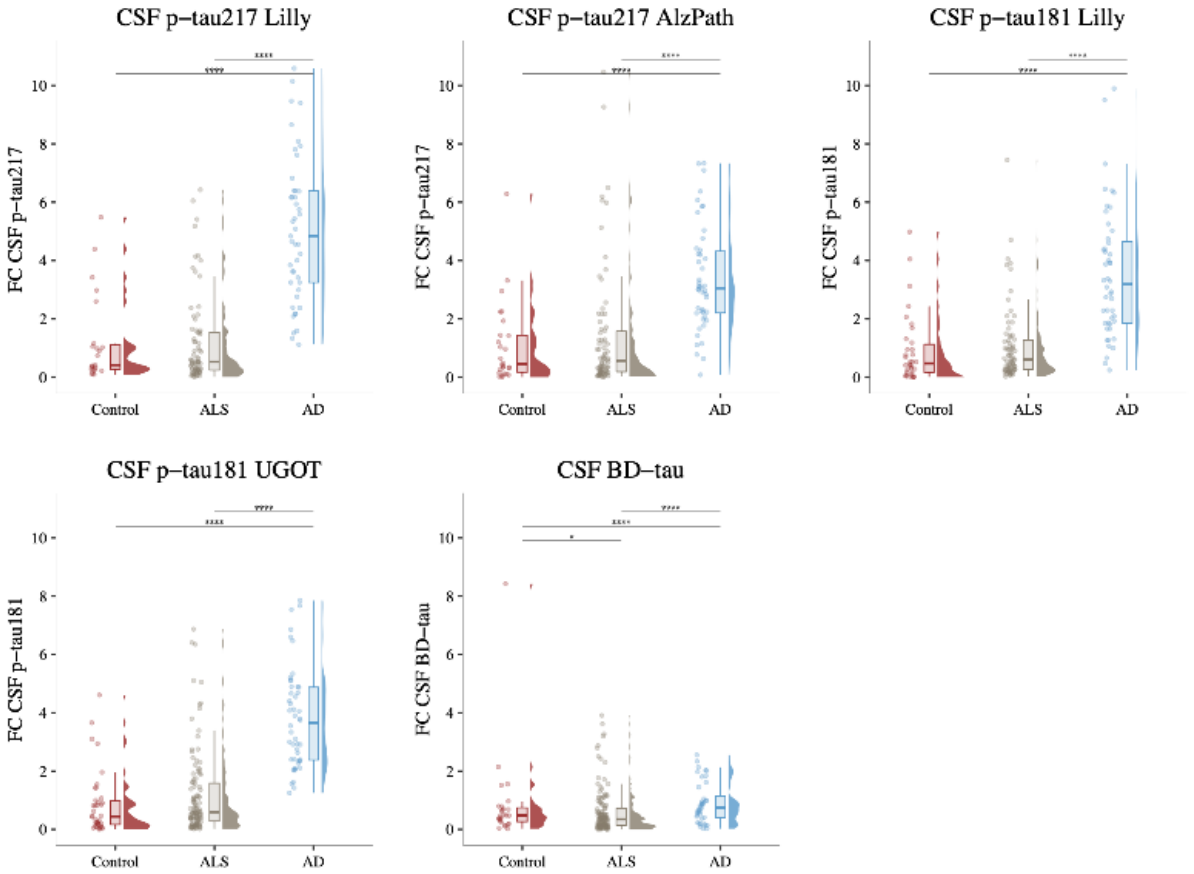
Aims: Assays with a high specificity for detecting plasma p-tau released from the brain in Alzheimer's disease (AD) compared to p-tau released from peripheral nerves in for example Amyotrophic Lateral Sclerosis (ALS) will be preferred for use in diverse communities where people with peripheral nerve injury are likely to be assessed.
Methods: The study included control participants (CN, N=101) and patients with ALS (N=321) and AD (N=48) (Table-1). Cerebrospinal fluid (CSF) and plasma samples were analyzed with immunoassays including antibodies that (1) preferentially bind to tau expressed in the brain, i.e., p-tau217-Lilly, p-tau181-Lilly, brain-derived (BD)-tau, or (2) do not differentiate between brain-derived and peripheral p-tau, i.e., p-tau217-AlzPath and p-tau181-UGOT.
Results: All CSF p-tau assays distinguished AD from both CN and ALS (AUC=0.96-0.98), but not ALS from CN (AUC=0.52-0.59), indicating that p-tau levels are not increased in the brains of ALS patients (Figure-1). On the contrary, plasma p-tau levels were increased in both AD ($p<0.001$) and ALS ($p\leq0.01$) compared with CN (Figure-2). However, fold increases in ALS vs CN were significantly smaller for the more brain specific p-tau assays (p-tau217-Lilly and p-tau181-Lilly) compared with respective assays that largely detect peripheral p-tau (p-tau217-AlzPath and p-tau181-UGOT) ($p_{diff}<0.001$). Furthermore, fold increases in AD vs CN were significantly larger for p-tau217-Lilly and p-tau181-Lilly than p-tau217-AlzPath ($p_{diff}=0.048$) and p-tau181-UGOT ($p_{diff}=0.002$), respectively. Plasma BD-tau levels were only increased in AD ($p=0.0043$ vs CN; $p=0.0036$ vs ALS) and not ALS. Plasma p-tau217-Lilly (AUC=0.94) and p-tau181-Lilly (AUC=0.89) accurately discriminated AD from ALS, with significantly higher AUCs than p-tau217-AlzPath (AUC=0.74) and p-tau181-UGOT (AUC=0.54).
Conclusions: Certain p-tau assays are more specific at detecting mainly brain-derived tau and thereby less affected by peripheral release of tau seen in e.g. ALS.

Table-1. Participant characteristics

	Controls	ALS	AD	All
N	101	321	48	470
Age, years	73.8 (61.8 - 79.3)	65.3 (57.3 - 71.8)	74.0 (69.8 - 78.0)	67.8 (58.7 - 75.1)
Sex, Male N(%)	45 (44.6%)	182 (56.7%)	30 (62.5%)	257 (54.7%)
CSF p-tau217-Lilly, (pg/ml)	8.3 (6.4 - 11.5) N=97	7.7 (5.5 - 11.9) N=321	77.4 (52.7 - 100.1) N=48	8.4 (5.9 - 15.5) N=466
CSF p-tau217-AlzPath, (pg/ml)	8.8 (6.2 - 14.5)	8.6 (5.8 - 13.9)	65.5 (50.9 - 88.9)	9.5 (6.2 - 19.0)
CSF p-tau181-Lilly, (pg/ml)	36.1 (27.0 - 47.7)	31.2 (22.4 - 41.3)	120.5 (90.3 - 162.5)	34.4 (24.7 - 51.0)
CSF p-tau181-UGOT, (pg/ml)	101.1 (80.2 - 114.0)	96.7 (81.5 - 118.8)	242.2 (194.7 - 287.9)	101.0 (83.2 - 129.2)
CSF BD-tau, (pg/ml)	198.2 (149.7 - 290.1)	230.3 (164.2 - 311.7)	426.6 (301.5 - 522.9)	233.0 (167.2 - 349.0)
CSF NfL, (ng/ml)	0.834 (0.571 - 1.2)	5.3 (3.2 - 9.4)	1.3 (1.0 - 1.6)	3.5 (1.3 - 7.4)
Plasma p-tau217-Lilly, (pg/ml)	0.258 (0.199 - 0.341)	0.300 (0.226 - 0.380)	0.754 (0.573 - 0.927)	0.258 (0.199 - 0.341)
Plasma p-tau217-AlzPath, (pg/ml)	0.348 (0.272 - 0.464)	0.745 (0.427 - 1.232)	1.2 (1.0 - 1.7)	0.348 (0.272 - 0.464)
Plasma p-tau181-Lilly, (pg/ml)	2.1 (1.8 - 2.8)	2.4 (2.0 - 3.0)	4.5 (3.8 - 5.8)	2.4 (2.0 - 3.2)
Plasma p-tau181-UGOT, (pg/ml)	6.8 (5.0 - 9.3)	13.2 (8.8 - 22.7)	12.7 (9.5 - 15.1)	11.1 (7.4 - 18.9)
Plasma BD-tau, (pg/ml)	3.3 (2.6 - 4.3)	3.3 (2.5 - 4.1)	4.8 (3.6 - 5.4)	3.4 (2.6 - 4.5)
Plasma NfL, (pg/ml)	14.5 (10.1 - 19.9)	59.0 (39.5 - 94.3)	20.9 (16.4 - 27.7)	44.1 (20.5 - 78.2)

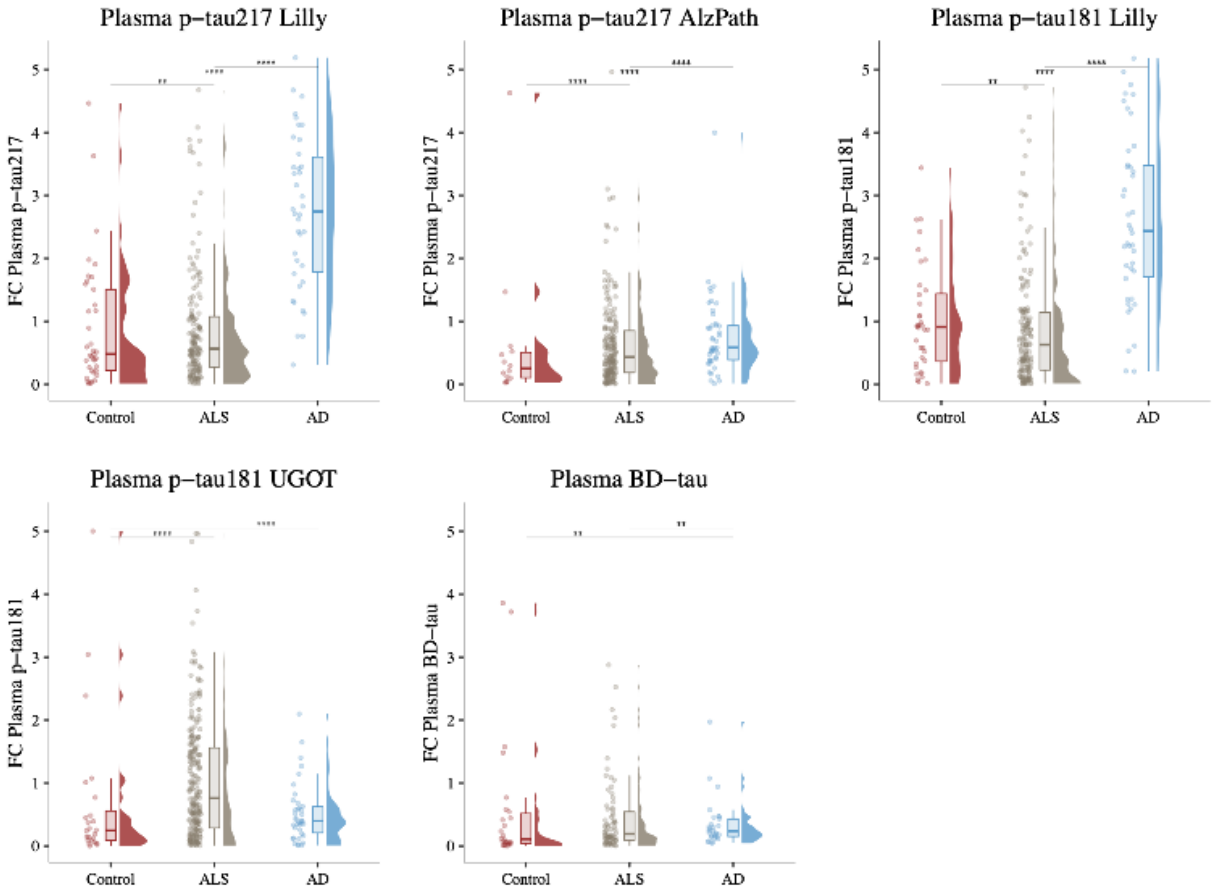
Data are shown as median (interquartile range) unless otherwise specified.
CSF samples were available for 97 controls, 321 patients with ALS and 48 patients with AD.
Plasma samples were available for 96 controls, 320 patients with ALS and 48 patients with AD.
Plasma p-tau217-AlzPath and BD-tau data were missing for 13 and 19 participants, respectively.

Figure-1



Cerebrospinal fluid (CSF) levels of phospho-tau (p-tau) and brain-derived total tau (BD-tau) across diagnostic groups. Fold increases in CSF levels of p-tau217-Lilly, p-tau217-AlzPath, p-tau181-Lilly, p-tau181-UGOT, and BD-tau in patients with Alzheimer's Disease (AD) and amyotrophic lateral sclerosis (ALS) and control (CN) participants. P-values adjusted for multiple comparison using the Bonferroni method (3 comparisons for each biomarker) are from the analysis of variance with log-transformed biomarkers as dependent variables and diagnosis as independent variable adjusting for age.

Figure-2



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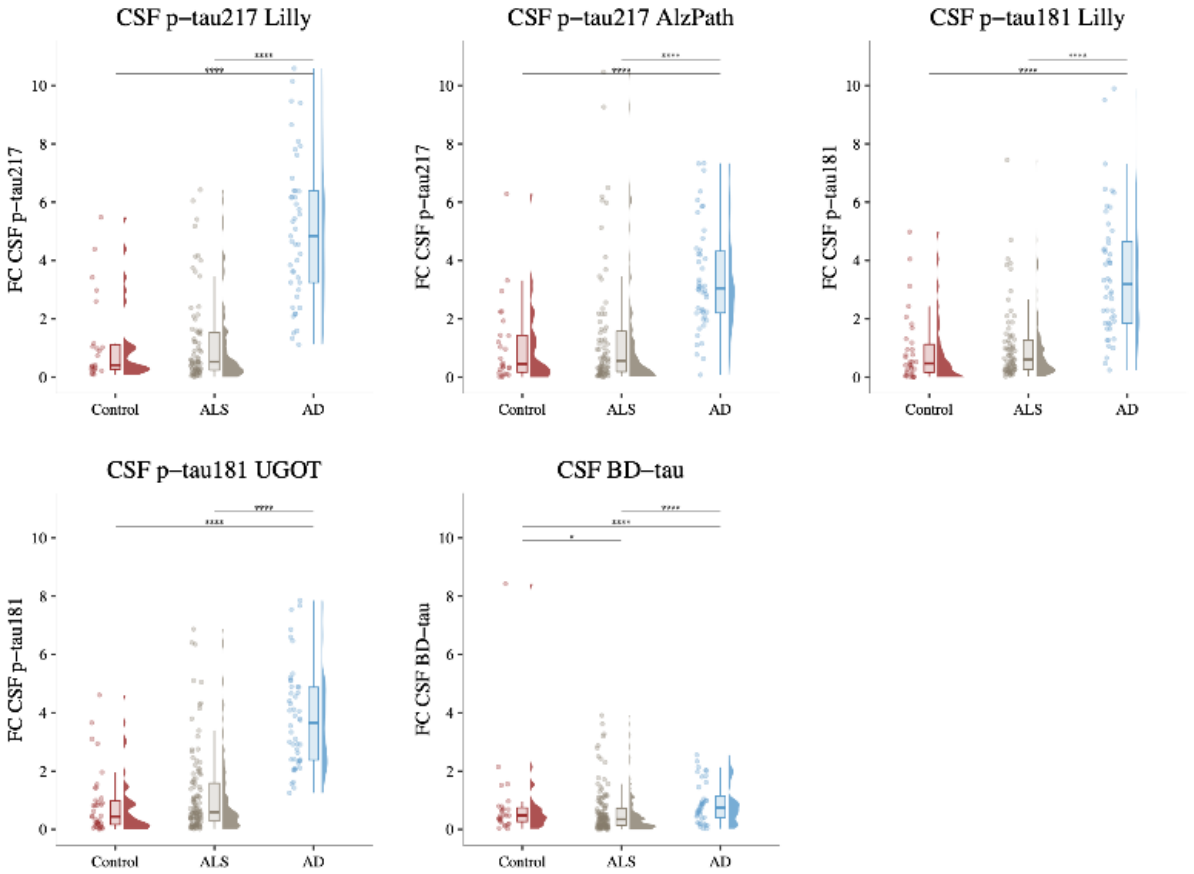

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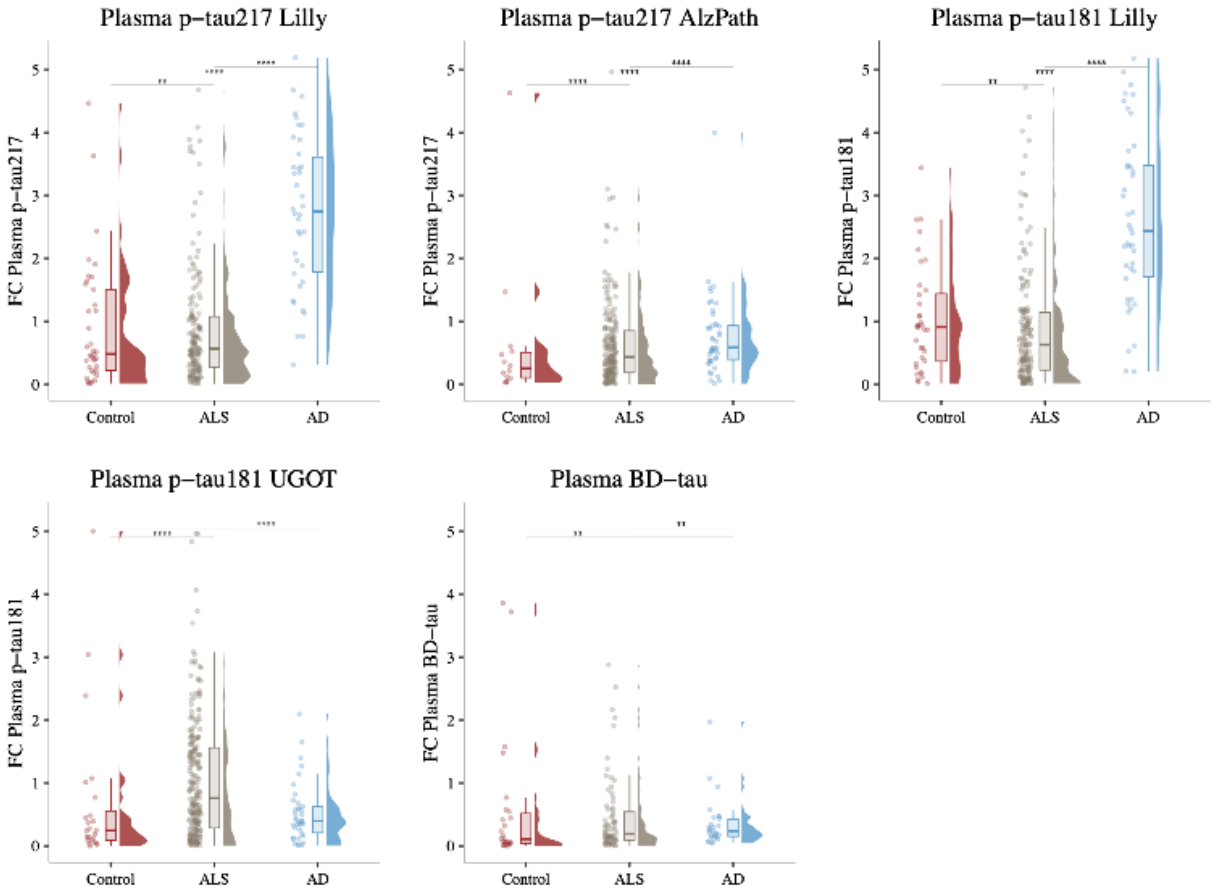
Figure-2



Plasma levels of phospho-tau (p-tau) and brain-derived total tau (BD-tau) across diagnostic groups. Fold increases in plasma levels of p-tau217-Lilly, p-tau217-AlzPath, p-tau181-Lilly, p-tau181-UGOT, and BD-tau in patients with Alzheimer's Disease (AD) and amyotrophic lateral sclerosis (ALS) and control (CN) participants. P-values adjusted for multiple comparison using the Bonferroni method (3 comparisons for each biomarker) are from the analysis of variance with log-transformed biomarkers as dependent variables and diagnosis as independent variable adjusting for age.

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ASSESSING THE STABILITY OF PLASMA BIOMARKERS IN STRECK BCT TUBES® FOR NEURODEGENERATIVE DISEASE RESEARCH WITH DELAYED PROCESSING

Kübra Tan[1], Andrea Benedet[1], Burak Arslan[1], Hlin Kvartsberg[1,2], Kaj Blennow[1,2,3,4], Henrik Zetterberg[1,2,5,6,7], Nicholas Ashton[1,8,9]
[1]University of Gothenburg, Institute Of Neuroscience And Physiology, Mölndal, Sweden, [2]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Gothenburg, Sweden, [3]Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France, [4]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, [5]UCL Institute of Neurology Queen Square, Department Of Neurodegenerative Disease, London, United Kingdom, [6]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong PRC, [7]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, [8]Banner Alzheimer's Institute and University of Arizona, Phoenix, United States of America, [9]Banner Sun Health Research Institute, Sun City, United States of America

Aims: In biomarker research, particularly in Alzheimer's disease and other neurodegenerative conditions, the stability of plasma proteins during sample collection and processing is critical. This study aims to assess the stability of plasma biomarkers in Streck Protein Plus Blood Collection Tubes (BCT)® after a 5-day processing delay, compared to immediate processing in EDTA tubes, focusing on biomarkers linked to neurodegenerative diseases.
Methods: Methods:
Blood samples from 22 individuals were collected in EDTA and Streck BCT tubes.EDTA plasma was processed within one hour following standard procedures and stored at -80,while BCT plasma was separated after 5 days at room temperature and stored at -80.Biomarkers Aβ40, Aβ42, neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and p-Tau 217 were quantified using the Single Molecule Array (SIMOA) platform.In addition, p-Tau 217 was also measured using the Lumipulse G1200 Analyzer for cross-platform comparison.Spearman's rank correlation was used to assess the association between EDTA and BCT sample measurements, with p-values<0.05 considered significant.
Results: Aβ40(rho=0.696,p<0.001) and Aβ42(rho=0.736,p=0.00255) demonstrated a moderate positive correlation between EDTA and BCT samples (rho=0.696,p<0.001), as did Aβ42(rho=0.736,p=0.00255) (Fig 1A, Fig 1B).NfL(rho=0.984,p<0.001) and GFAP(rho=0.970,p< 0.001) showed very strong correlations (rho=0.984,p<0.001 and rho=0.970,p<0.001,respectively) (Fig 2A, Fig 2B).For p-Tau 217,measured using the SIMOA platform, no significant correlation was found between EDTA and BCT samples (rho = -0.174, p =

0.4489) , (Fig 3A). However, p-Tau 217 measured using the Lumipulse platform showed a strong correlation (rho=0.871,p<0.001) (Fig 3B)

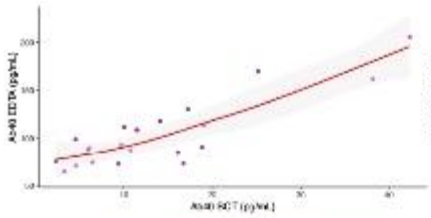

Fig 1A. Correlation of EDTA Ab40 and BCT Ab40 (SIMOA)

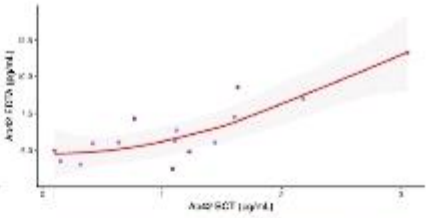

Fig 1B. Correlation of EDTA Ab42 and BCT Ab42 (SIMOA)

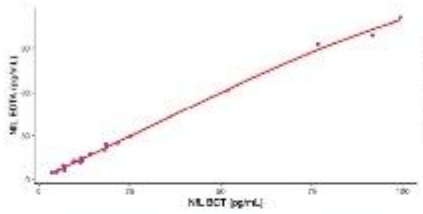

Fig 2A. Correlation of EDTA NfL and BCT NfL (SIMOA)

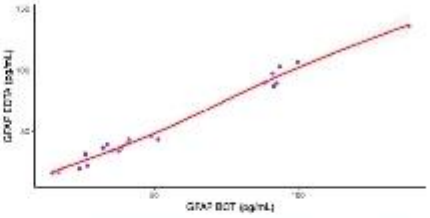

Fig 2B. Correlation of EDTA GFAP and BCT GFAP (SIMOA)

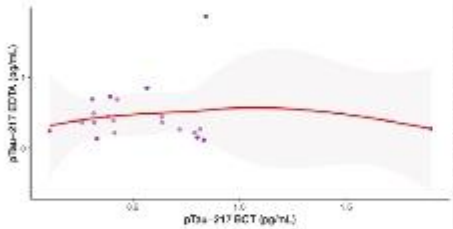

Fig 3A. Correlation of EDTA p-Tau 217 and BCT p-Tau 217 (SIMOA)

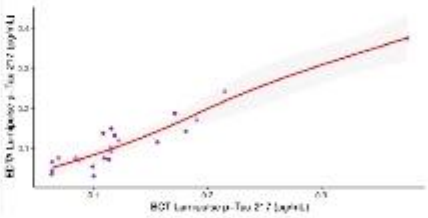

Fig 3B. Correlation of EDTA p-Tau 217 and BCT p-Tau 217 (Lumipulse G1200)

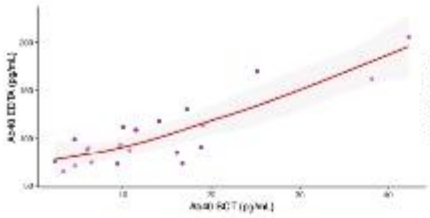

Fig 1A. Correlation of EDTA Ab40 and BCT Ab40 (SIMOA)

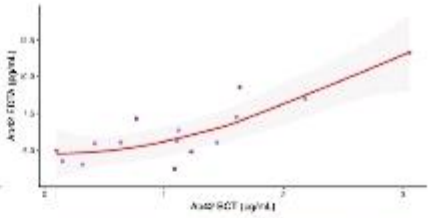

Fig 1B. Correlation of EDTA Ab42 and BCT Ab42 (SIMOA)

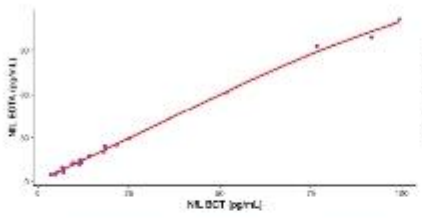

Fig 2A. Correlation of EDTA NfL and BCT NfL (SIMOA)

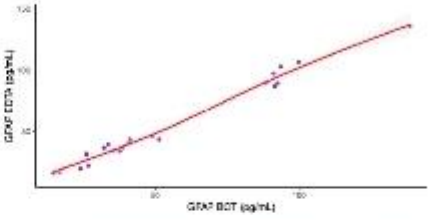

Fig 2B. Correlation of EDTA GFAP and BCT GFAP (SIMOA)

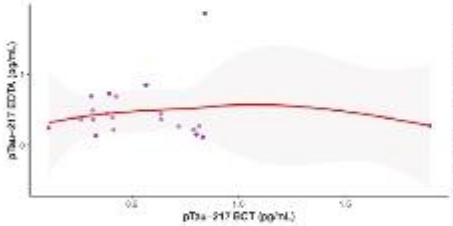

Fig 3A. Correlation of EDTA p-Tau 217 and BCT p-Tau 217 (SIMOA)

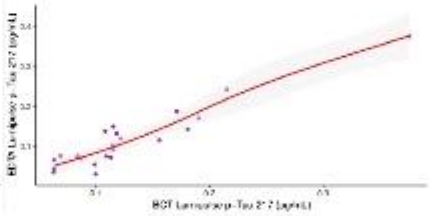

Fig 3B. Correlation of EDTA p-Tau 217 and BCT p-Tau 217 (Lumipulse G1200)

Conclusions: Streck Protein Plus BCT tubes effectively preserve NfL,GFAP,and p-Tau 217, even with a 5-day processing delay, making them suitable for large-scale or multi-site studies.Moderate correlations for Aβ40 and Aβ42 indicate reasonable stability.The strong performance of p-Tau217 with Lumipulse,but lack of correlation with SIMOA,suggests that assay-specific factors may influence results,warranting further investigation.

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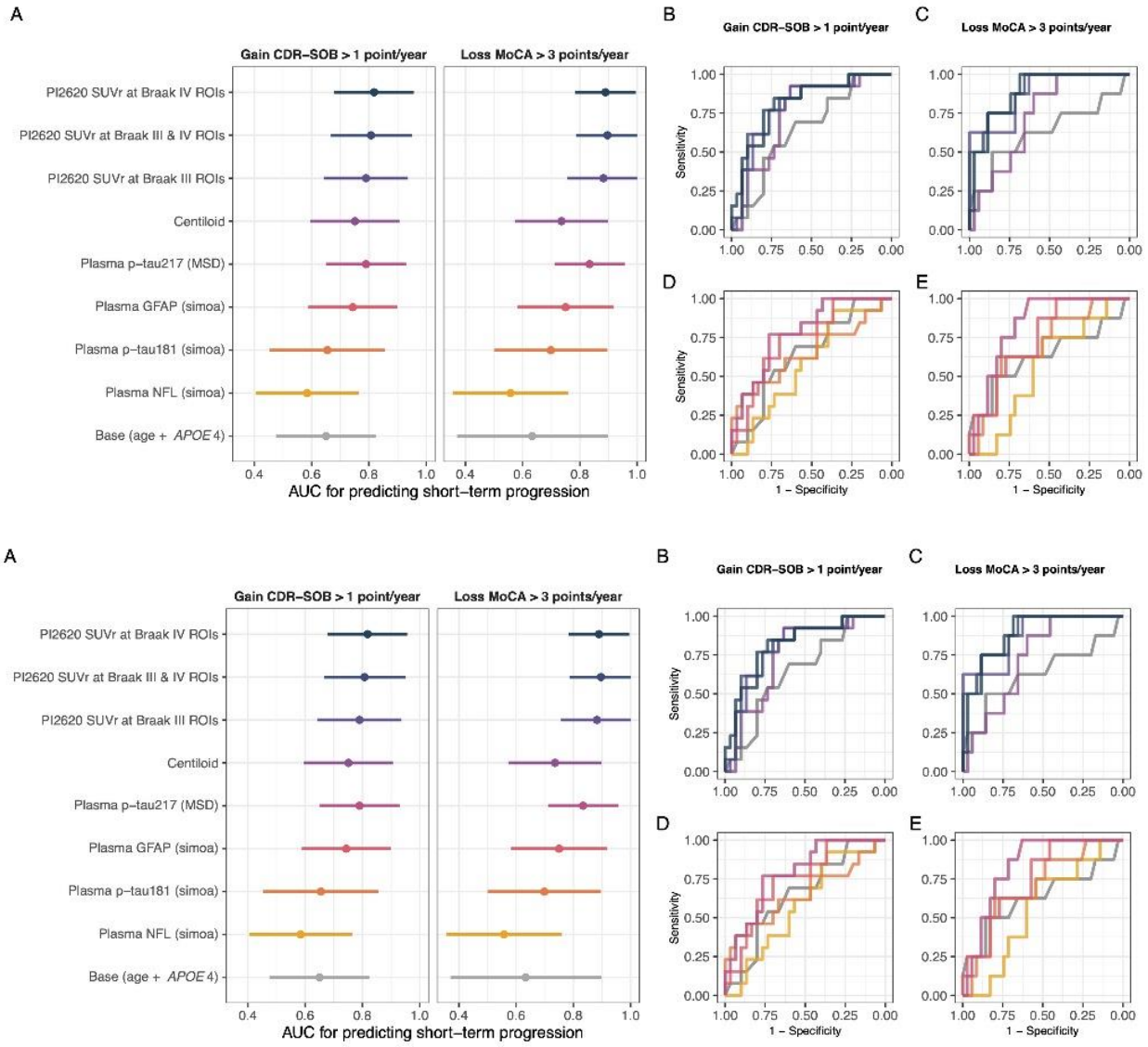
PREDICTORS OF SHORT-TERM PROGRESSION IN A PROSPECTIVE REAL-WORD MEMORY CLINIC STUDY

Poosanu Thanapornsangsuth[1], Kittithatch Booncharoen[2], Watayuth Watayuth Luechaipanit[1], Thanaporn Haethaisong[1], Adipa Chongsuksantikul[1], Yuthachai Sarutikriangkri[2], Suchart Tangnimitchok[3], Yuttachai Likitjaroen[2]
[1]Thai Red Cross Emerging Infectious Diseases Health Science Centre, Bangkok, Thailand, [2]Division of Neurology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3]Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC), King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Aims: This study compared the performance of PET and plasma biomarkers for predicting short-term cognitive and functional decline in real-world memory clinics in Thailand.
Methods: Patients in early symptomatic stages (no more than mild dementia) with memory impairment were consecutively enrolled. All participants underwent baseline clinical assessments, plasma biomarker testing (p-tau217, p-tau181, GFAP, and NFL), and PET using Florbetaben, PI-2620, and FDG. Short-term cognitive progression was defined as a loss of >3 points/year on the MoCA, while functional decline was defined as an increase of 1 point/year on the CDR sum of boxes within the 24-month follow-up period. Biomarker performance was assessed using ROC analysis, with comparisons made via DeLong's test.
Results: Of the 43 participants (median age: 71 years, 67.4% female), 18.6% experienced cognitive progression and 30.2% showed functional progression. PI2620 SUVr at Braak stage III-IV yielded the highest AUC for predicting cognitive (0.90, 95%CI 0.79-1.0) and functional (0.82, 95%CI 0.68-0.96) decline. Among plasma biomarkers, p-tau217 had the highest AUC for both cognitive (0.83, 95%CI 0.71-0.96) and functional decline (0.79, 95%CI 0.65-0.93). Differences between PI2620 and p-tau217 were not statistically significant.
Baseline characteristics

	All (n=43)
e, years	71(64.0-75.5)
nale(%)	29(67.4)
ucation, years	16(12-16)
nical staging(%)	
D	4(9.3)
I	28(65.1)
d dementia	11(25.6)
morbidities(%)	
pertension	13(30.2)
betes	9(20.9)
slipidemia	15(34.9)
vious stroke	3(7.0)
ronic kidney disease	3(7.0)
OE e4 carrier(%)	22(51.2)
seline MoCA	21(16.5-24)
erall CDR(%)	
	5(11.6)
	29(67.4)
	8 (18.6)
	1 (2.3)
R sum of boxes	3(1.8-3.0)
low-up duration, months	24.0(23.5-24.8)

Note: Unless specified, values are presented as median (interquartile range).



Conclusions: Tau-PET uptake in later Braak stages is a strong predictor of short-term cognitive and functional decline. Plasma p-tau217 shows comparable predictive power to Tau-PET for both outcomes.

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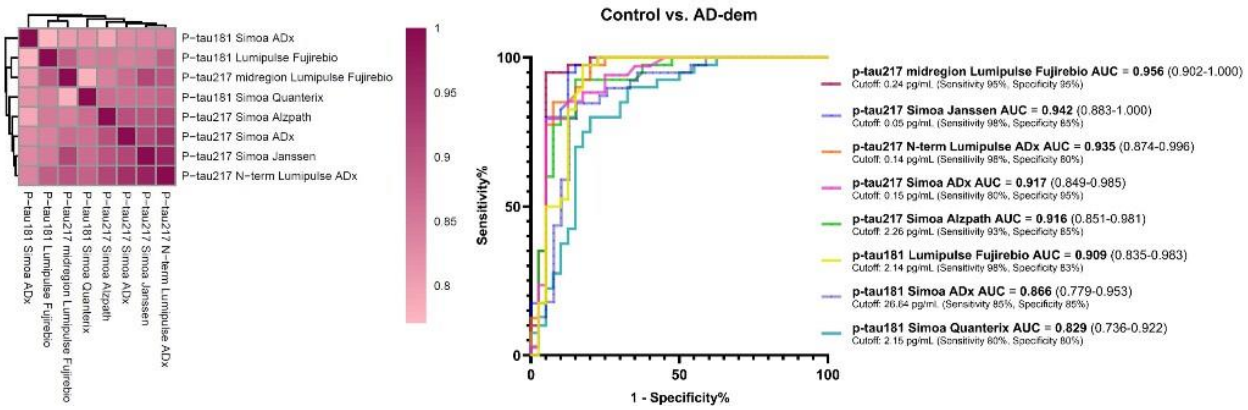
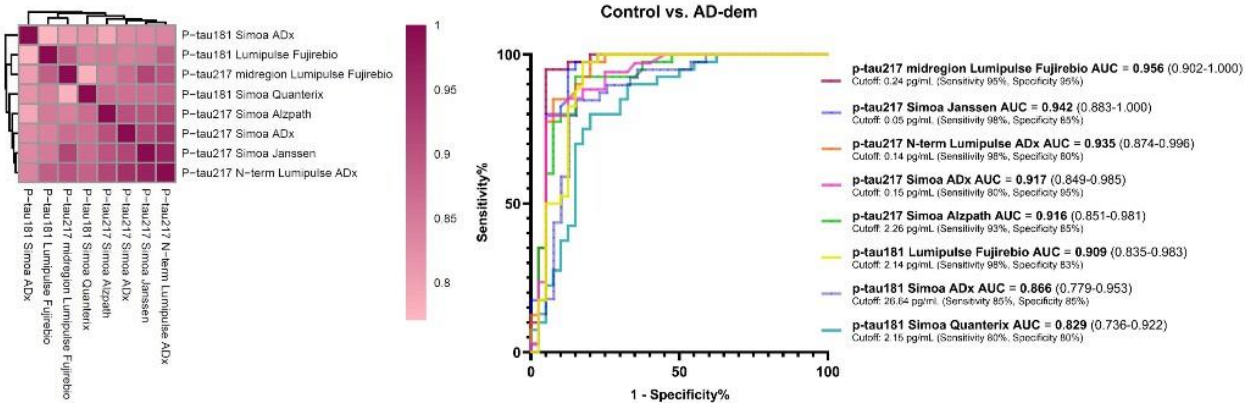
ANALYTICAL AND CLINICAL PERFORMANCE OF EIGHT SIMOA® AND LUMIPULSE® ASSAYS FOR AUTOMATED MEASUREMENT OF PLASMA P-TAU181 AND P-TAU217

Anna Wojdała[1], Jeroen Vanbrabant[2], Sherif Bayoumy[1], Daniel Antwi-Berko[1], Nathalie Le Bastard[3], Wiesje Van Der Flier[4], Andreas Jeromin[5], Charlotte Lambrechts[2], Maxime Van Loo[2], Manu Vandijck[3], Erik Stoops[2], Inge Verberk[1], Charlotte Teunissen[1]
[1]Amsterdam UMC, Neurochemistry Lab, Dept Of Laboratory Medicine, Amsterdam, Netherlands, [2]ADx NeuroSciences NV, Ghent, Belgium, [3]Fujirebio Europe NV, Ghent, Belgium, [4]Alzheimer Center, Department Of Neurology, Amsterdam Umc, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, Amsterdam, Netherlands, [5]Alzpath Inc., Carlsbad, United States of America

Aims: Among the Alzheimer's disease (AD) blood-based biomarkers, phosphorylated forms of tau (p-tau) show a particularly high diagnostic potential. Here, we performed a comprehensive method comparison study, followed by evaluation of the diagnostic performance of eight recent plasma p-tau immunoassays targeting different tau phosphorylation sites, different tau fragments, and that are measured by two distinct platforms.
Methods: We enrolled n=40 patients with dementia due to AD (AD-dem) and n=40 cognitively healthy participants (Control), to compare three p-tau181 and five p-tau217 assays run on the Simoa® HD-X™ or Lumipulse® G600II/G1200. The assays differed by: 1) tau phosphorylation site targeted by the capture antibody (T181 or T217), 2) epitope of the pan-tau detector antibody (N-terminal or mid-region). We determined precision, analytical sensitivity, and used Passing-Bablok regression and Bland-Altman plots for pairwise comparison of p-tau181 or p-tau217 assays. Subsequently, we evaluated the diagnostic accuracy of the assays in discriminating AD-dem vs. Control.
Results: We found a strong, positive correlation between all the measurements. Fixed and/or proportional bias was observed for each of compared assay pairs. While both plasma p-tau181 and p-tau217 levels were significantly increased in AD-dem vs. Control groups as measured by all assays, we observed higher median concentration AD-dem/Control fold change and AUC values for p-tau217 (assays range: fold change 3.72-6.74, AUC 0.916-0.956) compared with p-tau181 (assays range 1.81-2.94, AUC 0.829-0.909), independently of the platform used. No significant differences were observed between diagnostic performance of p-tau181 assays or p-tau217 assays targeting tau N-terminus or mid-region.
Conclusions: P-tau217 assays showed the highest robustness, independently of the pan-tau detector antibody and platform used. Considering the observed method disagreement in measured absolute concentrations, we stress the need for development of certified reference material, harmonizing measurements across different platforms.


P-tau181 Simoa ADx
P-tau181 Lumipulse Fujirebio
P-tau217 midregion Lumipulse Fujirebio
P-tau181 Simoa Quanterix
P-tau217 Simoa Alzpath
P-tau217 Simoa ADx
P-tau217 Simoa Janssen
P-tau217 N-term Lumipulse ADx
1
0.95
0.9
0.85
0.8
Control vs. AD-dem
Sensitivity%
1 - Specificity%
0
50
100
p-tau217 midregion Lumipulse Fujirebio AUC = 0.956 (0.902-1.000)
Cutoff: 0.24 pg/mL (Sensitivity 95%, Specificity 95%)
p-tau217 Simoa Janssen AUC = 0.942 (0.883-1.000)
Cutoff: 0.05 pg/mL (Sensitivity 98%, Specificity 85%)
p-tau217 N-term Lumipulse ADx AUC = 0.935 (0.874-0.996)
Cutoff: 0.14 pg/mL (Sensitivity 98%, Specificity 80%)
p-tau217 Simoa ADx AUC = 0.917 (0.849-0.985)
Cutoff: 0.15 pg/mL (Sensitivity 80%, Specificity 95%)
p-tau217 Simoa Alzpath AUC = 0.916 (0.851-0.981)
Cutoff: 2.26 pg/mL (Sensitivity 93%, Specificity 85%)
p-tau181 Lumipulse Fujirebio AUC = 0.909 (0.835-0.983)
Cutoff: 2.14 pg/mL (Sensitivity 98%, Specificity 83%)
p-tau181 Simoa ADx AUC = 0.866 (0.779-0.953)
Cutoff: 26.64 pg/mL (Sensitivity 85%, Specificity 85%)
p-tau181 Simoa Quanterix AUC = 0.829 (0.736-0.922)
Cutoff: 2.15 pg/mL (Sensitivity 80%, Specificity 80%)


P-tau181 Simoa ADx
P-tau181 Lumipulse Fujirebio
P-tau217 midregion Lumipulse Fujirebio
P-tau181 Simoa Quanterix
P-tau217 Simoa Alzpath
P-tau217 Simoa ADx
P-tau217 Simoa Janssen
P-tau217 N-term Lumipulse ADx
1
0.95
0.9
0.85
0.8
Control vs. AD-dem
Sensitivity%
1 - Specificity%
0
50
100
p-tau217 midregion Lumipulse Fujirebio AUC = 0.956 (0.902-1.000)
Cutoff: 0.24 pg/mL (Sensitivity 95%, Specificity 95%)
p-tau217 Simoa Janssen AUC = 0.942 (0.883-1.000)
Cutoff: 0.05 pg/mL (Sensitivity 98%, Specificity 85%)
p-tau217 N-term Lumipulse ADx AUC = 0.935 (0.874-0.996)
Cutoff: 0.14 pg/mL (Sensitivity 98%, Specificity 80%)
p-tau217 Simoa ADx AUC = 0.917 (0.849-0.985)
Cutoff: 0.15 pg/mL (Sensitivity 80%, Specificity 95%)
p-tau217 Simoa Alzpath AUC = 0.916 (0.851-0.981)
Cutoff: 2.26 pg/mL (Sensitivity 93%, Specificity 85%)
p-tau181 Lumipulse Fujirebio AUC = 0.909 (0.835-0.983)
Cutoff: 2.14 pg/mL (Sensitivity 98%, Specificity 83%)
p-tau181 Simoa ADx AUC = 0.866 (0.779-0.953)
Cutoff: 26.64 pg/mL (Sensitivity 85%, Specificity 85%)
p-tau181 Simoa Quanterix AUC = 0.829 (0.736-0.922)
Cutoff: 2.15 pg/mL (Sensitivity 80%, Specificity 80%)

Virtual OO - 063

Virtual E-Posters and Oral On-Demand
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COMBINED PLASMA AMYLOID BETA AND TOTAL TAU PROTEIN PREDICT BRAIN AMYLOID PLAQUES AT AUTOPSY: A PILOT STUDY

Charles S.Y. Yang
MagQu Co., Ltd., New Taipei City, Taiwan

Aims: Immunomagnetic reduction (IMR) is an ultra-sensitive technology able to assay amyloid β 1-42 peptide ($A\beta_{1-42}$) and total tau protein (T-Tau) in plasma. The published results reveal that the predict power of amnesic mild cognitive impairment (aMCI) and early-stage Alzheimer's disease (AD) using levels of $A\beta_{1-42}$xT-Tau is higher than 85%. Moreover, a negatively moderated correlation between the plasma T-Tau levels and hippocampal volume is evidenced. Hence, plasma $A\beta_{1-42}$xT-Tau assayed with IMR has been used for the assistant diagnosis of aMCI and AD in clinical practice. Although tremendous clinical validations of plasma $A\beta_{1-42}$xT-Tau have been done, the comparison between plasma $A\beta_{1-42}$xT-Tau and amyloid neuropathology is rare. In this work, the discriminations in amyloid-neuropathology-confirmed autopsies using plasma $A\beta_{1-42}$xT-Tau are investigated.
Methods: Fifteen autopsies with amyloid plaque and tau tangle neuropathology were enrolled. Plasma samples were collected within 1.5 years before death. IMR was used to assay $A\beta_{1-42}$, T-Tau and other biomarkers in plasma.
Results: According to clinical diagnosis, 7 autopsies are normal controls (NC), 4 are AD dementia, 5 are non-AD dementia. 3 and 12 autopsies are amyloid neuropathology negative (A-) and positive (A+), respectively. All autopsies in A- are tau-tangle-neuropathology negative (A-T-). 7 of A+ are tau-tangle-neuropathology positive (A+T+) and 5 of A+ are tau-tangle-neuropathology negative (A+T-). The plasma $A\beta_{1-42}$xT-Tau shows significantly different levels between A- and A+. In A+, A+T+ shows significantly lower levels of plasma Ab_{1-42}xT-Tau as compared to A+T-. In NC, A+ shows significantly higher levels of $A\beta_{1-42}$xT-Tau as compared to A-. The results reveal that plasma $A\beta_{1-42}$xT-Tau is superior in predicting A+.
Conclusions: This implies that $A\beta_{1-42}$ and T-Tau co-contribute to the deposition of amyloid β in brain. More autopsies shall be enrolled for further investigation in future studies.

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DIAGNOSTIC PERFORMANCE OF P-TAU217 IN DETECTING ALZHEIMER'S DISEASE PATHOLOGY IN INDIVIDUALS WITH DOWN SYNDROME

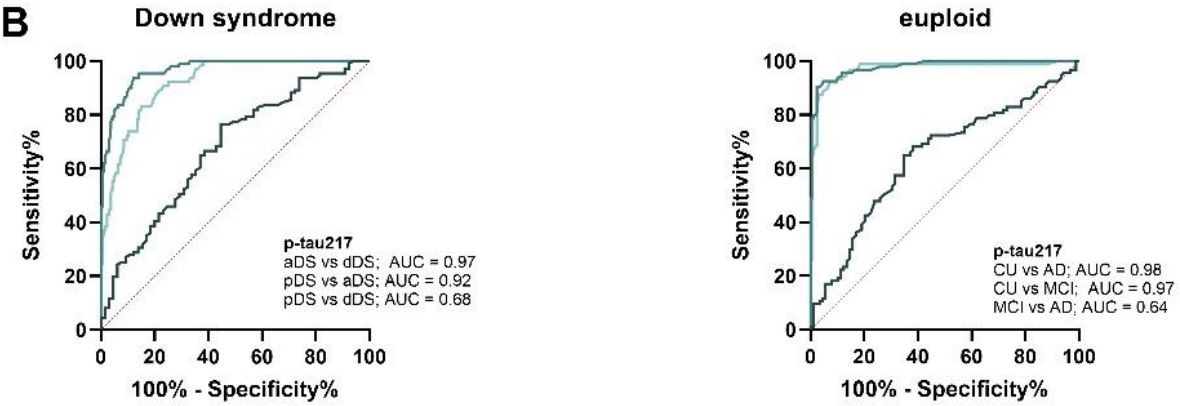
Burak Arslan[1], Hanna Huber[1], Laia Montoliu-Gaya[1], Guglielmo Di Molfetta[1], Yara Yakoub[2], Oscar Kittel[1], Kaj Blennow[1], Henrik Zetterberg[1], Daniel Alcolea[3], Juan Fortea[4], Nicholas Ashton[1]
[1]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, [2]Douglas Mental Health University Institute, Centre for Studies on the Prevention of Alzheimer's Disease (StoP-AD), Montreal, Quebec, Canada., montreal, Canada, [3]Hospital de la Santa Creu i Sant Pau - Biomedical Research Institute Sant Pau - Universitat Autònoma de Barcelona, 1. sant Pau Memory Unit, Barcelona, Spain, [4]Hospital of Sant Pau, Neurology Department, BARCELONA, Spain

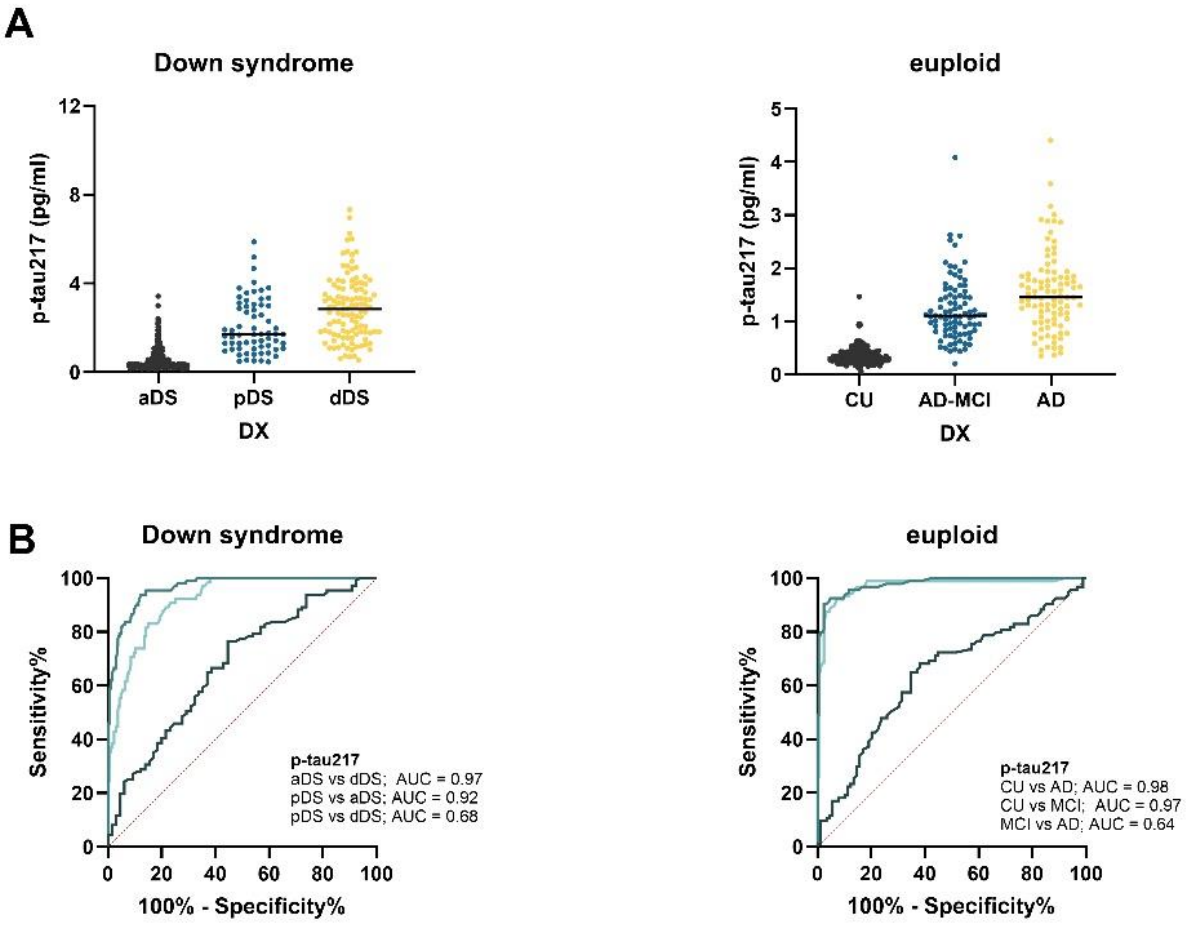
Aims: Individuals with Down syndrome(DS) exhibit Alzheimer's disease(AD) neuropathology by age 40.Diagnosing dementia in DS is challenging due to the inherent intellectual disability,underscoring the need for accessible biomarkers.This study evaluated plasma p-tau217 as a biomarker for detecting amyloid pathology in DS and compared results with euploid controls.
Methods: DS participants were categorized as asymptomatic(aDS),presymptomatic(pDS),or demented(dDS),while euploid individuals were classified by clinicians as cognitively unimpaired(CU),mild cognitive impairment due to AD(MCI-AD),or AD.Blood samples were collected from all participants and measured using the ALZpathp-tau217.CSF biomarker information was available for a subset(191DS and 206euploid individuals)where amyloid-beta positivity was defined as a CSF$A\beta_{42/40}$ ratio < 0.072 .Receiver operating characteristic(ROC) was used to calculate the area under the curve(AUC) to distinguish between the diagnostic groups.
Results: The study included 1138 participants with DS(mean[SD]age, 44.1[10.5]years;588 females[51.7%]) and 470 euploid individuals(mean[SD] age,62.9[12.5]years;277 females[58.9%]).In the DS cohort,the highest p-tau217 levels were observed in the dDS group(mean[SD],3.04 pg/mL[1.49]) and the pDS group(1.91 pg/mL[1.07]),which significantly differed from the aDS group(0.59 pg/mL[0.52]),with AUC values of 0.97 [95%CI, 0.95-0.98]and 0.92[95%CI, 0.90-0.95],respectively.Euploid individuals exhibited a similar pattern,with the highest p-tau217 levels in AD (mean[SD],1.55 pg/mL[0.75])and MCI-AD(1.23 pg/mL[0.61])compared to CU(0.35 pg/mL[0.16]),with AUC values of 0.98[95%CI,0.97-0.99]and 0.97[95%CI,0.95-0.99],respectively.Additionally,p-tau217 effectively discriminated CSFAβ-positive from CSFAβ-negativeDS individuals with an AUC of 0.95[95%CI,0.92-0.99].A single cut-off concentration of 0.71 pg/mL demonstrated a sensitivity of 95% and a specificity of 85%.

A


Down syndrome
p-tau217 (pg/ml)
12
8
4
0
aDS
pDS
dDS
DX
euploid
p-tau217 (pg/ml)
5
4
3
2
1
0
CU
AD-MCI
AD
DX

B


Down syndrome
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%
p-tau217
aDS vs dDS; AUC = 0.97
pDS vs aDS; AUC = 0.92
pDS vs dDS; AUC = 0.68
euploid
Sensitivity%
p-tau217
CU vs AD; AUC = 0.98
CU vs MCI; AUC = 0.97
MCI vs AD; AUC = 0.64
100% - Specificity%



Conclusions: We showed that plasma p-tau217 has a high diagnostic accuracy in discriminating dDS individuals from both aDS and pDS. Moreover,p-tau217 showed a high performance in detecting CSFAβ positivity in DS.We suggest that plasma p-tau217 could be a useful biomarker to diagnose AD with high performance and low burden in DS patients.Notably,the results and cut-offs for brain amyloid positivity will be further validated in independent samples.

Virtual OO - 065

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ASSOCIATION BETWEEN PLASMA BIOMARKERS, AMYLOID-BETA PET, AND CORTICAL THICKNESS IN A RACIALLY DIVERSE COMMUNITY COHORT: THE HUMAN CONNECTOME PROJECT

Shayna Brodman[1], Nick Heaton[2], Rebecca Deek[2], Xuemei Zeng[1], Tara Lafferty[1], Anuradha Sehrawat[1], Alexandra Gogola[3], Ilyas Kamboh[4], Victor Villemagne[5], Oscar Lopez[6], Ann Cohen[5], Thomas Karikari[7]
[1]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [2]University of Pittsburgh, Biostatistics, Pittsburgh, United States of America, [3]University of Pittsburgh, Radiology, Pittsburgh, United States of America, [4]University of Pittsburgh, Human Genetics, Pittsburgh, United States of America, [5]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [6]University of Pittsburgh, Neurology, Pittsburgh, United States of America, [7]University of Pittsburgh Medical Center, Psychiatry, Pittsburgh, United States of America

Aims: The traditional diagnostic test for Alzheimer's disease (AD) uses cerebrospinal fluid (CSF) which is incredibly invasive, time-consuming, and expensive. Blood biomarkers are critical for early detection and pre-clinical preventive measures.
Methods: We included 228 participants from the diverse Human Connectome Project (HCP) cohort based on available PET-PiB images for amyloid pathology (A-status), MRI screening for neurodegeneration pathology (N-status), and associated traditional plasma biomarkers (p-tau181, p-tau217, p-tau231, GFAP, NfL, Aβ40, Aβ42).
Results: Plasma p-tau217 is the best predictor of Aβ PET followed by GFAP and Aβ ratio. All biomarkers perform poorly for N-status. All increase according to combined A/N status. Correlation of p-tau217, p-tau181, and Aβ42/40 with Aβ PET is significantly stronger in NHW.
Conclusions: The use of p-tau217 and the consideration of racial effects in developing blood tests for Aβ pathology is critical in the effort to independently diagnose AD preclinically and symptomatically.

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CLINICAL AND ANALYTICAL PERFORMANCE OF DURITECT: A NOVEL BLOOD-BASED AUTOANTIBODY DIAGNOSTIC SCREENING PLATFORM FOR ALZHEIMER'S AND PARKINSON'S DISEASES

Cassandra Demarshall[1], Jeffrey Viviano[1], Anuradha Krishnan[1], Thomas Borge[1], Dennis Hutchison[1], Mert Sahin[1], Robert Nagele[1,2]
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Aims: In the present study we demonstrate the clinical and analytical utility of the Duritect™ platform, a diagnostic screening solution comprised of panels of customized blood-based autoantibody biomarkers capable of detecting disease-related processes resulting from ongoing Alzheimer's or Parkinson's disease pathology, using a proprietary risk score capable of predicting an individual's likelihood of developing AD or PD.
Methods: Blinded sera samples from ADNI subjects with confirmed presymptomatic, prodromal (MCI), and mild-moderate AD, as well as early-stage PD subjects (Hoehn and Yahr stages 1-2.5) from various sources, together with healthy age- and-sex-matched control subjects, were screened to detect the presence of AD or PD-related pathology utilizing Duritect™'s autoantibody biomarker panels and Luminex xMAP® technology. Autoantibody levels were evaluated using a proprietary machine learning algorithm to calculate an individual Disease Risk Score (DRS) for each patient sample, indicating whether that individual has a typical vs. increased risk of ongoing AD or PD pathology.
Results: demonstrate that Duritect™'s disease-specific panels of autoantibody biomarkers corresponding to a patient's AD or PD risk score successfully differentiated both AD and PD subjects from age- and sex-matched controls, demonstrating greater than 90% overall accuracy, sensitivity, and specificity in both diseases.
Conclusions: Duritect™ is the first blood-based autoantibody diagnostic platform for the detection of neurodegenerative diseases. Our CLIA validated tests against AD or PD-related pathology in patients presenting in primary care settings with signs or symptoms for suspected Alzheimer's or Parkinson's disease are already on the market.Duritect™ is an accurate, minimally invasive, and inexpensive diagnostic screener for the detection of early AD-related pathology associated with prodromal (MCI), later stages of AD, and early-stage PD-related pathology.

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IMPACT OF RENAL FUNCTION ON PLASMA BIOMARKERS OF NEURODEGENERESCENCE

Etienne Mondesert[1], Jean-Paul Cristol[2], Constance Delaby[1], Anne-Sophie Bargnoux[2], Marie Durichon[3], Germain Busto[4], Christophe Hirtz[3], Genevieve Barnier-Figue[5], Florence Perrein[6], Cédric Turpinat[7], Snejana Jurici[5], Audrey Gabelle[4], Karim Bennys[7], Sylvain Lehmann[1]
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Aims: There is a growing interest about blood biomarkers for management of neurocognitive disorders. However, the impact of renal function on their interpretation has not yet been extensively studied. We studied this latter by taking advantage of simultaneous creatinine, plasma and cerebro-spinal fluid (CSF) biomarkers measurements in two prospective and multicenter cohorts (ALZAN and RENALZ) of patients seen in memory clinics
Methods: Plasma creatinine was measured on Roche Cobas, estimated glomerular filtration rate (eGFR) was determined with chronic kidney disease-epidemiology collaboration (CKD-Epi) 2021 equation. CSF and plasma pTau217 assays were performed on Fujirebio Lumipulse while Eclecsys Roche assays were used for plasma Aβ40/42, pTau181, neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP) measurements.
Results: 422 patients were included (mean age: 71.1 years, %woman/man: 53.6/46.4%), with 36 patients having an eGFR under 60 ml/min/1.73m^2. eGFR correlated significantly with all plasma biomarkers (Aβ40, Aβ 42, pTau181, pTau217, NfL, GFAP) but not with plasma Aβ42/40 and pTau217/Aβ42 ratios. Furthermore, mean levels of plasma Aβ40, Aβ42, pTau181, pTau217, NfL, and GFAP were all statistically higher for patients with eGFR under 60 ml/min/1.73m^2 than for patients with eGFR above 60 ml/min/1.73m^2. Plasma Aβ42/40 and pTau217/Aβ42 ratios were not different between the two groups. Receiving operator curve analysis showed that the cut-off levels for cerebral amyloidosis detection of ptau181, GFAP, Aβ42/40 ratio in the whole cohort are not applicable for patients with eGFR under 60 ml/min/1.73m^2 changes (reduction of sensitivity and/or specificity).
Conclusions: Kidney function is an important factor to consider when interpreting plasma biomarkers. Impaired renal function characterized by an eGFR lower than 60 ml/min/1.73m^2 decreases biomarkers excretion rates, which may lead to a misdiagnosis of neurodegenerative disease.

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USE OF SERUM AB1-42 AND TAU BIOMARKERS IN THE DIAGNOSIS OF POSTOPERATIVE COGNITIVE DYSFUNCTION

Narangerel Purevdorj
MNUMS, School Of Medicine, Clinical Laboratory, Ulaanbaatar, Mongolia

Aims: Use of new novel serum biomarkers in the diagnosis of postoperative cognitive dysfunction
Methods: A total of 34 people aged 65 and over who underwent surgery under general or regional anesthesia were included in the study. Baseline cognitive parameters were determined by the "Montreal Cognitive Assessment (MoCA)" within 24 hours before anesthesia and surgery, and the amount of Aβ1-42 and Tau protein in blood plasma before surgery and anesthesia was determined by biomarker analysis.Within 24 hours postoperative and anesthesia, delirium was assessed by the 3D-CAM method, and serum Aβ1-42 and Tau protein levels were repeatedly analyzed
Results: A total of 26 (76.47%) patients did not detect delirium, while 8 (23.53%) patients detected delirium. Within 24 hours preoperative and anesthesia, the score of "The Montreal Test for Assessment of Basic Cognitive Parameters (MoCA)" was 19.88±4.017 in patients who were not delirium, and (13.38±9.07) delirium in patients who were (13.38±9.07). Patients with moderate cognitive impairment had dementia. The level of Tau protein preoperative was 10.52 (3.22-15.78)pg/ml, postoperative it was 10.31 (3.37-14.28) in patients who were not detected delirium (P=0.9751). In the group with delirium, it was 17.75 (3.59-25.69) preoperative and 7.57 (3.07-15.95) postoperative, which was a statistically significant decrease (P=0.0391). In the group without delirium, the preoperative Aβ1-42 protein level was 11.55 (9.180-13.92) and 12.83 (10.05-15.60) , or not statistical difference was observed (P=0.3767). The level of Aβ1-42 protein preoperative was 11.73 (9.736-13.73) , and postoperative it was 12.39 (9.89-14.87) pg/ml, and no statistical difference was observed (P=0.6406).
Conclusions: It was observed that patients aged 65 years and older who postoperative under general or regional anesthesia had higher levels of Tau protein in the blood plasma before anesthesia, and were more likely to postoperative delirium.

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DIAGNOSTIC UTILITY OF PLASMA PTAU217 IN ROUTINE CLINICAL CARE: A PROSPECTIVE STUDY FROM A SINGLE MEMORY CLINIC

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Aims: The study aimed to evaluate the diagnostic accuracy of plasma pTau217 in routine clinical care compared to established cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease (AD) in patients with cognitive disorders. Additionally, it sought to investigate the influence of renal function on plasma biomarker levels.
Methods: A prospective cohort of 131 consecutive patients was recruited from the Pitié-Salpêtrière Memory Clinic (Paris, France) between January and July 2024. Plasma pTau217 and other biomarkers (pTau181, Aβ42, Aβ40) were measured using Meso Scale Discovery S-Plex assays. Parallel CSF biomarker analyses (pTau181, T-Tau Aβ42, Aβ40) were performed using Fujirebio Lumipulse to evaluate the concordance between plasma and CSF results, with additional assessment of renal function impact.
Results: 39 patients were classified as CSF A-T-, 61 as A+T+, 20 as A+T-, and 11 as A-T+. Plasma pTau217 exhibited a high diagnostic accuracy with an area under the curve (AUC) of 0.97, outperforming other plasma markers. Strong correlations were found between plasma pTau217 and CSF pTau181/Aβ42 ratio ($\rho = -0.73$, $p < 0.0001$), demonstrating its reliability. The use of a 2-threshold approach could reduce the need for lumbar punctures by 80%. Renal function (glomerular filtration rate) had a minimal effect on pTau217 levels ($\rho = -0.196$, $p = 0.2135$).
Conclusions: This study is one of the first to show that plasma pTau217 can be effectively used in routine clinical care for the biomarker assessment of AD in memory clinics. Its high diagnostic accuracy and potential to reduce invasive procedures make it a transformative tool in memory clinic settings. Additionally, it provides practical thresholds from commercially available assays that might be used in other centers.

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PLASMA AMYLOID BETA 1-42, TOTAL TAU PROTEIN AND TOTAL ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE WITH COGNITIVE IMPAIRMENT

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Aims: In addition to α-synuclein, amyloid and Tau pathologies have been found in patients with Parkinson's disease (PD). Although the results of assaying these proteins in body fluid have been reported, comprehensive studies on the discriminating power between PD and normal control (NC), as well as PD with normal cognition (PD-NC) and PD dementia (PDD), are rare, especially in plasma. In this study, total plasma a-synuclein, amyloid β 1-42 ($A\beta_{1-42}$) and total Tau in NC, PD-NC, and PDD subjects were assayed to explore the roles of these three proteins in PD.
Methods: One hundred and eighty-seven NC's, one hundred and twenty-eight PD-NC patients and seventy-nine PDD patients were enrolled at five hospitals in Taiwan. Plasma Tau, $A\beta_{1-42}$ and α-synuclein were assayed for each enrolled subject using ImmunoMagnetic Reduction (IMR) assay.
Results: Plasma $A\beta_{1-42}$, Tau and α-synuclein were significantly increased in PD compared to NC. Further increases in plasma Tau and α-synuclein were found in PDD dementia compared to PD-NC. α-synuclein levels showed a relatively strong discriminating power between PD and NC, as well as PDD and PD-NC. Tau levels showed a relatively strong correlation with cognitive decline. In NC, the three proteins were independent of age.
Conclusions: The results suggest that both Tau and α-synuclein play roles in the occurrence of PD and cognitive impairment in PD. However, Tau levels are not associated with a-synuclein levels in PD, which implies that Tau and α-synuclein should be regarded as independent biomarkers in PD.

Virtual OO - 071

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CLINICAL MEANINGFULNESS OF COGNITIVE DECLINE THROUGH PRECLINICAL TO SYMPTOMATIC STAGES OF ALZHEIMER'S DISEASE, MEASURED USING THE PRECLINICAL ALZHEIMER'S DISEASE COGNITIVE COMPOSITE SCORE (PACC).

Rodrigo Canovas[1], Rosita Shishegar[2,3], Marcela Cespedes[4], Christopher Fowler[5], Stephanie Rainey-Smith[6,7], Hamid Sohrabi[7,8], Jurgen Mejan-Fripp[4], Yen Lim[9], Jason Hassenstab[10], Colin Masters[11], Paul Maruff[12], James Doecke[13]
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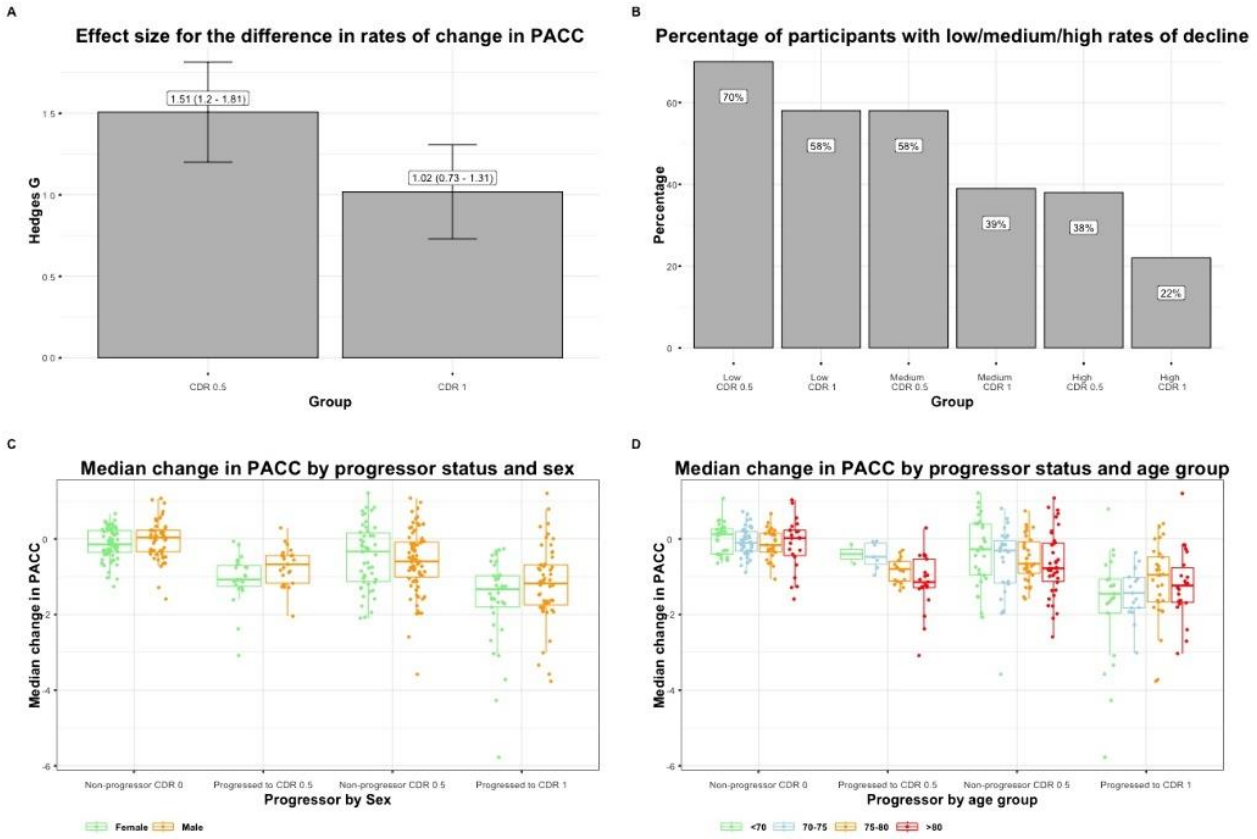
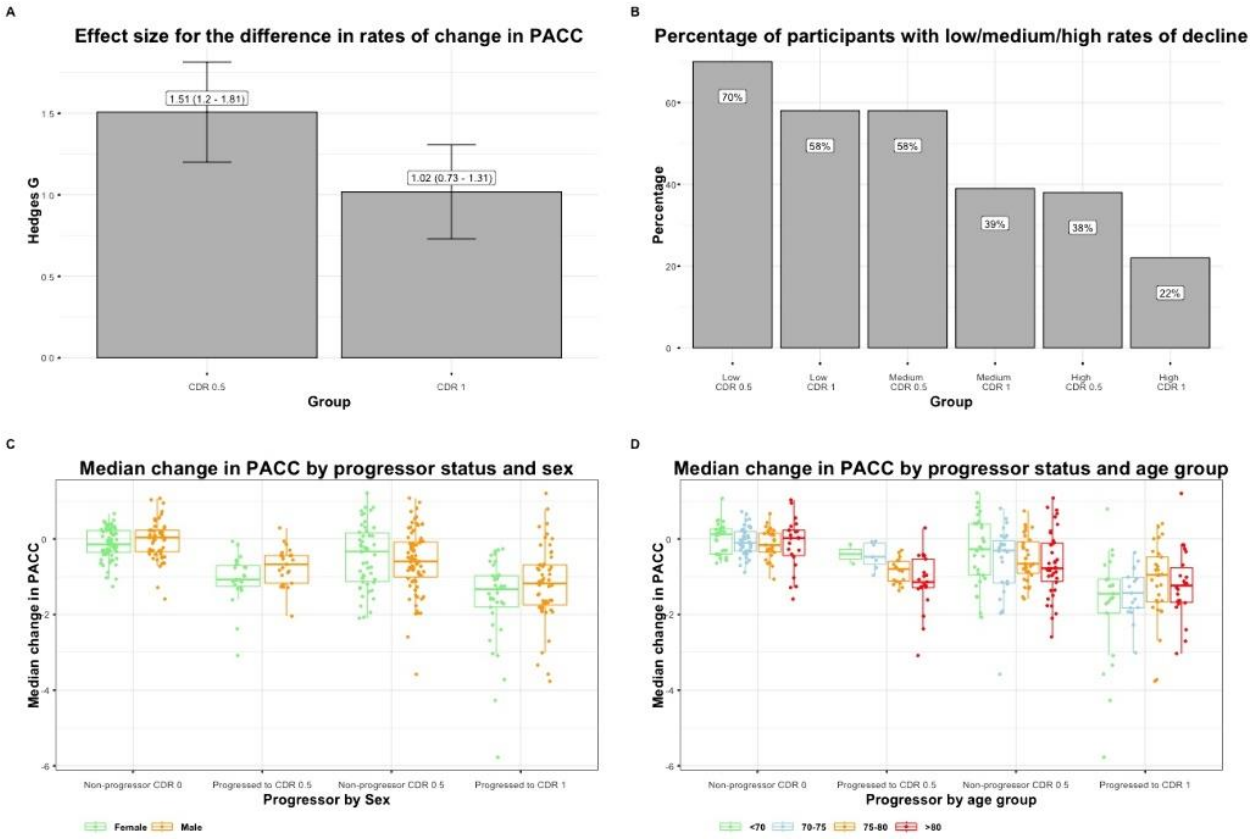
Aims: In early AD clinical trials, cognitive decline is a main clinical outcome. Clinical disease progression is an inevitable event in AD, providing anchoring events for establishment of estimates of clinically meaningful cognitive change. Progression from CDR-0 to CDR-0.5 and from CDR-0.5 to CDR-1 were used as anchors to estimate meaningful change and minimal within person change (MWPC) in cognition in very early AD.
Methods: Demographic, clinical, and harmonized PACC data were obtained from preclinical and prodromal AD groups from pooled ADNI, AIBL and OASIS cohorts. Participants were classified as progressing from CDR-0 to CDR-0.5 or CDR-0.5 to CDR-1 (progressor), or not (non-progressor), over three-years. Reliability of PACC was determined using ICCs and mean (SD) of three-year-change in non-progressors. Responsiveness to change was estimated by comparing three-year PACC change between progressor/non-progressor groups. Mean (SD) change in PACC in non-progressors was used to develop criteria for small (-0.5SD), medium (-1SD), and large (-1.5SD) meaningful-within-person-change (MWPC).
Results: Three-year PACC data were available for 140 CDR-0 non-progressors and 61 progressors, and for 155 CDR>0.5 non-progressors and 120 progressors. Progressors showed greater PACC change than non-progressors (Fig_1A). In non-progressors, PACC reliability was high, CDR-0 (ICC=0.80), CDR-0.5 (ICC=0.81). Fig_1B indicates 70% of CDR-0, and 58% of CDR-0.5 progressors showed a small or greater MWPC. Three-year-change in PACC for CDR-0 and CDR^{3}0.5 progressors was greater for females than males (Fig_1C). For

age, three-year-change in PACC was greater in older CDR-0 progressors, and in younger CDR-0.5 progressors (Fig_1D).





Conclusions: With clinical disease progression as an anchor, clinically meaningful decline in cognition over 3-years was evident in 70% of participants whose disease progressed. These estimates provide a basis for interpreting the meaningfulness of change on the PACC in early AD clinical trials.

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NEUROPSYCHOLOGICAL ASSESSMENT USING EYE TRACKING FOR EARLY DETECTION OF ALZHEIMER´S DISEASE

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Aims: The aim of the study is to assess value of a cognitively informative eye-tracking protocol in Alzheimer´s disease (AD). This protocol has the potential to improve early diagnostics. It is easy to conduct, reliable and could also be used to evaluate stages of symptomatic AD.
Methods: Eye-tracking data on 80 patients from a memory clinic (Karolinska University Hospital, Sweden) will be collected. Our cognitively informative eye-tracking protocol (anti-saccadic task, verbal memory, visual memory, processing speed, executive functions) takes approximately 20 minutes. Other information about the patients (paper-and pencil neuropsychological test battery, demographic information, cerebrospinal fluid biomarkers, AI-computed volumetry from magnetic resonance imaging - Combinostics) will also be utilized. Various eye-tracking measures (e.g., latencies, durations) will be statistically analysed (ANOVA, t-test, regression models, Cox regression analysis, Kaplan-Meier analysis).
Results: An anti-saccadic task tested in our clinical population has shown good ability to distinguish cognitively normal from cognitively impaired patients. For example, the measure of latency of a correction saccade was able to distinguish between high and low atrophy grade in all cortical brain regions with the highest effect size found in the right parietal lobe ($d = 1.234$, $p < .002$). This measure helped creating two clusters which distinguish high and low cognitive function in verbal delayed recall ($d = 1.061$, $p < .001$), and visual immediate recall ($d = 1.027$, $p < .001$). We did not detect any differences in the fluid biomarkers between the clusters when only using the anti-saccadic task.
Conclusions: Further research is needed to improve screening and diagnostic value of eye-tracking tools. This cognitively informative protocol has a potential to improve specificity and sensitivity of clinically used diagnostic tools, as well as to better evaluate cognitive continuum of AD.

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REGION-SPECIFIC MEASURES OF METABOLISM DIFFERENTIATE COGNITIVELY UNIMPAIRED INDIVIDUALS WITH ELEVATED LEVELS OF ALZHEIMER'S DISEASE NEUROPATHOLOGY FROM INDIVIDUALS WITH AD DEMENTIA

Sara Fernandes-Taylor[1,2], Matthew Glittenberg[1,2], Ira Driscoll[1,2], Brianne Breidenbach[1,2], Tobey Betthauser[1,2], Sanjay Asthana[1,2], Sterling Jonhson[1,2], Ozioma Okonkwo[1,2]
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Aims: Objectives: Cerebral blood flow (CBF) measures nutrient delivery to brain tissue, FDG-PET estimates neural cell glucose metabolism, and white matter hyperintensities (WMH) reflect chronic ischemia due to cerebral small vessel disease. Reports show these physiological processes are impaired in Alzheimer's disease (AD) dementia. We describe the role of nutrient transport, metabolism, and WMH in resilience to AD among cognitively unimpaired individuals with high levels of AD neuropathology [β-amyloid(A); tau (T)].
Methods: Methods: Our cohort was composed of 373 participants from the Wisconsin Registry for Alzheimer's Prevention and Alzheimer's Disease Research Center with available data. We differentiated A-T-cognitively unimpaired ["controls"; n=308] from cognitively unimpaired A+T+ individuals ["mismatches"; n=33; A+=global PiB>1.19, T+=PET-derived Braak stage III-VI] and AD [n=32; A+T+ and cognitively impaired]. ROIs relevant to AD were extracted for CBF, FDG, and WMHs. Linear regressions with robust standard errors examined group differences in regional (1) CBF (2) FDG-PET (collected mean=5 years preceding tau/PiB-PET; subset of n=146), and (3) WMHs. Models adjusted for age, APOE-ε4+, sex, gray matter volume (CBF only), and intracranial volume (WMH only).
Results: Results: The cohort was 66.7 years old (mean), 69% female, and 37% APOE-ε4+. CBF was significantly higher for mismatches (and controls) than AD in all regions examined: hippocampus (β=0.224[0.063];p<.001), precuneus (β=0.280[0.095];p=.003), entorhinal cortex (β=0.215[0.057];p<.001), and posterior cingulate gyrus (β=0.279[0.085];p=.001). Mismatches (and controls) had significantly higher glucose metabolism than AD in the right amygdala (right β=0.050[0.021];p=.020; left β=0.039[0.024];p=.104) and hippocampus (right β=0.053[0.025];p=.036; left β=0.062[0.023];p=.007). WMH differentiated AD from controls (β=-0.676[0.208];p=0.001) but not mismatches (p=0.212).
Conclusions: Conclusions: Region-specific differences in CBF and FDG-PET distinguish cognitively unimpaired A+T+ individuals from probable AD. These findings further our understanding of how the preservation of functional neural activity may contribute to resilience to AD dementia.

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ADHERENCE TO BIOMARKER-BASED DIAGNOSIS RECOMMENDATIONS OF COGNITIVE IMPAIRMENT IN CLINICAL ROUTINES: A MULTICENTER STUDY

Claudio Singh Solorzano[1], Cristina Festari[1], Stefania Orini[2], Eleonora Castagna[3], Matteo Cotta Ramusino[4], Fabrizia D'Antonio[3], Adolfo Di Crosta[5], Alessia Masòtino[5], Federico Massa[6], Alice Mazzonetto[7], Massimiliano Panigutti[3], Noemi Ravì[7], Michela Pievani[1], Laura Bonanni[5], Giuseppe Bruno[3], Annachiara Cagnin[7], Roberto Gatta[8], Giovanni Frisoni[9]
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Aims: The assessment of the feasibility and applicability of recommendations in routine practice is uncommon. This study evaluated the adherence in clinical practice of three memory clinics to the biomarker-based work-up as outlined in the Italian Inter-societal Consensus Recommendations (IICR; Boccardi, 2020).
Methods: The diagnostic pathway of consecutive new patients with cognitive complaints was retrospectively evaluated by reviewing medical charts from 2018-19 (T0) and 2022-23 (T1; i.e., before and after IICR publication). Adherence was assessed using a modified Adherence Index (AI, Turro-Garriga, 2017), including five domains: clinical visit, blood exam, neuropsychological assessment, structural neuroimaging, and advanced biomarkers (e.g., biofluids and advanced imaging). The clinical value of each domain, except for advanced biomarkers, in the diagnostic process was weighted according to the mean opinion of three expert neurologists. For the advanced biomarker domain, we assessed adherence to IICR based on the first diagnostic hypothesis. The AI score for each domain ranged from 0 to 1, and the global AI ranged from 0 to 5, with higher scores indicating higher adherence to recommendations. Comparison analyses were performed using the Mann-Whitney (U) and chi-squared (X^2) tests.
Results: Of the 1035 reviewed medical charts, 317 (31%) described a diagnostic work-up based on biomarkers (T0=178; T1=139). After the publication of the recommendations, global AI significantly increased from 2.09±1.04 to 2.28±1.04 points (U=8107; p=0.047). In T1, the diagnosis work-up included a more complete neuropsychological assessment (U= 9492; p<0.001) and more appropriate use of advanced

biomarkers (X^2 (3)=39.66; p<0.001).

Conclusions: The IICR publication significantly impacted the clinical routine of Italian memory clinics, increasing awareness of the value of a complete neuropsychological assessment and a more appropriate use of advanced biomarkers.

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ADVANCED MULTI-SHELL DIFFUSION MRI IDENTIFIES UNIQUE IMAGING BIOMARKER TRAJECTORIES, PREDICTS DIFFERENTIAL COGNITIVE DECLINE, AND CLASSIFIES COGNITIVE IMPAIRMENT

Alex Guo, Zhaoyuan Gong, Jonghyun Bae, Noam Fox, Nathan Zhang, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

Aims: Early diagnosis of Alzheimer's disease (AD) is paramount for timely intervention and treatment monitoring. Alterations in gray and white matter, including demyelination, axonal loss, and synaptic degeneration, have been suggested to precede amyloid-β and tau depositions, while correlating strongly with dementias' severity. Further, advances in quantitative MRI have enabled probing tissue microstructure with increased specificity and sensitivity in human models. Our study analyzed a well-characterized cohort of cognitively normal (CN) and impaired (CI) subjects using statistical and biophysical diffusion MRI models, and explored the classification accuracy of these parameters.
Methods: We obtained 341 longitudinal multi-shell diffusion MRI scans across 210 subjects (118 male) in the ADNI 3 cohort. Our cohort included 115 CN individuals and 95 CI subjects (84 with mild cognitive impairment (MCI) and 11 with AD). Region-of-interest (ROI) values were calculated from imaging biomarkers derived using Mean Apparent Propagator (MAP) and Standard Model Imaging (SMI) diffusion models. Mixed-effects linear regression was used to analyze biomarker trajectories and their association with cognitive changes. Logistic regression, Random Forest (RF), Extreme Gradient Boosting (XGBoost), and Support Vector Machine (SVM) models were used for classification.
Results: The MAP parameters depict clearer trajectory differences among CN and CI subjects than the SMI parameters (Figure 1). Lower MAP quantiles are associated with steeper increases in Clinical Dementia Rating Sum of Boxes (CDRSB) scores, particularly in CI subjects (Figure 2). Machine learning models utilizing these biomarkers greatly distinguish CN from AD subjects, and moderately distinguish CN from MCI subjects, with the RF and SVM models performing best, respectively (Table

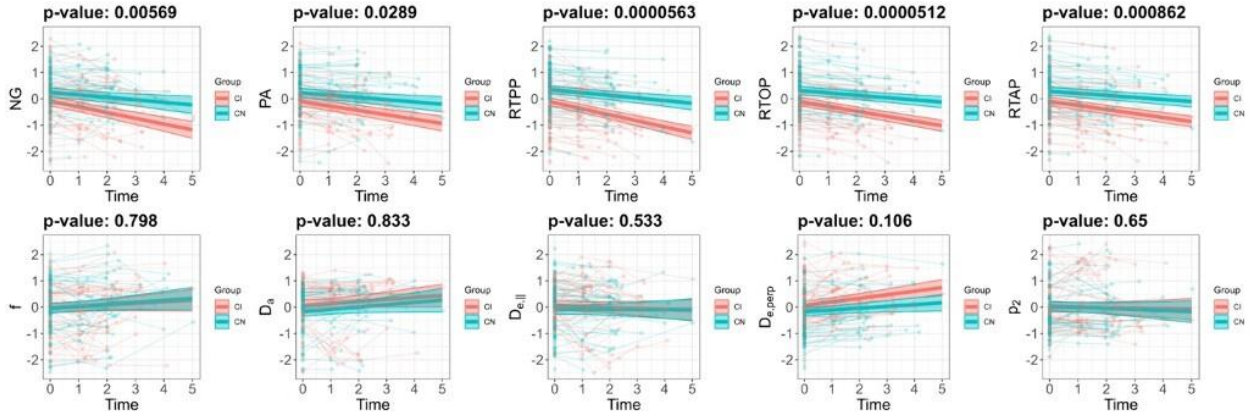


Figure 1: Mixed-effects linear regressions performed using the model : $\mathbf{MRI_{i,j}} = \beta_0 + \beta_{age} \times \mathbf{age_i} + \beta_{sex} \times \mathbf{sex_i} + \beta_{time} \times \mathbf{time_{i,j}} + \beta_{group} \times \mathbf{group_i} + \beta_{time \times group} \times \mathbf{time_{i,j}} \times \mathbf{group_i} + (1|\mathbf{RID}_i)$. $MRI_{i,j}$ represents the ROI value of the respective MAP or SMI parameter. In the statistical MAP model, *NG* (non-Gaussianity) describes diffusion deviations, *PA* (propagator anisotropy) measures how diffusion varies in different directions, *RTOP* (return to origin probability) measures tissue complexity in three dimensions, *RTPP* (return to plane probability) measures planar complexity, and *RTAP* (return to axis probability) measures one-directional complexity. In the biophysical SMI model, f (axon fraction) describes axonal density, D_a (intracellular axial diffusion) measures axonal injury, $D_{e,\parallel}$ (extracellular parallel diffusion) measures inflammation, $D_{e,\perp}$ (extracellular perpendicular diffusion) measures demyelination, and p_2 (2^{nd} order of the orientation distribution function) measures fiber alignment. Age_i is baseline age (in years) of subject i, defined as their age at their first visit. $Time_{i,j}$ is the time difference of subject i's age at year j from their baseline age. $Group_i$ is a binary variable representing subject i's classification as CN or CI (CI represents cognitively impaired subjects, including both MCI and AD participants). RID_i is the anonymized ID associated with subject i. Visualizations of the **time × group** interaction term shown for the whole-brain ROI for each MAP or SMI parameter, with associated p-values displayed. Shaded regions indicate 95% confidence intervals. Subject-level trajectories shown within the plot backgrounds.

1).

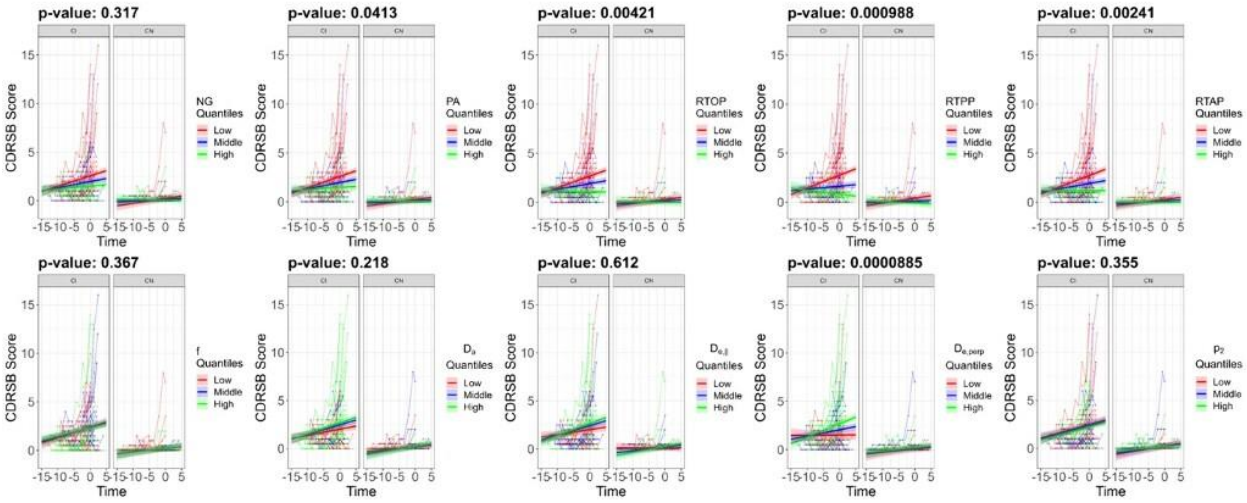
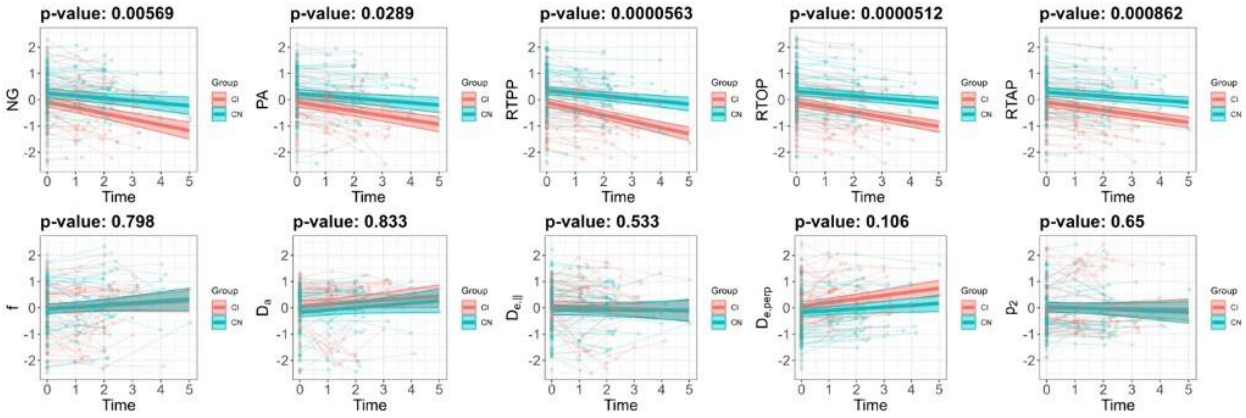


Figure 2 : Linear regressions performed using the model: $\mathbf{Cognition_{i,j}} = \beta_0 + \beta_{age} \times \mathbf{age_i} + \beta_{sex} \times \mathbf{sex_i} + \beta_{time} \times \mathbf{time_{i,j}} + \beta_{group} \times \mathbf{group_i} + \beta_{MRI} \times \mathbf{MRI_i} + \beta_{time \times group} \times \mathbf{time_{i,j}} \times \mathbf{group_i} + \beta_{time \times MRI} \times \mathbf{time_{i,j}} \times \mathbf{MRI_i} + \beta_{group \times MRI} \times \mathbf{group_i} \times \mathbf{MRI_i} + \beta_{time \times group \times MRI} \times \mathbf{time_{i,j}} \times \mathbf{group_i} \times \mathbf{MRI_i} + (1|\mathbf{RID_i})$. Representative graphs shown for the cognition measure CDSRB. Visualizations shown for the **time × group × MRI** interaction term for each MRI parameter with associated p-values displayed. Red, blue, and green lines: longitudinal changes in CDRSB at low, median, and high MAP or SMI quantiles, respectively. Shaded regions indicate 95% confidence intervals. Subject-level trajectories shown within the plot backgrounds.

Control vs. AD Classification Performance				
	Mean Precision	**Mean Recall**	**Mean F-1 Score**	**Mean Accuracy**
Logistic Regression	0.889	0.817	0.838	0.817
Random Forest (RF)	**0.909**	**0.929**	**0.918**	**0.929**
Extreme gradient boosting (XGBoost)	0.899	0.873	0.879	0.873
Support-vector machine (SVM)	0.863	0.841	0.849	0.841
Control vs. MCI Classification Performance				
	Mean Precision	**Mean Recall**	**Mean F-1 Score**	**Mean Accuracy**
Logistic Regression	0.642	0.633	0.633	0.633
Random Forest (RF)	0.607	0.613	0.606	0.613
Extreme gradient boosting (XGBoost)	**0.653**	0.638	0.639	0.638
Support-vector machine (SVM)	0.646	**0.648**	**0.654**	**0.648**

Table 1: Table displaying performance metrics of the four machine learning models tested for cross-sectional classification of subjects into CN vs AD or CN vs MCI categories. Model training and testing was conducted using 5-fold stratified cross-validation and used covariates of age, sex, and one-hot encoded MRI site ID along with all MRI parameters. Synthetic Minority Oversampling Technique (SMOTE) was performed to balance group counts. Representative results using whole-brain ROI MRI parameters shown. The best performing models are in bold.



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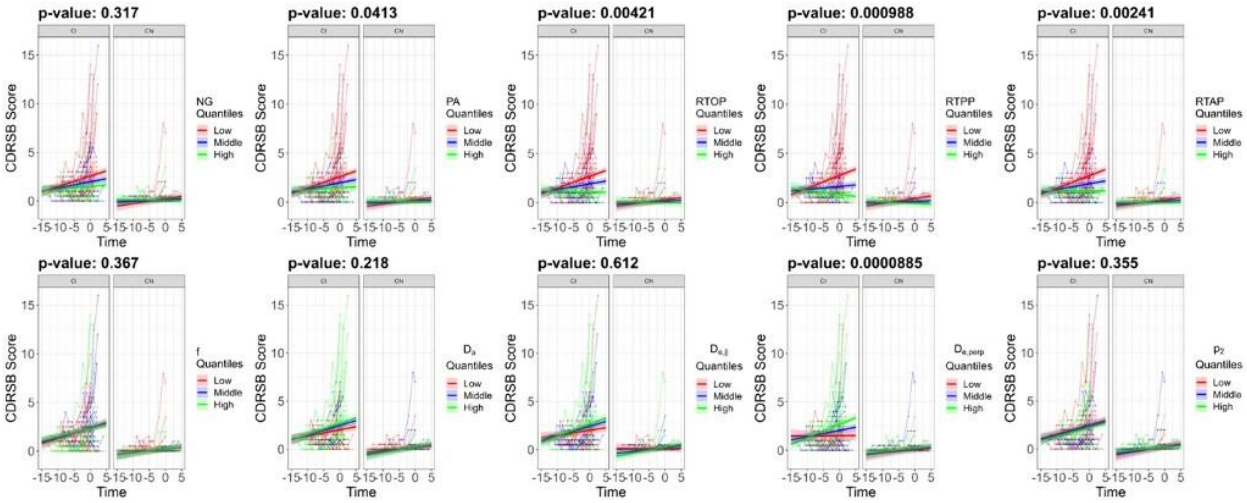

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Conclusions: Diffusion MRI models provide diagnostic abilities in monitoring early AD progression, however, more data is needed to conclude robust classification potential.

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THE SCOTTISH BIOHERMES DATA CHALLENGE: DEMOCRATISING DEMENTIA DATA ACCESS

Kalliopi Mavromati[1], Terry Quinn[2]
[1]University of Glasgow, School Of Cardiovascular And Metabolic Health, Glasgow, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom

Aims: Direct access to individual participant data (IPD) from completed research studies is an aspiration, but frequently 'open' data are not equally open to all in the research community. Through a partnership of Scottish Brain Health Alliance for Research Challenges, Global Alzheimer's Platform, and Alzheimer's Disease Data Initiative (ADDI), we attempted to truly democratise data access, creating The Scottish Data Challenge data sharing initiative.
Methods: We used the BioHermes dataset, containing clinical, demographic and test data, including a variety of novel dementia biomarkers, from over 1000 participants. The cohort is uniquely drawn from populations typically underrepresented in dementia research. Hosted on the ADDI workbench, we made the BioHermes IPD available to teams wishing to explore new hypotheses. We ensured ethics and data governance were in place to minimise administrative burden, and offered end-to-end support from developing the research question, to running analyses and dissemination. The only request of applicants was to prioritise collaboration, support early career researchers and consider equality, diversity, and inclusion in the composition of their teams.
Results: Following expressions of interest, 40 international teams, comprising over 100 individual researchers from multidisciplinary backgrounds have accessed the resource. Active projects include describing the effect of frailty on dementia risk, incorporating biomarkers into cognitive reserve models, and assessing the moderating effect of cardiovascular risk factors.
Conclusions: By allowing researchers to focus on what they do best – research, our easy access, open data resource succeeded in facilitating innovation through collaboration. The quality and volume of results produced in the 10 months since the launch are testament to the potential of open data. We hope the Challenge will act as a model for future data sharing initiatives.

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PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS IN MCI AND DEMENTIA

Giulia Rugarli[1,2,3], Roberto Santangelo[4,5], Giordano Cecchetti[1,4,5], Elisa Sibilla[1], Francesca Caso[4], Giuseppe Magnani[4], Massimo Filippi[1,3,4,5], Federica Agosta[1,3,4]
[1]IRCCS San Raffaele Scientific Institute, Neuroimaging Research Unit, Division Of Neuroscience, Milan, Italy, [2]IRCCS San Raffaele Scientific Institute, Neurology Unit, Milan, Italy, [3]Vita-Salute San Raffaele University, Milan, Italy, [4]IRCCS San Raffaele Scientific Institute, Neurology, Milano, Italy, [5]IRCCS San Raffaele Scientific Institute, Neurophysiology Service, Milan, Italy

Aims: Alzheimer's disease (AD) is a growing global health issue with increasing social and economic impacts. The retina holds potential for assessing Central Nervous System pathology, which can be evaluated using Optical Coherence Tomography (OCT). OCT studies in AD patients have revealed alterations, such as reduced retinal nerve fiber layer (RNFL) and macular ganglion cell/inner plexiform layer (GCL-IPL) thickness. This study explores retinal thickness in patients along the AD continuum, those with other dementias, and healthy controls.
Methods: We recruited 67 patients. Participants underwent OCT, neurological and neuropsychological exams, lumbar puncture, and APOE genotyping. The cohort was divided into Mild Cognitive Impairment (MCI, n=30), AD dementia (n=16), other dementias (OD, n=5), and healthy controls (HC, n=16). Group differences in RNFL and GCL-IPL thickness were evaluated using the Kruskal-Wallis test, with correlations assessed by Spearman's test. Significance was set at $p<0.05$.
Results: The Kruskal-Wallis test showed significant differences in global RNFL thickness ($p = 0.046$) across groups. Post-hoc analyses revealed the AD dementia group had significantly lower global RNFL thickness than healthy controls (90.56 ± 7.31 µm vs. 99.56 ± 8.86 µm, $p = 0.007$), irrespective of APOE status. MCI patients also had thinner RNFL compared to controls (93.93 ± 10.97 vs. 99.56 ± 8.86 µm), though the difference was not statistically significant ($p = 0.051$). A positive correlation between nasal RNFL thickness and Mini-Mental State Examination (MMSE) scores was observed ($r = 0.265$, $p = 0.043$).
Conclusions: AD and MCI patients exhibit thinner RNFL, supporting the neuro-retina as a marker of neurodegeneration. RNFL thickness is positively correlated with MMSE scores, potentially reflecting disease severity. OCT may serve as a proxy for neurodegeneration and cognitive impairment.

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VISUALISING PREVENTING EFFECTS USING ELECTROPHYSIOLOGICAL TECHNIQUE

Keisuke Fukasawa[1], Hideyuki Hoshi[2], Yoko Hirata[1], Momoko Kobayashi[1], Keita Shibamiya[1], Sayuri Ichikawa[1], Yoshihito Shigihara[2]
[1]Kumagaya General Hospital, Kumagaya, Japan, [2]Hokuto Hospital, Precision Medicine Centre, Obihiro, Japan

Aims: Regular physical activity is a major preventing factor for dementia. If its accumulated effect in the brain can be estimated, it would help physicians to design therapeutic strategies. We hypothesised that electrophysiological brain activity would capture the effect.
Methods: We retrospectively obtained clinical data from 275 patients who visited our outpatient department for dementia. One hundred twenty-two patients had a habit of physical activity and 153 were not. The clinical data included electrophysiological brain activity measured using magnetoencephalography (MEG) and cognitive state measured using Mini-Mental State Examination (MMSE). To represent the state of the brain activity, spectral parameters were calculated from MEG data. Previous studies have shown that the parameters are correlated with the MMSE score. Each of the parameters was subjected to a multiple regression model with three predictors (1) a categorical predictor of regular physical activities (i.e., with or without the habit) (2) the MMSE score, and (3) their interaction term, which were examined by ANOVA.
Results: The ANOVA on the regression models revealed that both main effects of regular physical activities and the MMSE score were significant, while the interaction was not.
Conclusions: Electrophysiological brain activity carries information about the effect of regular physical activity as well as the current cognitive state independently. We can estimate the amount of major preventing factor of dementia, namely regular physical activity, using the MEG data. The information allows physicians to provide effective well-being advice to their patients for preventing dementia.

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WHAT IS ALZHEIMER'S DISEASE? AN EPISTEMOLOGICAL, HISTORICAL, AND CROSS-DISCIPLINARY PERSPECTIVE

Nicolas Villain[1,2], Robin Michalon[3,4], Bernard Hanseeuw[5,6], Vincent Planche[7,8]
[1]Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - ICM, Paris, France, [2]AP-HP Sorbonne Université, Pitié-Salpêtrière Hospital, Department of Neurology, Institute of Memory and Alzheimer's Disease, Paris, France, [3]Espace Éthique de la région Île-de-France, Paris, France, [4]CAK-CRHST - Centre Alexandre Koyré - Centre de Recherche en Histoire des Sciences et des Techniques, Paris, France, [5]Université catholique de Louvain, Leuven, Belgium, [6]UCLouvain, Institute Of Neurosciences, Brussels, Belgium, [7]Univ. Bordeaux, CNRS, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux, France, [8]Pôle de Neurosciences Cliniques, Centre Mémoire de Ressources et de Recherche, CHU de Bordeaux, Bordeaux, France

Aims: The development of Alzheimer's biomarkers in the 2000s allowed the detection of Alzheimer's pathology in cognitively unimpaired individuals (CUIs), influencing diagnostic criteria. The International Working Group (IWG) defined two entities: presymptomatic Alzheimer's Disease (AD) (near 100% risk of symptoms) and asymptomatic-at-risk for AD (risk below 100%). In contrast, the Alzheimer's Association (AA) proposed a pathophysiological continuum from preclinical AD to dementia. This abstract explores the epistemological foundations of disease, the evolution of AD definitions and compares these definitions to other medical fields to assess their implications.
Methods: We conducted a literature review across philosophy, cancer, infectious, metabolic, cardiovascular, and genetic diseases, and a historical review of AD nosology, focusing on key periods and figures in disease classification.
Results: Epistemology identifies two main disease concepts: 1)biological diseases, defined by biological anomalies regardless of symptoms (Boorse's theory), 2)clinico-biological diseases, defined by biological causes of disabling symptoms (Nordenfelt's theory). Historically, AD was a clinico-pathological disease. The AA's biological definition departs from this, while the IWG's definition aligns with historical concepts. Cross-disciplinary examples revealed multiple asymptomatic nosological entities, particularly when significant differences in prognosis exist between asymptomatic and symptomatic conditions. Examples include asymptomatic cancers and precancerous conditions, latent tuberculosis infection and active tuberculosis, distinction between ≤39 (reduced penetrance) and ≥40 (Huntington's disease) asymptomatic CAG repeat expansions in the HTT gene.
Conclusions: IWG and AA definitions reflect different AD concepts. The IWG's symptom-based framework aligns with historical definitions, while the AA's biological approach may risk misdiagnosis, misinterpretation of prognosis, and increased disparities in care. Additionally, this shift may hasten drug approvals, particularly in CUIs with positive amyloid biomarkers, without clear clinical benefits. The AA

framework reinforces the β-amyloid cascade hypothesis, while the IWG emphasizes a probabilistic, multifactorial disease model.

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MULTI-ALLELIC LINKAGE ANALYSIS FOR ALZHEIMER DISEASE PROTECTIVE VARIANTS IN THE U.S. AMISH

Yeunjoo Song[1], Weihuan Wang[1], Renee Laux[1], Sarada Fuzzell[1], Sherri Hochstetler[1], Kristy Miskimen[1], Audrey Lynn[1,2], Ping Wang[1], Yining Liu[3], Noel Moore[3], Alexander Gulyayev[4], Michael Prough[4], Larry Adams[4], Laura Caywood[4], Jason Clouse[4], Sharlene Herington[4], Daniel Dorfsman[4], Jeffery Vance[4], Michael Cuccaro[4], Paula Ogrocki[5], Alan Lerner[5], William Scott[4], Margaret Pericak-Vance[4], Jonathan Haines[1,2]
[1]Case Western Reserve University School of Medicine, Population And Quantitative Health Sciences, Cleveland, United States of America, [2]Case Western Reserve University, Cleveland Institute For Computational Biology, Cleveland, United States of America, [3]Case Western Reserve University School of Medicine, Systems Biology And Bioinformatics, Cleveland, United States of America, [4]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [5]Case Western Reserve University School of Medicine, Department Of Neurology, Cleveland, United States of America

Aims: While Alzheimer Disease (AD) risk has a large genetic component, under 50% of the genetic risk has been identified. A multi-allelic variant (MAV) in a genome is a variant with two or more non-reference alleles. MAVs account for ~10% of the variant sites based on deep sequence datasets of >10,000 samples and many of them are functional and disease-relevant. As inclusion of all types of variants is critical to the success of a sequencing study, we examined whole genome sequencing data from the Midwestern Amish, a genetically and culturally isolated population of European descent, performing a genome-wide linkage analysis of cognitive status, in search of protective genes and variants to AD.
Methods: The cognitive status, cognitively unimpaired (CU) vs. cognitively impaired (CI), of each individual was assigned via consensus review of medical history and neuropsychological testing. Allele frequency estimation and Mendelian error checking was done using S.A.G.E. package. The MAVs with the rarest allele frequency > 0.01 were included. MERLIN was used for autosomal two-point parametric linkage analysis.
Results: Over 2 million MAVs with 2 to 6 non-reference alleles (11%) were analyzed. We included 982 individuals, 519 CU (mean age=81.06±5.86, 63% female) and 463 CI (mean age=83.45±5.51, 56% female). Individuals were grouped into 519 pedigrees (range [3-35 people], mean=4.6±3.26). Linkage analysis identified significant (LOD > 3.3) regions on 14 chromosomes for a dominant model and all chromosomes for a recessive model, with 14 MAVs from 10 chromosomes (1, 2, 5, 9, 10, 11, 12, 14, 15 and 17) in common.
Conclusions: This preliminary analyses of MAVs suggest evidence of linkage to regions across the genome, providing a rich resource for further investigation of genes that may provide protection from cognitive impairment.

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GENETIC ANALYSIS OF GLUT10 (SLC2A10) GENE IN PAKISTANI PATIENTS WITH DIABETES MELLITUS

Hira Mubeen, Amna Saleem
UCP, Lahore, Pakistan

Aims: This study aim was to investigate the single nucleotide variants in the coding region of the Glut10 (SLC2A10) gene in Pakistani patients to develop effective diagnostic and medical treatment methods.
Methods: We have performed DNA sequencing of eight patients in glucose transporter genes to identify disease-causing variations that were confirmed by nucleotide-blast. Six single nucleotide variations were detected in 5 of the patients in which two similar deletion variations (c.T>del24, c.A>del31) were found within the region of Exon 3 (111bp) in three diabetic individuals whereas the other four variations (c.T>del23, c.A>del30, c.T>del30, c.A>del37) were detected in two affected individuals.
Results: The findings of the present study revealed that six deletion variations in five patients seem to be the most probable disease-causing variations leading to the development of diabetes, whereas none were found in the remaining three patients.
Conclusions: To conclude, our research emphasizes the importance of finding DNA variations using DNA sequencing in the molecular diagnosis of diverse genetic diseases.

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THERAPEUTIC POTENTIAL OF MASITINIB FOR ALZHEIMER'S DISEASE: INSIGHTS FROM MOLECULAR DOCKING AND TWO-SAMPLE MENDELIAN RANDOMIZATION

Xindi Li[1], Tingwei Liu[1], Davis Cammann[2], Jeffrey Cummings[1], Lingyun Xu[3], Jingchun Chen[1]
[1]University of Nevada, Las Vegas, Department Of Brain Health, Las Vegas, United States of America, [2]University of Nevada, Las Vegas, School Of Life Sciences, Las Vegas, United States of America, [3]Wuhan Polytechnic University, Wuhan, China

Aims: In this study, we employed molecular docking and Mendelian Randomization (MR) analysis to evaluate the potential therapeutic targets of masitinib in Alzheimer's disease (AD).
Methods: We first identified shared target genes between AD and masitinib as candidate therapeutic targets by collecting significant genes from AD, AD endophenotypes, and masitinib-targeted genes from the SwissTargetPrediction database. Molecular docking was then performed to assess the binding affinity between masitinib and the candidate target genes. Subsequently, MR analysis was conducted to evaluate the causal relationships between candidate gene expression in the brain and AD using brain cis-eQTL data as exposure and AD or cognitive function genome-wide association studies (GWAS) data as the outcome. Sensitivity analyses were used to rule out the heterogeneity and horizontal pleiotropy. Finally, we performed a colocalization analysis to determine whether the candidate gene expression and AD shared the same genetic variants.
Results: Two candidate genes, epidermal growth factor receptor (*EGFR*, also known as Erb-B1) and tyrosine-protein kinase FYN (*FYN*), were identified as potential drug targets, showing strong binding affinities with masitinib (EGFR: -12.4 kcal/mol; FYN: -7.8 kcal/mol). MR analysis found that higher EGFR expression in the cortex had a significant causal effect on AD [P-value = 1.56×10^{-8}, odds ratio (OR) = 1.09] or cognitive decline [P-value = 1.34×10^{-3}, OR = 0.98]. Similar results were observed in an independent AD GWAS (from FinnGen) in Finnish population. Sensitivity analyses did not show evidence of heterogeneity or horizontal pleiotropy. Colocalization analysis identified a known AD-risk variant, rs74504435, in the *EGFR* gene as the shared causal variant.
Conclusions: Our findings provide evidence that masitinib is a potential AD treatment through the inhibition of EGFR expression in the brain.

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GLOBAL GENETIC DIVERSITY IN PARKINSON'S DISEASE AND RELATED DISORDERS RESEARCH: THE GLOBAL PARKINSON'S GENETICS PROGRAM

Mary Makarious
Global Parkinson's Genetics Program, New York City, United States of America

Aims: The Global Parkinson's Genetics Program (GP2) enhances Parkinson's Disease (PD) research by incorporating data from over 60,000 globally diverse participants. Using advanced genotyping and whole genome sequencing (WGS), GP2 aims to deepen the understanding of PD's genetic basis across populations. A major focus is improving the representation of admixed populations, often underrepresented in genetic studies. GP2 also promotes open data sharing and global scientific collaboration to advance PD research.
Methods: GP2 ensures data quality using GenoTools (v1.0.0) for rigorous quality control, filtering low-confidence variants. WGS is processed with DeepVariant and GLnexus for accurate variant identification. Participant ancestry is classified into 11 groups using a machine learning model based on 1000 Genomes and other datasets to capture population admixtures. Clinical data for 16,000 individuals, including assessments and disease metrics, is integrated with genetic data. GDPR-compliant data collection is managed through the Verily Viewpoint Workbench, ensuring adherence to privacy regulations.
Results: GP2's dataset includes genotyping for 29,000 PD cases, 16,000 controls, and 10,000 other phenotypes. WGS is available for 6,000 PD cases, 600 controls, and 1,000 participants with other phenotypes. Ancestry classification into 11 groups provides insights into underrepresented populations. The integration of clinical data for 16,000 participants allows for in-depth exploration of clinical-genomic correlations in PD, enhancing understanding of the disease across diverse populations.
Conclusions: GP2's expanded dataset offers a unique opportunity to study PD genetics across diverse populations. Advanced quality control, GDPR-compliant samples, and precise ancestry classification enhance data accuracy. This resource aims to accelerate discoveries in disease progression and precision medicine, driving breakthroughs in PD research and treatment for global populations.

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PRIORITISING PROTEOMIC FEATURES FOR ENDOPHENOTYPES OF ALZHEIMER'S DISEASE: INSIGHTS FROM MENDELIAN RANDOMISATION ANALYSIS

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Aims: Amyloid-beta (Aβ) plaque accumulation is a key feature of Alzheimer's disease (AD) and linked to cognitive decline. While Aβ deposition is well-studied, the molecular mechanisms driving its accumulation remain incompletely understood. We aimed to identify proteins related to brain Aβ levels using large-scale proteomics and genomics data in individuals of Europeans.
Methods: We applied proteome-wide Mendelian randomization to assess potential causality of 2,923 plasma proteins on Aβ levels. We obtained genetic instruments for proteins from the UK Biobank (N=54,000). GWAS for Aβ levels were sourced from ADNI (N = 4314). Our primary approach involved the Wald ratio, or inverse-variance weighted methods, followed by weighted median and MR-Egger, with statistical significance set at FDR < 0.05. Bayesian colocalization assessed shared causal variants between proteome and Aβ levels, with high posterior probability (PPH4 > 0.8) indicating strong colocalization evidence.
Results: Our analysis identified 110 proteins showing nominal significance with Aβ levels (P<0.05) of which four proteins survived 5% FDR. In addition to APOC1 and APOE, we found evidence that genetically predicted higher levels of CA9 (β=1.69, 95% CI, 0.86 to 2.52) and lower levels of ATP5IF1 (β=−2.32, 95% CI, −3.40 to −1.25) were potentially causally associated with Aβ levels. Colocalization showed shared causal variants for APOE and ATP5IF1 (PPH4 > 0.95) with Aβ levels, with weaker evidence for CA9 (PPH4 = 0.69). In a UKB sub-study investigating plasma biomarkers of AD, we found plasma CA9 to show modest correlation with plasma levels of Tau-181, a biomarker for brain Aβ deposition.
Conclusions: Integrated analysis of proteomic and genomic data provided novel causal support for ATP5IF1 and CA9 as potential therapeutic targets for Aβ deposition. Further triangulation of this evidence from functional and preclinical studies is warranted.

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IDENTIFYING INDIVIDUALS AT HIGH RISK FOR ALZHEIMER'S DISEASE AMONG HISPANICS USING SINGLE AND MULTI-ANCESTRY POLYGENIC RISK SCORES

Yuexuan Xu[1], Min Qiao[1], Tamil Iniyan Gunasekaran[1], Yian Gu[1], Dolly Reyes-Dumeyer[1], Angel Piriz[1], Danurys Sanchez[1], Belisa Soriano[2], Yahaira Franco[3], Zoraida Coronado[4], Patricia Recio[5], Diones Rivera[6], Martin Medrano[7], Rafael Lantigua[1], Jennifer Manly[1], Adam Brickman[1], Badri Vardarajan[8], Richard Mayeux[9]
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Aims: The polygenic risk score (PRS) has proven effective in predicting AD risk among Europeans but remains understudied in Hispanics. Findings suggest that diverse genome-wide association studies (GWAS) data across multiple ancestries may improve predictions. We evaluated PRS performance using novel methods in the largest available African, European, and Hispanic GWAS for AD.
Methods: Prediction performance of *APOE*, ancestry-specific PRS, and multi-ancestry PRS derived from GWAS-focused and method-focused approaches to clinical AD, incident AD, and cognition were evaluated in Hispanics from two large studies. Ten repetitions of 5-fold cross-validation were used. In a subset, plasma biomarker data were used in a tuning-validation split to examine PRS performance in predicting single and combined biomarkers.
Results: The PRS excluding *APOE,* constructed using the method-focused approach, outperformed both single-ancestry and multi-ancestry PRSs from the GWAS-focused approach. The best method-focused PRS, incorporating GWASs from African, European, and Hispanic populations, explained up to 1.6%, 3.9%, and 1.7% of the variance in clinical AD, incident AD, and cognition, respectively - comparable to or even higher than the variance explained by the *APOE*. Similar findings were observed in biomarker analyses. *APOE* accounted for more variation in P-tau levels and PRS explained more variation in Ab levels.
Conclusions: Integrating novel multi-ancestry PRS methods with GWASs across ancestries enhances prediction accuracy for AD risk among Hispanics. *APOE* and PRS may point to different biological aspects of AD.

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CROSS-ANCESTRY PREDICTION OF PLASMA PHOSPHORYLATED TAU-217 IN ALZHEIMER'S DISEASE USING POLYGENIC RISK SCORES FOR EARLY AMYLOID AND TAU PATHOLOGIES

Yuexuan Xu[1], Min Qiao[1], Tamil Iniyan Gunasekaran[1], Yian Gu[2], Dolly Reyes-Dumeyer[1], Angel Piriz[1], Danurys Sanchez[1], Belisa Soriano[3], Yahaira Franco[4], Zoraida Coronado[5], Patricia Recio[6], Diones Rivera[7], Martin Medrano[8], Rafael Lantigua[1], Lawrence Honig[9], Corinne Engelman[10], Sterling Jonhson[11], Badri Vardarajan[12], Richard Mayeux[9]
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Aims: Plasma phosphorylated tau 217 (P-tau217) is a specific biomarker for Alzheimer's disease (AD), with abnormal levels reflecting amyloid beta and tauopathy pathways. Developing cross-ancestry polygenic risk scores (PRS) for amyloid and tau may help identify individuals across diverse populations likely to show abnormal P-tau217, supporting early detection and targeted prevention.
Methods: Using the largest AD GWAS in European and Hispanic populations, and a European-specific GWAS on amyloid and tau PET imaging, we developed APOE-independent tau and amyloid PRS via two approaches: (1) direct PRS from amyloid/tau PET imaging GWAS, and (2) a supervised classification method for disease subtypes using pathway-specific PRS, integrating tau and amyloid pathways identified from bioinformatic databases with ancestry-specific AD GWAS summary statistics. For both approaches, we implemented 100 repetitions of 5-fold nested cross-validation for hyperparameter tuning and performance evaluation in both populations.
Results: In Europeans, the amyloid PRS from European-focused amyloid PET imaging GWAS explained ~4% of plasma P-tau217 variance (ΔR^2 = 0.04, 95% CI [0.034–0.045]), while tau PRS explained significantly less (ΔR^2 = 0.005, 95% CI [0.004–0.007]). The pathway-specific amyloid PRS explained ~1.9% of P-tau217 variance (ΔR^2 = 0.019, 95% CI [0.018–0.020]), and tau PRS explained ~1% (ΔR^2 = 0.01, 95% CI [0.009–0.0107]). In Hispanics, European-focused amyloid/tau PRS explained only 0.1–0.2% of P-tau217 variance, while pathway-specific amyloid PRS explained ~0.7% (95% CI [0.006–0.008]) and tau PRS ~1% (95% CI [0.008–0.012]).
Conclusions: The European-focused amyloid PET-based PRS more effectively predicts plasma P-tau217

levels than the tau PET-based PRS in Europeans. For populations lacking ancestry-specific amyloid/tau GWAS, leveraging existing AD GWAS with pathway-specific PRS provides a viable approach for predicting plasma P-tau217 across diverse populations.

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RETENTION OF OLDER ADULTS IN A LONGITUDINAL STUDY OF ALZHEIMER DISEASE IN THE RURAL MID-WESTERN U.S. AMISH

Sarada Fuzzell[1], Yeunjoo Song[2], Jonathan Haines[3], Margaret Pericak-Vance[4], Renee Laux[2], Sherri Hochstetler[2], Kristy Miskimen[2], Audrey Lynn[5], Larry Adams[4], Laura Caywood[4], Jason Clouse[4], Sharlene Herington[4], Michael Cuccaro[4], Michael Prough[4], Jeffery Vance[4], Paula Ogrocki[6], Alan Lerner[7], Scott William[4]
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Aims: Understanding the lifecycle of longitudinal study enrollments from initial enrollment to the study endpoint helps to improve study retention, increasing the size of cohorts and thereby the power for statistical analysis and external validity. Retention of study participants is essential to advancing Alzheimer disease (AD) research and developing therapeutic interventions. We are examining enrollments from a long-term longitudinal study that seeks to identify genetic factors associated with memory and aging in Old Order Amish communities.
Methods: Participants are 65 and older and members of Old Order Amish communities in Ohio and Indiana. Participants completed in-person exams at average 2-year intervals. Cognitive status (CDX) was assessed by a panel of neurologists and neuropsychologists and divided into four categories: AD, Cognitively Impaired Not AD (CINAD), Mild Cognitive impairment (MCI), and Cognitively Unimpaired (CU). Participants reach a study endpoint by becoming AD or CINAD, deceased, or declining the follow-up exam. The cohort retention for the study and the reasons for attrition were analyzed.
Results: All 953 participants with the baseline CDX and 366 follow-up CDX were included. The mean age was 80.9 (±4.9) years. The overall retention rate was 71.9% (68.4% (652) for the 1st follow-up and 81.1% (297) for the 2nd follow-up). Reasons for overall attrition: reaching the study endpoint (24.9%; 6.9% classified as AD, and 18.0% deceased and declining the follow-up exam (3.1%). Of eligible participants, 86% and 57.9% were examined so far with a median follow-up time of 3.1 and 2.2 years for the 1st and 2nd follow-ups respectively.
Conclusions: This examination of longitudinal study enrollments explores ascertainment, re-enrollment,

attrition, and overall retention. Planning for attrition is key to maintaining and increasing the size of cohorts over the lifespan of longitudinal studies.

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RACIAL DISPARITIES IN CARDIOMETABOLIC DISORDERS AMONG ALZHEIMER DISEASE PATIENTS: A FOCUS ON NATIVE HAWAIIANS AND PACIFIC ISLANDERS

Justin Wong[1], Anna Gan[1], Lauren Nguyen[1], Lea Zoe El-Hage[2], Keao Kawaako[3], Meliza Roman[4], Chathura Siriwardhana[4], Enrique Carrazana[1], Kore Liow[5]
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Aims: Cardiometabolic disorders may accelerate the progression of Alzheimer Disease (AD), potentially impacting ethnic-racial groups with a higher prevalence of diabetes, obesity, and cardiovascular disease, though limited data exists on Native Hawaiians and Pacific Islanders (NHPI) populations. This study aims to examine the prevalence of diabetes and associated comorbidities among AD patients from different ethnic-racial groups—Asians, Whites, and NHPIs—in Hawaii, with a focus on identifying risk factors linked to AD.
Methods: A retrospective review was conducted on AD patient records from a single center in Hawaii, spanning June 2018 to June 2024. Variables assessed included age at diagnosis, sex, race, insurance type, alcohol use, comorbidities, and Mini-Mental State Examination (MMSE) scores. Statistical comparisons were conducted to identify group differences.
Results: Among 540 patients (286 Asians, 89 NHPIs, 182 Whites, and 13 Others), NHPIs exhibited the highest rates of hypertension (66.3%), diabetes (31.5%), obesity (23.6%), congestive heart failure (13.5%), and coronary artery disease (6.7%). Whites exhibited a higher prevalence of anxiety (18.1%), cardiac arrhythmia (15.4%), and alcohol use (37.4%) compared to Asians and NHPIs. Females had lower mean MMSE scores compared to males (18.3 ± 7.4 vs 21.0 ± 6.2, respectively), along with higher rates of anxiety (16.3%), hypertension (62.2%), hyperlipidemia (47.4%), and underweight body mass index (10.8%).
Conclusions: NHPI AD patients in Hawaii face a higher prevalence of diabetes and a greater burden of cardiometabolic disorders compared to other racial groups. White AD patients show higher rates of anxiety, alcohol consumption, and cardiac arrhythmia compared to Asians and NHPIs. Females with AD exhibited worse cognitive function and more vascular comorbidities compared to males.

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THE APP-PROCESSING PROTEASE RHBDL4 AFFECTS CEREBRAL GLUCOSE METABOLISM.

Lisa Marie Munter, Sandra Paschkowsky, Ylauna Penalva
McGill Pharmacology and Therapeutics Department, Montreal, Canada

Aims: The rhomboid-related protease-4 (RHBDL4) cleaves the amyloid precursor protein (APP) multiple times in the endoplasmic reticulum, thus preventing APP from trafficking to the cell surface and reducing the formation of amyloid-beta peptides. Therefore, we continued to study the physiological functions and regulation of RHBDL4 in order to better understand APP's biology. We found that the absence of RHBDL4 causes a defect in glucose metabolism.
Methods: We use mouse embryonic fibroblasts (MEFs) and mouse models deficient for RHBDL4. We measured abundance and functionality of the glucose transporter 1 (GLUT1) using western blot, flow cytometry and glucose uptake assays. Cerebral glucose uptake was assessed by PET imaging.
Results: Loss of RHBDL4 in MEFs caused a decrease in glucose uptake which was due to a defect in GLUT1. Transfecting RHBDL4 back into knockout MEFs rescued GLUT1 abundance. Since RHBDL4 and GLUT1 are highly expressed in endothelial cells of the brain, we assessed GLUT1 abundance in brain vessels and found GLUT1 indeed to be decreased. This decrease is biologically meaningful since cerebral glucose uptake was diminished in the absence of RHBDL4.
Conclusions: We conclude that RHBDL4 carries an important role in the regulation of cerebral glucose metabolism. We will investigate if this effect relates to APP processing by RHBDL4.

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APP FUNCTIONS AS A NOVEL REGULATOR OF GLUCOSE METABOLISM.

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Aims: Cerebral glucose hypometabolism precedes AD symptoms and predicts progression from mild cognitive impairment to AD. This defect is mainly attributed to decreased glucose transporter 1 (GLUT1) expression in the cerebral endothelium. In APP overexpressing mice, GLUT1 deletion in endothelial cells accelerates memory impairment and neurodegeneration. Studies in APP knockout (KO) mice implicate APP in metabolic processes such as mitochondrial function and insulin action. However, GLUT1 regulation and glucose metabolism at the blood-brain barrier have yet to be investigated.
Methods: We performed biochemical analyses in APP KO mouse embryonic fibroblasts (MEFs), mouse primary cerebral endothelial cells, and vessels from 3-month-old mouse brains. RNAseq data from APP KO MEFs and proteomics data from 3-month-old APP KO mouse hippocampi were used to investigate mechanisms underlying observed phenotypes.
Results: In APP KO MEFs, glucose utilization decreased by 60%, while mitochondrial respiration declined 4-fold. GLUT1 protein levels decreased by 50%, leading to a 3-fold drop in glucose uptake. Exogenous APP expression in KO MEFs rescued GLUT1 defects. The PI3K/Akt/mTORC signaling pathway, which positively regulates GLUT1 through integration of extracellular matrix (ECM) and growth factor stimuli, was downregulated in APP KO MEFs. Primary cerebral endothelial cells and vessels from APP KO murine brains recapitulated the GLUT1 and PI3K/Akt/mTORC phenotypes. MEFs RNAseq data revealed that 45% of ECM genes were differentially regulated in the absence of APP and hippocampus proteomics data confirmed ECM proteins within significant hits.
Conclusions: We propose that APP dysfunction leads to impaired GLUT1 levels and disrupted glucose metabolism, likely through APP-mediated changes in ECM and growth factor signaling. Novel therapies targeting APP function may help address early cerebral glucose hypometabolism and improve AD outcomes.

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ELUCIDATION OF EARLY BIOMARKERS ASSOCIATED WITH ALZHEIMER'S DISEASE AND THERAPEUTIC INTERVENTION FOR EARLY AND ADVANCED ONSET OF DISEASE

Kalyani Chaubey[1], Lijun Dou[2], Edwin Vázquez-Rosa[1], Sarah Barker[1], Kathryn Franke[1], Coral Cintrón-Pérez[1], Jaymie Voorhees[3], Andrew Pieper[4]
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Aims: No animal model of Alzheimer's Disease (AD) is perfectly representative of the human disease. To effectively utilize any animal model, one must understand the aspects of human AD pathophysiology that are faithfully recapitulated. Here, we report brain proteomic changes held in common between human AD and the TgF344AD rat model as a function of disease progression and therapeutic treatment.
Methods: Nine-month-old TgF344AD rats at the beginning stage of AD-like disease were treated with the NAD^+/NADH-normalizing neuroprotective compound P7C3-S243 or vehicle every day for 6 months. This P7C3-S243 treatment was previously shown to protect TgF344AD rats from cognitive and behavioral impairment. Here, we analyzed their brains with label-free proteomics via UPLC-MS/MS on Q-Exactive Orbitrap HF-X analysis. Proteins normalized back to wild-type levels by P7C3-S243 treatment were compared against a human AD proteome database.
Results: Proteomic analysis showed 141 down-regulated and 205 up-regulated proteins in Tg4344AD rat brain compared to wild-type littermates. P7C3-S243 restored 27 down-regulated and 32 up-regulated proteins back to normal wild-type littermate levels in TgF344AD rats. Many normalized proteins in each group were found to change in the same direction in human AD brain proteome analysis, identifying key pathways in common between the TgF344AD rat and human AD that are normalized by treatment with P7C3 compounds.
Conclusions: This study offers proof of principle for disease pathways in TgF344AD rats that prevent disease when restored to normal by a therapeutic treatment, as well as the relevant aspects held in common with human AD. This provides a proof of principle for treating particular pathophysiologic processes in human AD with P7C3 compounds, and also illustrates an approach to assessing the human AD-relevant features of any given animal model of AD.

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SILK METABOLIC IMAGING GUIDED SPATIAL BIOLOGY TO FOLLOW ALZHEIMER PATHOLOGY IN SPACE AND TIME

Jörg Hanrieder[1,2]
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Aims: It is of critical importance to our understanding of Alzheimer's disease (AD) pathology to determine how Aβ plaque formation begins and how ongoing plaque deposition proceeds and initiates subsequent neurotoxic mechanisms. The primary aim of our research is to elucidate the biochemical processes underlying early Aβ plaque formation in brain tissue.
Methods: We developed a dynamic mass spectrometry imaging (MSI) paradigm to track in vivo Aβ build up and deposition by imaging stable isotope labelling kinetics (iSILK). Here, APP NLF knock-in mice are metabolically labeled with stable isotopes to track the fate of aggregating Aβ species through precipitating plaque pathology. The iSILK approach timestamps plaques during the period of initial plaque deposition allowing plaque age to be tracked. We integrated iSILK with single plaque spatial transcriptomics performed on adjacent tissue sections. This enables to track changes in spatial gene expression as a function of plaque age distinct from changes due to the chronological age or pathological severity.
Results: We identified that plaque age correlates negatively with genes expression patterns associated with synaptic function as early as in 10-month-old animals but persists into 18 months. We further integrated our multiomic approach with hyperspectral microscopy to image amyloid structural polymorphs, revealing a positive correlation between plaque age and amyloid structural maturity. This identified three categories of plaques, each with a distinct impact on the surrounding microenvironment, where older, more compact plaques were associated with the most significant synapse loss and toxicity.
Conclusions: We show how isotope-encoded chemical imaging can delineate Aβ aggregation dynamics in vivo. Through, functional integration with spatial transcriptomics, this approach facilitated to resolve some of the earliest events of precipitating amyloid pathology, amyloid aggreation and how Aβ modulates synaptotoxic mechanisms.

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SINGLE-CELL TRANSCRIPTOMICS ANALYSES REVEAL BROAD ALTERATIONS IN RNA PROCESSING IN IPSC-DERIVED NEURONS AND GLIAL CELLS FROM ALZHEIMER'S DISEASE PATIENTS

Marcel Schilling[1], Ana Gutiérrez-Franco[1], María Varea[1], Franz Ake[1], Hui Chen[2], Loris Mularoni[1], Lei Li[2], Mireya Plass[1]
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Aims: Alzheimer's Disease (AD) is the most common age-related neurodegenerative disease worldwide. Several studies have shown that RBP and mRNA isoform alterations are characteristic in AD brains. However, it is not clear if these changes are a consequence of the presence of protein aggregates or if they were preexistent and contribute to disease onset.
Methods: To tackle this question, we have used scRNA-seq to investigate the transcriptomic changes in cells derived from iPSCs from AD patients and controls. To assess the impact of isoform diversity to the molecular phenotype of AD, we have used SCALPEL, a new tool developed in the lab to quantify isoform expression in individual cells.
Results: We have profiled over 60,000 cells including stem cells, NPCs, neurons, and astrocytes. Using isoform expression data from SCALPEL, we have identified 24 cell populations. Comparison between AD and control cells shows multiple cell-type-specific alterations including changes in the expression of genes previously associated to AD such as TTR and ERBB4, and in the expression of RBPs such as HNRNPA2B1 and ELAVL4. These changes are paired with cell-type specific isoform usage changes in hundreds of genes.
Conclusions: Together, our results show that isoform analysis at the single-cell level provides a new layer of complexity to study pathological alterations in AD. Our results identified changes in the expression of genes involved in RNA metabolism and hundreds of isoform switches, underlining the importance of RNA processing in AD. Additionally, we found alterations in pathways related to neuronal projection morphogenesis, suggesting early neuronal cell communication defects in AD. Together, our work highlights the importance of RBPs and RNA metabolism in AD and suggest a more prominent role of RNA processing in early AD pathogenesis.

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ALTERATIONS IN CIRCULATING NEURONAL-DERIVED EXTRACELLULAR VESICLE MICRORNAS IN PRESYMPTOMATIC ALZHEIMER'S DISEASE: INSIGHTS FROM A MULTIETHNIC COHORT

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Aims: Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting approximately 50 million people worldwide. It is the leading cause of dementia, accounting for 60-70% of all cases. With the global aging population, this number is expected to triple by 2050, making AD a growing public health challenge. There is an urgent need for accessible, non-invasive, brain-specific biomarkers to improve early detection and enhance the diagnostic accuracy of Alzheimer's disease. Extracellular vesicles (EV) are cell-specific cargos released by cells, carrying lipids, metabolites, and nucleic acids that play an important role in cell-to-cell communication. Neurons are the primary targets of neurodegeneration and neuronal-derived EVs (NDEV) may represent a promising source of biomarkers in AD.
Methods: We isolated NDEVs from plasma and performed a transcription-wide association study (TWAS) exploring the association between AD and NDEV-microRNAs (miRNA) involving 46 AD patients, 14 presymptomatic AD participants, and 60 neurologically healthy controls. We quantify the expression of 2,083 miRNAs and, after quality control filtering steps, a total of 383 miRNAs were available for the study.
Results: We identified fourteen unique miRNAs associated with Alzheimer's disease. Among them, miR-3940-5p and miR-27b-3p stand out as particularly interesting given their previous associations with neurodegenerative disorders. Notably, presymptomatic AD subjects showed more pronounced alterations compared to clinical AD cases, suggesting a potential role in the early stages of disease progression. The functional enrichment analysis revealed an enrichment of miRNA-target genes linked to neurodegeneration, highlighting key genes such as *SNCA*, *CYCS*, and *MAPT*.
Conclusions: Our results highlight the potential role of neuronal-derived EVs in neurodegeneration and suggest that NDEV miRNAs may serve as valuable biomarkers for Alzheimer's disease, especially in the context of early diagnosis.

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Virtual OO - 096

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LIMITED PROTEOLYSIS–MASS SPECTROMETRY REVEALS AGING-ASSOCIATED CHANGES IN CEREBROSPINAL FLUID PROTEIN ABUNDANCES AND STRUCTURES

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Aims: Aging is a major contributing factor to neurodegenerative diseases such as Alzheimer's disease (AD). A better understanding of brain aging would aid in our understanding of these diseases. Many of the successful biomarkers and targets for aging-associated diseases such as AD are specific proteoforms and complexes of proteins. Although the structures of proteins are critically relevant, a high-throughput screen for changes in protein structures has never been performed in a mammalian system. We set out to use LiP–MS to screen for new aging-associated proteoforms and complexes in cerebrospinal fluid (CSF).
Methods: We performed limited proteolysis-mass spectrometry (LiP-MS) on cerebrospinal fluid (CSF) collected from young and aged mice, analyzing the data with a modified pipeline to maximize sensitivity and minimize false discoveries. We cross-referenced statistically significant changes with SOMAmer-based measurements of CSF proteins in human Alzheimer's patients and controls. We followed up on major hits with follow-up experiments including enzyme activity assays and non-reducing Western blots.
Results: We found 38 protein groups that change in abundance with aging, predominantly immunoglobulins of the IgM subclass. We discovered six high-confidence candidates that underwent structural changes with aging, of which Kng1, Itih2, Lp-PLA2 and 14-3-3 proteins have binding partners or chemical forms known previously to change in the brains of patients with Alzheimer's disease. Orthogonal validation by western blotting identified that the LiP–MS hit Cd5l forms a covalent complex with IgM in mouse and human CSF, the abundance of which increases with aging. In human CSF, SOMAmer probe signals for all six LiP–MS hits were associated with cognitive function and/or biomarkers of neurodegeneration, especially 14-3-3 proteins YWHAB and YWHAZ.
Conclusions: Our findings show that LiP–MS can uncover age-related structural changes in CSF with relevance to neurodegeneration.

Virtual OO - 097

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PROTEOMIC ANALYSIS OF EARLY-STAGE ALZHEIMER'S DISEASE: UNCOVERING CRITICAL NEURONAL PROTEINS INFLUENCED BY AMYLOID BETA OLIGOMERS IN AN IN VITRO MODEL.

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Aims: This study aims to investigate the impact of Aβo on neuronal cells, focusing on oxidative stress and apoptosis, and to identify differentially expressed proteins that may serve as biomarkers and therapeutic targets for early-stage AD.
Methods: SHSY-5Y cells were exposed to Aβo, followed by the assessment of intracellular reactive oxygen species and apoptosis levels. Comprehensive proteomic profiling was conducted using LC-MS/MS, leading to the identification of differentially expressed proteins. The NeuroPro database facilitated the identification of AD-related proteins.
Results: A total of 2,966 proteins were identified as differentially expressed, with 123 significantly modulated. Among these, 80 were confirmed as AD-related, alongside 43 novel candidates. Seven AD-related proteins with a NeuroPro score ≥ 5 were highlighted. Notably, proteins such as VGF, LTF, PARP1, and MAOA were associated with key AD mechanisms, while MYH9, CISD1, and SNRNP70 emerged as critical players in cytoskeletal dynamics, mitochondrial function, and RNA splicing.
Conclusions: This study elucidates the complex pathophysiology associated with Aβo-induced oxidative stress and neuronal damage in AD. The identification of potential biomarkers and therapeutic targets lays a foundation for future research aimed at early diagnosis and intervention strategies in Alzheimer's disease.

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LIPID PROFILING REVEALS DYSLIPIDEMIA SPECIFIC FOR WOMEN WITH ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is a devastating disease at an individual level and for the wider society. Despite extensive research the underlaying causes of AD are still not well understood.
Lipid metabolism is essential for brain health. Several key risk factors for AD, such as the presence of the APOE4 allele and biological sex influence lipid composition. This study aims to analyze the lipid variations linked to AD and its associated risk factors.
Methods: In this post-hoc study, data from the AddNeuroMed cohort were analyzed. This cohort consisted of 841 participants, 306 of whom
were diagnosed with AD, 165 had mild cognitive impairment (MCI) and 370 participants were considered cognitively healthy.
Mass spectrometry was used to measure 278 different lipid molecules from the participants' blood plasma. Lipid molecules were clustered
into modules based on correlation networks using weighted gene correlation network analysis (WGCNA) and investigated with regression analysis.
Results: We have identified AD-induced changes in the lipidome that are exclusive to the women in this cohort. This finding suggests that AD
manifests metabolically differently between sexes, which could help inform precision medicine approaches.
We found that lipids downregulated in women with AD tend to be omega fatty acid-containing phospholipids and triglycerides with a combined carbon number between 52-58.
Conclusions: Our findings reveal distinct AD-induced lipidome changes that are specific for women, indicating that Alzheimer's disease may exhibit separate metabolic profiles between sexes. This difference should be considered in future AD research.

Virtual OO - 099

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THE CONTRIBUTION OF LONG NONCODING RNAS TO THE DEVELOPMENT OF WORSE COGNITIVE FUNCTION OF ALZHEIMER'S DISEASE

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Aims: Growing evidence show that long noncoding RNAs (lncRNAs) play a critical role in the progression of Alzheimer's disease (AD). Despite their various roles in AD (e.g., modulating amyloid production, tau hyperphosphorylation, and neuroinflammation), their contribution to the development of worse cognitive function remains under-studies. We sought to investigate the molecular contribution of lncRNAs in promoting worse cognitive function (WCF) of AD through the integration of multiple modalities of omics data.
Methods: To identify AD WCF profiles and associated lncRNAs, we leveraged machine learning approaches to integrate multiple modalities of *omics* data from multiple brain regions and AD cohorts, including the *parietal cortex* from Knight ADRC, the *dorsolateral prefrontal cortex* from ROSMAP cohort, and the *parahippocampal gyrus* from MSBB study. To determine the regulatory mechanisms of lncRNAs, we performed co-expression, gene network, and protein-protein interaction analyses.
Results: We identified and replicated a distinct molecular profile of AD associated with WCF. We identified 177 Worse Cognitive Function Associated LncRNAs (WCFALs) commonly dysregulated in this profile. We prioritized WCFAL1 (the most up-regulated lncRNA in the discovery cohort) due its strongest association with WCF profile and its interaction with AD-related genes. Subsequent GSEA analyses showed that WCFAL1 is enriched in transcriptional regulatory pathways. Co-expression and network analyses revealed that WCFAL1 has a strong positive correlation with FOXN3. Protein-protein interaction exhibited that FOXN3 strongly interacts with SIN3A (a protein known to regulate Amyloid-beta (Aβ)).
Conclusions: Multi-omics integration identified lncRNAs associated with WCF of AD. We hypothesize that WCFAL1 may be required for FOXN3 interaction with the SIN3A for SIN3A to regulate Aβ. To test this hypothesis, future work will require in vitro and in vivo experiments to verify the expression of FOXN3 and SIN3A by overexpressing/knocking down WCFAL1.

Virtual OO - 100

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MULTIOMIC PROFILING OF IPSC DERIVED ASTROCYTES REVEAL ANCESTRY-SPECIFIC REGULATION OF APOE AND OTHER AD RISK GENES

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Aims: This study aims to elucidate the impact of ancestry on the genomic regulatory architecture (GRA) related to late-onset Alzheimer's disease (AD) risk genes. It focuses on identifying ancestry-specific differences in GRA by examining induced pluripotent cell (iPSC) derived neural spheroids from African (AF), Amerindian (AI), and European (EU) backgrounds, particularly within the astrocytic population.
Methods: iPSCs were generated from individuals with AD and those without cognitive impairment, each with over 85% global ancestry from one of the specified backgrounds. These iPSCs were differentiated into neural spheroids for 76 days. Multiomic profiling was then conducted, including Single Cell ATAC-seq for chromatin accessibility, RNA-seq for transcriptome analysis, and Hi-C analyses for chromatin interactions.
Results: We identified 60 AD GWAS genes with differential expression across ancestries, including key genes *like APOE, ABCA1, CLU, SORL1*, and *IGFR1*. It was found that AF astrocytes with *APOE 3/3* genotype expressed more APOE than their EU counterparts. Conversely, EU astrocytes with *APOE 4/4* showed higher APOE expression than both EU and AI astrocytes. Additionally, AD patient-derived lines expressed more *APOE* compared to non-demented controls.
Conclusions: The findings highlight significant ancestry-specific differences in the expression of AD risk genes and underscore the importance of considering ancestry in the study of AD's genomic regulatory architecture. The differential expression of *APOE* across ancestries and disease statuses suggests that genetic risk variants and ancestry have a complex relationship that influences the pathogenesis of late-onset AD. This research provides critical insights into the interplay between genetics, ancestry, and AD, which could inform more personalized approaches to its diagnosis and treatment.

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AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE INCEPTION AND PROGRESSION IN MARMOSETS CARRYING PSEN1 RISK MUTATIONS.

Stacey Sukoff Rizzo[1,2], Lauren Bailey[3], Jung Eun Park[1], Gregg Homanics[4], Nicholas T. Seyfried[5], Catrina Spruce[6], Annat Haber[6], David Schaeffer[1], Lauren Schaeffer[1], Gregory Carter[6], Afonso Silva[1]
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Aims: Studies as early in life as possible in those with genetic risk for Alzheimer's disease (AD) are critical for identifying mechanisms that trigger the emergence of AD that precede the cascade of known molecular events to identify targets for treatment and prevention. Here, we present a study of genetically engineered marmosets carrying PSEN1 point mutations that cause autosomal-dominant AD in humans.
Methods: Viable founders carrying the PSEN1-C410Y point mutation were generated using CRISPR/Cas9 and gave birth to germline F1 offspring via natural mating to wild-type partners (Homanics et al., 2024). The F1 carriers are evaluated longitudinally using noninvasive measures, including neuroimaging (PET/MRI), fluid-based biomarkers, and comprehensive cognitive and behavioral assessments, and compared to age- and sex-matched non-carriers. As a surrogate for the brain, fibroblasts are generated annually from skin biopsies and derived directly to neurons to evaluate transcriptomic and proteomic signatures with aging and disease onset.
Results: PSEN1-C410Y carriers present increases in plasma AB42 and AB42:40 relative to age- and sex-matched non-carriers by 12-months (~8-year-aged humans). Baseline cognitive assessments in adolescent mutation carriers, including spatial working memory, reversal learning, and recognition memory, were not impaired versus non-carriers, consistent with reports of human PSEN1 carriers before diagnosis. The oldest PSEN1-C410Y are 2-years old and actively breeding to produce the next generation. Longitudinal analyses of changes in biomarkers, multi-omics, behavior, and cognition are ongoing throughout the lifespan (~12 years).
Conclusions: The comprehensive study of these marmosets longitudinally from birth will provide fundamental knowledge towards our understanding of the biological processes that precede the known cascade of events and enable the discovery of mechanisms that underlie AD inception and pathogenesis.

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MODELING LATE-ONSET ALZHEIMER'S DISEASE NEUROPATHOLOGY VIA DIRECT NEURONAL REPROGRAMMING

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Aims: Establishing a patient-derived neuronal model that endogenously recapitulates key AD neuropathological features (Aβ deposition, tauopathy, and neurodegeneration) for studying disease mechanisms and identifying therapeutic targets.
Methods: By optimizing the potency of microRNA-mediated direct neuronal conversion of patient fibroblasts, we developed a matrigel-based three-dimensional (3D) culture system for generating cortical neurons with retained age signatures.
Results: We found that 3D ADAD neurons exhibited extracellular accumulation of Ab, formation of seed-competent and insoluble tau, bulged dystrophic neurites, and neurodegeneration. Importantly, applying this 3D neuronal reprogramming to fibroblasts from individuals with LOAD effectively manifested hallmark AD neuropathological features. Interestingly, inhibiting APP processing during the early phase of neuronal reprogramming, but not the late phase when pathology is already present, reduced the accumulation of Ab deposits, pathogenic tau, and neurodegeneration. Additionally, LOAD neurons exhibited gene expression changes enriched with gene networks related to neuroinflammation compared to age-matched controls. Interestingly, both aged healthy control (age 66-90) and LOAD (age 66-90) neurons manifested changes in retrotransposon elements (RTE) expression compared to young healthy control neurons (age 36-61). Disrupting age-associated RTE dysregulation in LOAD neurons by lamivudine led to the reduction of Ab, tau aggregation, neuronal death, and DNA damage, correlated with expression changes of genes associated with inflammation.
Conclusions: The findings demonstrate the feasibility and sufficiency of miRNA-induced directly converted LOAD neurons for modeling late-onset neuropathology of AD in a 3D environment. These neurons provide a platform to understand how aging influences vulnerability to late-onset neurodegeneration in LOAD patients.

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TDP-43 POTENTIATES INCREASED TAU BURDEN AND PATHOLOGICAL PROTEIN SPREAD IN THE MAMMALIAN BRAIN

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Aims: Alzheimer's disease (AD) is the leading cause of dementia and a devastating neurodegenerative disease of aging. More than 50% of AD patients have been described as having aberrant accumulation of TDP-43 protein. TDP-43 proteinopathy in AD can co-occur in neurons with one of the main hallmarks of the disease, neurofibrillary tangles containing hyperphosphorylated Tau, and the presence of TDP-43 pathology correlates with rapid progression and worse prognosis. However, the underlying mechanisms of pathogenic TDP-43 contributing to AD and its possible involvement as a trigger of neurotoxicity remain unclear. To address this, we explored the role of TDP-43 protein in a mouse model of tau-mediated toxicity.
Methods: We created a new mouse model of tau and TDP-43 co-pathology that combines constitutive transgenic expression of wild-type human tau with adeno-associated virus (AAV) driven expression of wild-type human TDP-43. We performed a unilateral intrahippocampal injection of AAV-9 carrying the human TDP-43 cDNA into 3-month-old transgenic mice expressing human 1N4R Tau in neurons. Animals were then perfused 2, 4, and 12 weeks after injection, and brains were collected for immunohistochemistry.
Results: We found that the presence of hTDP-43 promoted increased phosphorylated tau and TDP-43 species within the hippocampus. These data suggest a possible interaction between human tau protein and TDP-43 proteins leading to the increase and spread of pathological protein species. Additionally, the co-expression of both TDP-43 and Tau proteins induced a transient inflammatory state in transgenic animals. However, 12 weeks after injury, inflammation was resolved, and the presence of phosphorylated Tau species was significantly reduced.
Conclusions: This new mouse model provides a vehicle to explore causes and consequences of co-pathological tau and TDP-43.

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EARLY ONSET OF TAU PATHOLOGY IN THE OLFACTORY SYSTEM OF PS19 MICE: A PATHWAY FOR THE PROGRESSION OF TAUOPATHY IN THE CENTRAL NERVOUS SYSTEM

Marion Dourte, Pascal Kienlen-Campard, Mongia Bouchoucha
AGAD, UCLouvain (IONS), Woluwe-Saint-Lambert, Belgium

Aims: Clinical data strongly support olfactory impairment as an early indicator of neurodegenerative diseases (ND), including Alzheimer's disease. In AD patients, neurofibrillary tangles (NFTs) have been identified in the entorhinal cortex and olfactory bulbs, both crucial in olfactory information processing. We therefore investigated the hypothesis that typical ND lesions could appear early in olfactory system regions and wether tau pathology in the CNS could be modulated by intranasal administration of targeted treatments.
Methods: We used a tauopathy mouse model (PS19 mice) expressing the human tau protein (1N4R) carrying the P301S mutation. PS19 mice develop NFTs-like inclusions at six months, leading to progressive neurodegeneration at eight months. Immunohistochemistry and western blots were performed on brain samples to evidence the expression of hyperphosphorylated human tau protein (pTau). Specific olfactory regions such as the olfactory epithelium (OE) and bulbs (OB) were investigated to correlate tau profiles with data obtained in CNS regions.
Results: Detection of pathological pTau (Ser202, Thr205) was observed in PS19 mice. In the OE, pTau was detected in the olfactory neurons within the middle stratum as early as 3 months. In the OB, pTau was expressed in the olfactory nerve layer. Tau lesions were found in the piriform and entorhinal cortex from 6 months, along with the CA3 region and dentate gyrus in the hippocampus. Finally, OE disruption following $ZnSO_4$ intranasal administration resulted in a reduction of NFTs in the cortex at 6 months.
Conclusions: We hypothesize that pTau may appear early in the OE and subsequently spread to the CNS following neuroanatomical pathways, like the olfactory or perforant pathways. These findings highlight: the prognostic potential of the OE region in the tauopathy diagnosis and its likely contribution to the pathology progression in the CNS.

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UNTANGLING THE ROLE OF LIPID DROPLETS IN TAUOPATHY

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Aims: Current therapies aimed at directly reducing or blocking tau burdens have not demonstrated clinical success for tauopathies. Emerging data from GWAS, transcriptomics, and interatomic analyses, indicates that disrupted lipid balance and inflammation may be early cellular events that contribute to disease progression. However, the mechanisms leading to eventual neurodegeneration are still unclear. Aims 1) Longitudinal assessment of lipid droplets (LD) in neuronal models of FTD-tau; 2) Determine the link between LD and tau-mediated neurodegeneration *in vitro* and *in vivo*.
Methods: SH-SY5Y cells stably expressing tau-GFP variants (WT, P301L/S, V337M, K369I, R406W) and iPSC-derived cortical neurons carrying the aforementioned *MAPT* mutations were used. pTau and inflammation were evaluated through western blotting and qPCR. To investigate LD biology and neuropathology, we employed immunofluorescence and immunohistochemistry in our neuronal models and in transgenic mice expressing human K369I tau (K3).
Results: *In vitro*, pTau markers (i.e. S262 and PHF-13) were linked to a reduction in the number and size of LDs. This reduction triggered IFN-I signaling (indicated by pTBK1 and pSTAT1). Additionally, this process was due to accumulation of polyunsaturated fatty acids (PUFAs) through STING, leading to dysfunction in respiratory complex I and NAD^+ production in diseased neurons. Our *in vivo* studies further showed that LDs initially appear in healthy neurons but shift to glial cells as the disease progresses. STING inhibition ameliorated neuronal LD formation, neuronal loss and gliosis in the brain, lowered CSF NfL levels, and improved cognitive function in K3 mice.
Conclusions: Changes in LDs may indicate status of metabolic processes and therefore cellular health. This study explores how STING interplays with LDs in neurons impacted by tau pathology. This could reshape our understanding of tau-mediated neurodegeneration and advance preclinical development of STING inhibitors for treating tauopathies.

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UBIQUITINATION IMPAIRMENT AS A BIOMARKER AND CAUSATIVE AGENT OF TAUOPATHIES

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Aims: Tauopathies are defined as neurodegenerative disorders, characterized by abnormal tau accumulation. Their development is a multistep process probably driven by changes in post-translational modifications (PTMs). In addition to providing a better understanding of the pathophysiology of tauopathies, PTMs are a useful tool for identifying biomarkers. According to the literature and recent results from the lab, ubiquitination appears as the most promising PTM to discriminate between tauopathies and target the tau aggregation process. Our project aims at evaluating the predictive value of ubiquitination dysregulation in the tauopathies, as a tool for diagnosis and a mechanism of tau accumulation.
Methods: To achieve our goal, we studied both soluble and insoluble brain fractions from human with tauopathies (AD, PiD, FTLD, CBD) and controls, as well as PS19 (Tau P301S) mice. Tandem mass spectrometry and western blotting were used to study ubiquitination impairment. The post-analysis was performed using Proteome Discoverer and R.
Results: We found protein ubiquitination to be imbalanced in the brain samples with tauopathies. The imbalance provides ubiquitin hallmarks associated to specific tauopathies recapitulated in mice samples. Tau ubiquitination profile was investigated in these fractions, as well as the different polyubiquitin linkages, also found altered by the pathology.
Conclusions: Our study indicates that ubiquitination is dysregulated in tauopathies, in which ubiquitinated tau accumulates. This could arise either from impairment of tau clearance in autophagy/lysosomal compartments, or as a consequence of altered proteasome function, well-described in AD. The dysregulation of ubiquitination underscores the potentially significant role of this post-translational modification in the development of these pathologies.

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RAGE AGAINST THE TAU MACHINE: FIBRILLAR TAU-MEDIATES ENDOTHELIAL AND BARRIER DYSFUNCTION

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Aims: Aims: Aggregated tau can spread from neurons or astrocytes throughout the brain, ultimately reaching the vasculature, possibly leading to cerebrovascular and neurovascular unit dysfunction. Currently, the mechanisms responsible for the effects of tau on endothelial cells (ECs) lining the vessel walls remain understudied. We are aiming to understand whether and how protofibrillar tau mediates pro-inflammatory EC activation and bioenergetic alterations, culminating in loss of barrier function.
Methods: Methods: Immortalized human brain microvascular ECs (D3) were challenged with nM concentrations of protofibrillar 1N4R tau and/or co-treated with FPS-ZM1, an antagonist of the receptor for advanced glycation end-products (RAGE). Trans-endothelial electrical resistance (TEER) was measured by the ECIS Zθ system as an *in-vitro* model of the BBB. Cytokine production was assessed using an MSD V-Plex Neuroinflammatory Panel 1. Western blotting for VCAM-1, RAGE, and tau was performed. EC bioenergetics were measured by Seahorse Extracellular Flux Analyzer. Three months-old male and female P301S mice underwent vessel imaging and extraction for molecular analysis.
Results: Results: Reduced TEER was observed after protofibrillar tau challenge, independently of EC death. Aggregated tau caused an increase in glycolysis, which correlated with a proinflammatory EC phenotype. RAGE inhibition decreased entry of aggregated tau into ECs, reverting the pro-inflammatory phenotype *in vitro*. Increased expression of vascular inflammation markers, altered vascular bioenergetics, and loss of junction proteins was confirmed in P301S tauopathy mice compared to WT.
Conclusions: Conclusions: Our results suggest that fibrillar tau species trigger pro-inflammatory EC activation, coupled with metabolic alterations both *in-vitro* and *in-vivo*. These molecular changes, mediated by RAGE-dependent tau entry, can contribute to loss of barrier integrity, exacerbating cerebrovascular dysfunction, and are mitigated by a RAGE inhibitor

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UNDERSTANDING THE MECHANISM BY WHICH THE KETONE BODY B-HYDROXYBUTYRATE COUNTERACTS TAU PATHOGENESIS

Leigh-Ana Rossitto[1], Jamie Foo[1], Melina Brunelli[2], Daniel Muñoz-Mayorga[1], Leanne Lehmann[1], Yuhang Nie[1], Samuel Myers[2], Xu Chen[1]
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Aims: In Alzheimer's disease (AD) and related tauopathies, a notable shift from glucose to lipid metabolism occurs in the brain, sparking a growing interest in metabolism-based therapies including the ketogenic diet (KD)—a high-fat, low-carb diet inducing a state of ketosis. KD has shown promising but mixed results in recent clinical studies, calling for a better understanding of the molecular mechanism and the development of ketomimetic therapies. We aim to elucidate the effects of β-hydroxybutyrate (BHB)—the main ketone body produced during ketosis—in tauopathy, and to dissect the underlying mechanism.
Methods: We performed dietary supplementation of BHB or BHB precursor to tau-transgenic mouse and fly models, and assessed the effect on tauopathy phenotypes, using biochemistry, immunohistochemistry and behavorial assays. To disentangle the bioactive components of BHB, we used pharmacological and genetic approaches to determine the contribution of BHB's bioenergetic acitivity (i.e. as a fuel) and signaling activity. Lastly, we performed a mass spectrometry-based interactomic study to compare changes of tau interacting protein network in iPSC-derived neurons upon BHB treatment.
Results: We found that BHB supplementation reduced toxic tau accumulation and spreading, ameliorated neuropathology and neuroinflammation, and improved behavioral function in vivo. Interestingly, the protective effects of BHB were preserved when BHB metabolism was blocked, suggesting that the bioenergetic properties of BHB are dispensable. The effects of BHB on tau interactomics implicates the involvement of neuronal pathways including endolysome trafficking, vesicle release, and RNA binding. In neuronal cultures, tau proteostasis was improved by BHB, again mediated primarily by BHB's signaling activity.
Conclusions: Our results provide evidence that dietary BHB supplementation is sufficient to ameliorate tauopathy phenotypes in animal models. Mechanistically, BHB ameliorate tau pathogenesis primarily through its signaling activity to modulate neuronal proteostasis pathways.

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Virtual OO - 109

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HUMAN NUCLEUS INCERTUS PROJECTS TO THE HIPPOCAMPUS AND DISPLAYS PHOSPHORYLATED-TAU ACCUMULATION IN EARLY BRAAK STAGES

Camila De Avila Dal'Bo[1], Jennifer Nolz[1], Divyanshi Khatri[1], Anthony Intorcia[2], Shoshenna Chee[1], Addison Krupp[2], Sidra Aslam[2], Jessica Walker[2], Sanaria Qiji[2], Zerrin Uzum[3], Geidy Serrano[2], Andrew Gundlach[4], Thomas Beach[2], Diego Mastroeni[1]
[1]Arizona State University, Asu-banner Neurodegenerative Disease Research Center, Tempe, United States of America, [2]Banner Sun Health Research Institute, Sun City, United States of America, [3]Arizona State University, Regenerative Medicine Core, Tempe, United States of America, [4]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia

Aims: The brainstem is a critical region involved in autonomic and complex functions that are affected during early stages of Alzheimer's disease (AD). It contains the nucleus incertus (NI), which prevents contextual memory formation through direct inhibition of the hippocampus in mice. Recently, we characterized the human NI using the peptide, relaxin-3 (RLN3), as a neurochemical marker. Furthermore, we detected neurofibrillary tangles in NI neurons of AD patients. In this study, we investigated levels of phosphorylated-tau (p-tau) and RLN3 across Braak stages in human postmortem tissue; NI projections into the hippocampus (HIP) and cingulate cortex (CC); and the transcriptomic profile of NI RLN3-positive neurons.
Methods: Histochemical staining of human postmortem pons was conducted to reveal immunoreactivity (IR) for phosphorylated-tau (AT8 antibody) and RLN3. Groups: Non-demented (ND) Low-Braak; ND High-Braak; and AD High-Braak; N=6/group. We also conducted chromogenic in situ hybridization (RNAscope) in ND controls for the RLN3 receptor, RXFP3, in human HIP and CC, N=6. We also used laser-capture microdissection to analyze the transcriptomics of RLN3-positive neurons in AD and ND controls, N=6/group.
Results: Progressive and significant p-tau accumulation across Braak stages was detected in the NI, with no difference in RLN3-IR across groups. RLN3-IR was detected in layers of the HIP and in the CC, colocalizing with RXFP3 mRNA. Finally, genes involved in inflammation and cognitive decline (e.g., GNG4), and in microtubule function (e.g., CCDC17) were upregulated in the NI of AD patients.
Conclusions: Accumulation of p-tau in the human NI begins in Braak stages I-II, before memory decline. NI/RLN3 pathways project to the HIP and CC, key areas involved in cognition. The upregulation of GNG4 and CCDC17 in NI RLN3-positive neurons of AD patients suggests their potential involvement in p-tau dysregulation.

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APOE E4 AND AB MEDIATES TAU-RELATED FUNCTIONAL DISCONNECTION

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Aims: Altered functional connectivity has been reported in Alzheimer's disease (AD) which is linked to the accumulation of pathological proteins in the brain, such as amyloid-beta (Aβ) plaques and neurofibrillary tau tangles. It is believed that the tau aggregates are the main driver of functional disconnection and resulted in cognitive decline in AD. Tau propagates through connected neurons, a phenomenon often described as the "prion-like" properties of tau which can locally result in functional connectivity disruption. Apolipoprotein E (APOE) ε4 allele status and Aβ are tau-related pathological changes in AD. However, the potential role of APOE ε4 and Aβ in mediating the tau-related functional disconnection is not clear. I aimed to investigate the mediating effect of APOE ε4 and Aβ on the local influence of tau spreading on functional connections that acted as conduits.
Methods: I analyzed follow-up resting-state fMRI (non-baseline visit) and longitudinal tau-PET data from 211 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and 138 healthy elderly individuals from the Harvard Aging Brain Study (HABS).
Results: The analysis revealed that regions with stronger connectivity (shorter distance-based connectivity) to the baseline-defined tau epicenters showed higher rates of tau aggregate accumulation. Moreover, the association between functional connectivity to epicenters and tau spreading through functional connections was mediated by APOE ε4 and Aβ status in both ADNI and HABS participants.
Conclusions: Tau aggregates spread through functional connections and locally disrupt connectivity d between tau epicenter and non-epicenter regions which is mediated in APOE ε4 carriers and Aβ-positive participants. These findings have implications for trial designs proposing that APOE ε4 carriers and Aβ-positive participants might need earlier intervention to attenuate tau spreading and tau relative functional disconnection.

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CELL-TYPE SPECIFIC AGEING-RELATED PROTEOSTASIS LOSS DRIVES VULNERABILITY TO TAU ACCUMULATION

Mathieu Bourdenx
University College London, Uk Dementia Research Institute, London, United Kingdom

Aims: Ageing is the major risk factor for neurodegenerative diseases, especially Alzheimer's disease. We and others have proposed that the selective neuronal vulnerability observed in most neurodegenerative diseases is, at least in part, a consequence of aged neurons being close to catastrophic cliffs, depending on their function, location, history of stress exposure, and genetic predisposition. Such susceptibilities may explain why pathogenic aggregates, such as tau tangles, preferentially accumulate in certain types of neurons in each disease. Whilst ageing itself is multifactorial, ubiquitous and affects all organs and cells in the body, it is now increasingly evident that ageing is highly heterogeneous and even cell-type specific. Here, we aim to reveal how aging differentially affects cell populations and whether aging predisposes specific neurons to accumulation of tau pathology.
Methods: We have developed a method that combine fine cell typing, using spatial transcriptomic with coppaFISH (combinatorial padlock-probe-amplified fluorescence in situ hybridisation) or MERFISH, and phenotyping using multiplexed imaging.
Results: We identified neuronal populations with higher susceptibility to proteostasis defects, largely overlapping with the ones known to display tau pathology in early stages of the disease. Investigations using single-nuclei RNA sequencing identified an ageing-dependent cell-type specific transcriptional program in those vulnerable cells that differs from resilient cells.
Conclusions: By performing a targeted approach to compare vulnerable and resilient cell-types, we identified novel pathways of cellular resilience and vulnerability to ageing-related loss of proteostasis and neuropathology. Current investigations are aiming at harnessing resilience response to protect vulnerable cells.

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UNVEILING THE CAUSAL RELATIONSHIP BETWEEN CELLULAR SENESCENCE AND ALZHEIMER'S DISEASE

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Aims: With the rapid growth of the aging population, the prevalence of age-related neurodegenerative diseases such as Alzheimer's disease (AD) is rising at an alarming rate. However, the exact mechanisms through which aging becomes pathogenic and triggers neurodegeneration remain unidentified. Recent studies suggest that telomere attrition, a key driver of cellular senescence and pathological aging, may contribute to brain dysfunction and neurodegeneration with advancing age. The complexity of AD pathophysiology, the lack of an effective therapeutic strategy, and the limited evidence linking senescence and AD highlight the pressing need for further research in this field. We recently reported that telomere-induced senescence enhances intraneuronal Aβ accumulation. In this project, we aimed to unravel the relationship between brain senescence and the onset and progression of AD-related tau pathology.
Methods: We crossed a mouse model of telomere shortening and accelerated senescence ($Terc^{-/-}$) with the tauopathy mouse model Tau P301S (PS19). Utilizing brain sections and brain protein extracts, we employed biochemical and molecular biology techniques to investigate the expression of tau-related neuropathological features within a senescent context.
Results: Brain tissue from $Terc^{-/-}$ mice displayed chronic cellular senescence, marked by increased secretion of pro-inflammatory molecules, among other features. We observed that telomere-induced senescence exacerbates tau phosphorylation at specific residues in the hippocampal region. Additionally, this senescence context amplifies an inflammatory phenotype associated with astrocyte activation in tau pathology, which correlates with neuronal loss.
Conclusions: Our results indicate that telomere-induced senescence may act as an upstream regulator of tau pathology, aggravating it and driving tau-related neurodegeneration. Further elucidation of this process could reveal potential therapeutic targets for AD treatment.

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DURATION OF ICE HOCKEY PLAY AND CHRONIC TRAUMATIC ENCEPHALOPATHY

Jesse Mez[1], Bobak Abdolmohammadi[1], Fatima Tuz-Zahra[1], Madeline Uretsky[1], Raymond Nicks[1], Sydney Mosaheb[1], Jacob Labonte[1], Eukyung Yhang[1], Shruti Durape[1], Brett Martin[1], Joseph Palmisano[1], Christopher Nowinski[1], Jonathan Cherry[1], Victor Alvarez[1], Bertrand Huber[1], Kristen Dams-O'Connor[2], John Crary[2], Brigid Dwyer[1], Daniel Daneshvar[3], Lee Goldstein[1], Rhoda Au[1], Douglas Katz[1], Neil Kowall[1], Robert Cantu[1], Robert Stern[1], Michael Alosco[1], Thor Stein[1], Yorghos Tripodis[1], Ann Mckee[1]
[1]Boston University, Boston, United States of America, [2]Mount Sinai, New York, United States of America, [3]Spaulding Hospital, Boston, United States of America

Aims: Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy associated with repetitive head impacts (RHI). Prior research suggests a dose-response relationship between duration of American football play and CTE risk and severity, but this relationship has not been studied for ice hockey. We investigated relationships between duration of ice hockey play and presence and severity of CTE pathology.
Methods: This study included male former amateur and professional athletes whose primary sport was ice hockey whose brains were donated to the Understanding Neurological Injury and Traumatic Encephalopathy and Framingham Heart Study Brain Banks. We estimated the association of years of hockey played with CTE pathological status and cumulative phosphorylated tau (ptau) burden across 11 brain regions commonly affected in CTE. Simulation analyses quantified conditions that might lead to selection bias.
Results: A total of 42 of 77 donors (55%, median age:51; IQR:33-73) had CTE, including 27 of 28 (96%) professional players. Five of 26 (19%) donors who played <13 years of hockey, 14 of 27 (52%) who played 13-23 years and 23 of 24 (96%) who played >23 years had CTE. Increased years played was significantly associated with increased odds for CTE (odds ratio [OR]:1.35 per year; 95% confidence interval [CI]:1.17-1.56; p<0.001) and with increased ptau burden (standardized unit increase:0.036 per year; 95%CI:0.017-0.056; p<0.001) after adjusting for age at death and other contact sports played. Simulation demonstrated that years played remained associated with CTE when years played and CTE were both related to brain bank selection across widely ranging scenarios.
Conclusions: A dose-response relationship was observed between hockey years played and risk and severity of CTE. After accounting for brain bank selection, the magnitude of these relationships remained consistent.

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OGA INHIBITION AS A POTENTIAL THERAPEUTIC APPROACH FOR TAUOPATHIES: THE PROSPER STUDY, A PHASE 2 TRIAL IN PSP

Günter Höglinger[1], Lawrence Golbe[2], Adam Boxer[3], Yaroslau Compta Hirnyj[4], Huw Morris[5], Tania Nadal[6], Anna Colomé[6], Marta Nicolás[6], Lubia Álvarez[6], Begoña Fernández[7], Olalla Ramírez-Penas[8], Carla Varona[8], Carlos Sastré[8]
[1]Ludwig-Maximilians-Universität, Department Of Neurology, Munich, Germany, [2]Rutgers University, New Brunswick, NJ, USA and CurePSP, New York, NY, USA, New Jersey, United States of America, [3]University of California San Francisco, Department Of Neurology, San Francisco, United States of America, [4]Hospital Clinic de Barcelona, Barcelona, Spain, [5]UCL Queen Square Institute of Neurology, London, United Kingdom, [6]Clinical Development Department at Ferrer, barcelona, Spain, [7]R&D Portfolio Department at Ferrer, Barcelona, Spain, [8]Medical Affaris Department at Ferrer, Barcelona, Spain

Aims: To describe the FNP-223 development program and therapeutic potential of OGA inhibition as a treatment for progressive supranuclear palsy (PSP).
Methods: PSP is a primary tauopathy characterized by the accumulation of misfolded and aggregated tau protein. Tau oligomerization into tangles is primarily associated with tau hyperphosphorylation, yet it is also influenced by additional post-translational modifications. O-GlcNAcylation is a dynamic modification that competes with phosphorylation on some of the same tau residues, with the O-GlcNAcase (OGA) mediating the removal of O-GlcNAc moieties from tau. OGA inhibition has been shown to elevate tau O-GlcNAcylation and to impede the pathological aggregation of tau. Studies using different OGA inhibitors have consistently shown a reduction in tau-related pathology in multiple tau models. Based on this preclinical data, FNP-223, an OGA inhibitor, has emerged as a potential disease-modifying agent for PSP. To evaluate the efficacy, safety, and pharmacokinetics of FNP-223, 220 patients diagnosed within the previous 3 years with possible or probable PSP-Richardson's syndrome will be enrolled in a Phase 2 randomized, double-blind, placebo-controlled trial, the PROSPER study. Participants will be randomly assigned in a 1:1 ratio to receive oral FNP-223 or placebo three times daily to assess the change in rate of progression of the total PSPRS score over 52 weeks. Secondary and exploratory objectives will be to evaluate effects on progression rates of functionality, cognition, quality-of-life, neurodegeneration fluid biomarkers, and brain volume.
Results: The study is currently recruiting patients across 46 sites in Europe and the U.S.
Conclusions: FNP-223 is a promising disease-modifying therapy for PSP that is being studied to assess safety, tolerability, and efficacy in slowing disease progression in patients with PSP: the Phase 2 PROSPER study.

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TARGETING TAU REDUCTION TO INHIBIT TAU PATHOLOGY PROPAGATION IN ALZHEIMER'S DISEASE MOUSE MODEL

Andreea Kosa, Lidia López Gutiérrez, Emilie Doeraene, Carolina Quintanilla Sanchez, Emmanuel Aydin, Kunie Ando, Hinde Lasri, Alain Wathelet-Depauw, Jean-Pierre Brion, Karelle Leroy
Universite Libre de Bruxelles, Alzheimer Disease And Other Tauopathies Research Group, Ulb Center For Diabetes Research (ucdr) And Ulb Neuroscience Institute (uni), Brussels, Belgium

Aims: There is an increasing interest in direct therapeutic strategies that target mRNA to induce their degradation leading to a reduction of expression of a specific protein. Up to date, there are a few siRNAs targeting the brain that are in clinical trials. siRNAs showed promising effects on the reduction of tau level *in vivo*. However, no study has analyzed the effects of siRNA on tau expression in a mouse model of tau pathology propagation. In this study we aimed to assess the effects of siRNA targeting tau in a mouse model of tau pathology propagation when the reduction of tau level started immediately at the induction of tau pathology, or when tau reduction started after some development of tau pathology.
Methods: We used a mouse model of tau pathology propagation intracerebrally injected with pathological tau from human Alzheimer's cases (AD tau). Mice were treated with siRNA tau or siRNA non-targeting concomitantly with or after the injection of AD tau. The spatial learning of mice was assessed by Barnes maze and tau pathology was analyzed by immunolabelling.
Results: When starting the reduction of tau level simultaneously with the induction of tau pathology we observed a better performance in solving the Barnes maze and a decrease in tau pathology formation. However, treatment with siRNA in mice already developing tau pathology performed at similar levels as mice treated with siRNA non-targeting in solving the Barnes maze.
Conclusions: Taken together, our data suggest that siRNA targeting tau administered concomitantly with the induction of tau pathology rescues spatial learning and reduces tau pathology, but if administered when tau lesions are already present in the brain it has no effect on spatial learning.

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SILENCING OF TAU KINASES BY SIRNA IN A PRECLINICAL MODEL OF ALZHEIMER'S DISEASE

Lidia López Gutiérrez, Kunie Ando, Andreea Kosa, Hinde Lasri, Emilie Doeraene, Alain Wathelet-Depauw, Jean-Pierre Brion, Karelle Leroy
Universite Libre de Bruxelles, Alzheimer Disease And Other Tauopathies Research Group, Ulb Center For Diabetes Research (ucdr) And Ulb Neuroscience Institute (uni), Brussels, Belgium

Aims: Our project focuses on the effect of glycogen synthase kinase 3β (GSK3β) and cyclin dependent kinase 5 (CDK5) silencing on tau pathology propagation and to evaluate the potential therapeutic effect of siRNAs targeting these 2 kinases in AD.
Methods: Stereotaxic injection of 0.5 nmol of siRNA were performed in the dentate gyrus of mouse hippocampus. After 3 days, GSK3β and CDK5 expression was evaluated by immunohistochemistry, western blot and real-time quantitative PCR. Htau mouse model (expressing 6 wild-type human tau isoforms) was used to evaluate the effect of kinases silencing on tau pathology propagation. Stereotaxic injection of 1 µg of PHF fraction in the dentate gyrus of mouse hippocampus induced tau pathology in that area that propagated into the Ammon's horn of the hippocampus and in the entorhinal cortex. 3 months after concomitant injection of PHF fraction and 0.5nmol of siRNA-GSK3β or siRNA non-targeting (NT), brains were analysed by immunohistochemistry. Behavioral tests are performed to evaluate cognitive impairments.
Results: Both GSK3β and CDK5 silencing resulted in a reduction higher than 50% of their expression. According to NeuN labeling, the treatment does not lead to neuronal death. Stereotaxic injection cause neuroinflammation, but this effect was independent of the treatment. Regarding tau pathology propagation, preliminary analysis has shown a tendency to less positive structures between Bregma -1.22 mm and -2.3 mm (surrounding injection point), in mice treated with siRNA targeting GSK3β compared to siRNA NT. No significant differences have been found in mice treated with siRNA targeting CDK5.
Conclusions: siRNAs targeting tau kinase efficiently decrease the levels of GSK3β by itself, and preliminary data points towards a potential modificator of tau pathology propagation in AD.

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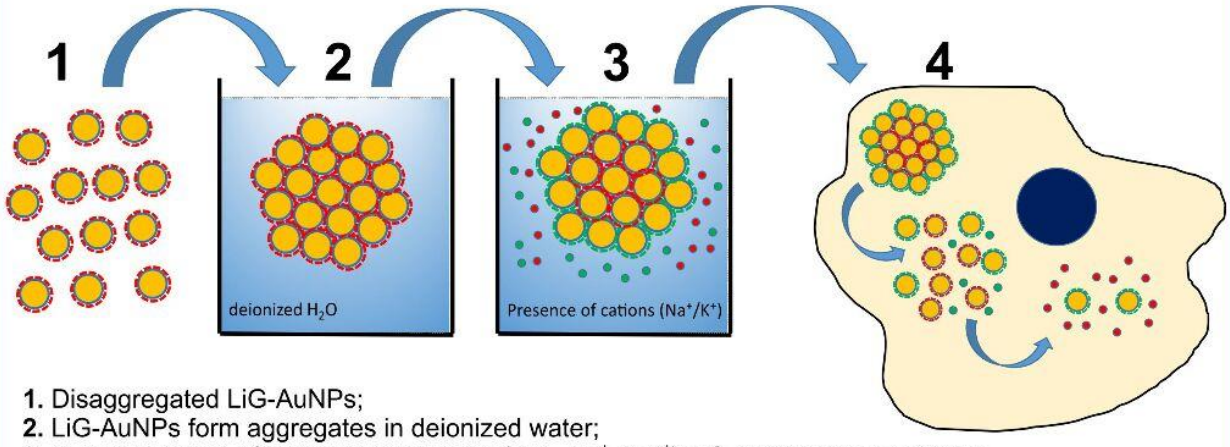
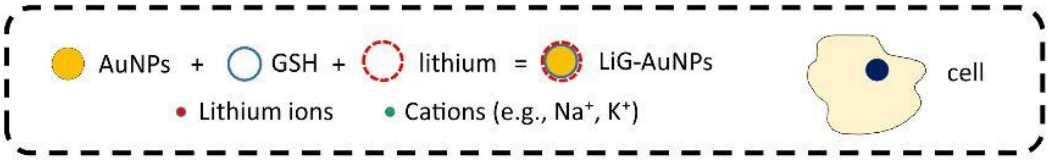
LITHIUM-CHARGED GOLD NANOPARTICLES: A NEW POWERFUL TOOL FOR LITHIUM DELIVERY AND MODULATION OF GLYCOGEN SYNTHASE KINASE 3 ACTIVITY

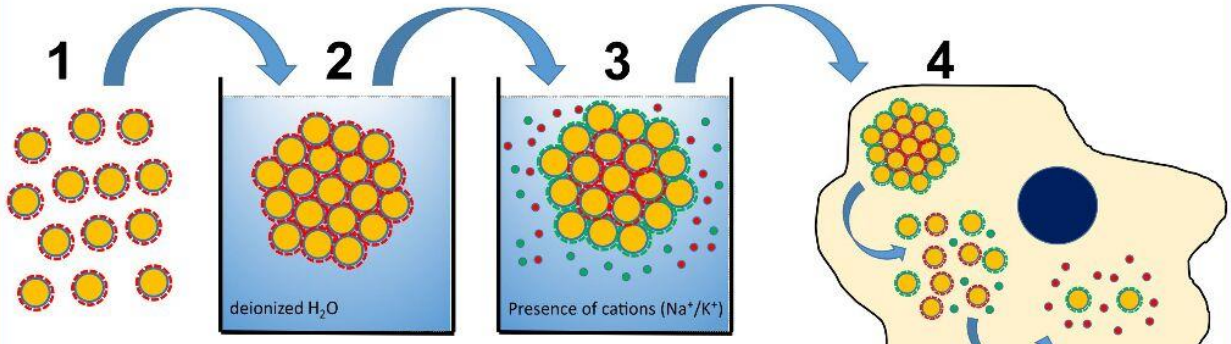
Giulia Puliatti[1], Antonio Buonerba[2], Beatrice Cannata[3], Domenica Li Puma[1], Laura Sposito[1], Irene Contento[2], Nicolina Castagno[2], Martina Albini[1], Silvia Baroni[3], Alfonso Grassi[2], Claudio Grassi[1], Roberto Piacentini[1]
[1]Università Cattolica del Sacro Cuore, Department Of Neuroscience, Rome, Italy, [2]University of Salerno, Department Of Chemistry And Biology, Fisciano, Italy, [3]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

Aims: The Glycogen Synthase Kinase 3β (GSK-3β) is a hub enzyme involved in various physiological processes. However, GSK-3β activation, triggered by dephosphorylation at Ser9, has also been associated with the development of several illnesses, including Alzheimer's diseases (AD), being the main kinase causing tau protein phosphorylation. The lithium cation (Li^+) is a potent GSK-3β inhibitor but its toxicity, particularly for kidneys and thyroid, severely limits its therapeutic use. We developed a novel tool based on gold nanoparticles functionalized with glutathione and Li^+ (LiG-AuNPs) capable of delivering lithium to the brain and modulating GSK-3β activity, bypassing the systemic administration.
Methods: Biochemical, spectroscopic, and molecular analyses were performed on *in-vitro* model (SH-SY5Y cells) and *ex-vivo* and *in-vivo* models from C57BL/6 mice.
Results: In water, LiG-AuNPs form aggregates permeating cell membranes and releasing Li^+ into the cytosol (figure).



1. Disaggregated LiG-AuNPs;
2. LiG-AuNPs form aggregates in deionized water;
3. In the presence of extracellular cations (e.g., Na^+ or K^+) LiG-AuNPs release lithium by ion exchange. The inner Li^+ ions are protected by aggregation and cannot be released
4. a-LiG-AuNPs rapidly enter cells, where they are disaggregated and nanoparticles efficiently release lithium into the cytosol by cation exchange.





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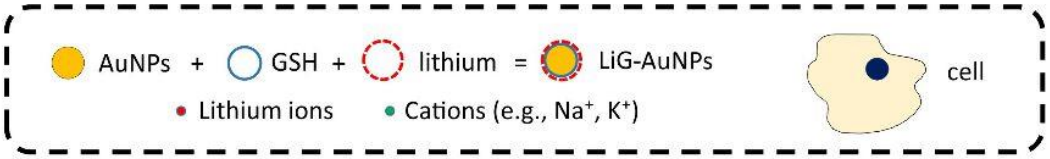

24-h application of LiCl (6 mEq_{Li+}/L) induced significant increases of pGSK-3β^{Ser9} (+145±29% vs. vehicle) in SH-SY5Y cells. Interestingly, LiG-AuNPs at half the concentration (3 mEq_{Li+}/L) induced similar increases (+123±26% vs. vehicle), accompanied by higher Li^+ levels in the cytosol (+26-fold vs. LiCl). At lower concentrations (0.15 mEq_{Li+}/L), LiG-AuNPs still modulated pGSK-3β, contrarily to LiCl. *In vivo*, LiG-AuNPs administered intranasally (3 µL/nostril of 300 mEq_{Li+}/L for 5 days, two times/month, up to 6 months) increased pGSK-3β^{Ser9} levels in the mouse hippocampi (up to 140% vs. vehicle) without significantly affecting plasma lithium levels or inducing gliosis. Noteworthy, LiG-AuNPs also reduced pTau^{Thr205} levels, a major substrate of GSK-3β, both *in vitro* and *in vivo*.

Conclusions: LiG-AuNPs: i) lower Li^+ concentrations requred to inhibit GSK-3β; ii) effectively deliver Li^+ to the brain; iii) inhibit GSK-3β *in situ* bypassing systemic administration and modulating its substrates. LiG-AuNPs could thus offer therapeutic benefits for AD treatment.

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UNVEILING THE INTERACTION BETWEEN TAU AND A-SYNUCLEIN AND CATHEPSIN D BY MD STIMULATION

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Aims: Cathepsin D is linked to neurodegenerative diseases due to its role in toxic protein accumulation, which causes neuronal damage. Under normal conditions, it degrades proteins during brain development and maintenance. Studies have explored its involvement in Alzheimer's disease, prion disease, Lewy body disease, multiple system atrophy, and tau-related conditions. However, the interaction between tau, a-synuclein, and cathepsin D is unclear due to their disease-specific folds. Therefore, this study aims to determine the interactions between cathepsin D and various folds of tau and a-syn.
Methods: The structure of various tau and a-synuclein folds were obtained from PDB bank and docked with cathepsin D, respectively. The most preferable docking structures were selected for further simulation using Zdock. Before molecular dynamic simulation, the docked structure was put in a 10Å water box with 0.15M NaCl to mimic a neutral environment. After system preparation, the whole system underwent energy minimization, heating, NPT, NVT, and equilibration to make sure the structure is stable for simulation, and 200ns simulation was performed using NAMD. RMSD and hydrogen bond occupancy were analyzed in the trajectory files to identify the important residues involved in the interaction.
Results: AD tau showed a higher conformational change during simulation with residues interacting within the catalytic pocket of cathepsin D, suggesting direct interaction. Regarding CBD tau and PSP tau, the interactions with cathepsin D were weaker and the conformational changes during simulation were smaller compared with AD tau. a-Synuclein folds also showed differences.
Conclusions: The result of this *in silico* study can interpret the potential interaction between tau, a-synuclein and cathepsin D under various diseases. Further research based on these results could expand the current pipeline of innovative treatments.

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EARLY INTERVENTION WITH AZP2006 DELAYS PROGRESSION IN PROGRESSIVE SUPRANUCLEAR PALSY: RESULTS FROM A PHASE 2A OPEN-LABEL EXTENSION

Philippe Verwaerde, Artin Karapet, Cécilia Estrella
Alzprotect, Loos, France

Aims: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder with no treatment options. The Phase 2a study of AZP2006, a novel therapeutic agent, aimed to assess its safety and efficacy. The open-label extension period sought to collect additional data on long-term safety and treatment effects. The primary objective of the Phase 2a study was to evaluate the safety and efficacy of AZP2006. The objective of the open-label extension was to gather further data on the long-term safety and treatment impact of AZP2006 in patients with PSP.
Methods: In the Phase 2a study, 15 patients with PSP (onset of symptoms ≤ 5 years) were treated with AZP2006 at a dosage of 60 mg once daily (qd) for 6 months. The open-label extension began approximately 2 years after the Phase 2a study concluded. The extension aimed to evaluate the long-term safety and efficacy of continued AZP2006 treatment. All extension patients received the active 60 mg qd AZP2006.
Results: Out of the 15 patients who entered the extension, 3 withdrew: 1 due to death unrelated to the study drug, and 2 due to disease progression and disability. Baseline PSP Rating Scale (PSPRS) scores and demographic characteristics were well balanced across patients at the start of the extension. Patients who had been previously treated with AZP2006 in Phase 2a maintained remarkable stability throughout the extension period; patients who had received placebo in Phase 2a initially showed a slight decline but demonstrated recovery and stability 3 months into the extension. No treatment related adverse events were observed in the extension.
Conclusions: Early intervention with AZP2006 in PSP patients is crucial for delaying disease progression. AZP2006 has demonstrated the ability to maintain stability and slow disease progression in PSP patients.

Virtual OO - 120

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LIVE CELL IMAGING OF A TAUOPATHY MODEL IDENTIFIES POLYPHARMACOLOGICAL COMPOUNDS ABLE TO INHIBIT TAU AGGREGATION AND RESTORE PHYSIOLOGICAL MICROTUBULE INTERACTION

Nicolò Bisi[1], Luca Pinzi[1], Christian Conze[2], Gabriele Dalla Torre[1], Ahmed Soliman[2], Nanci Monteiro-Abreu[2], Nataliya Trushina[2], Andrea Krusenbaum[2], Maryam Khodaei Dolouei[2], Andrea Hellwig[2], Michael Christodoulou[3], Daniele Passarella[3], Lidia Bakota[2], Giulio Rastelli[1], Roland Brandt[2]
[1]Università di Modena e Reggio Emilia, Department Of Life Sciences, Modena, Italy, [2]University of Osnabruck, Department Of Neurobiology, Osnabruck, Germany, [3]University of Milano, Department Of Chemistry, Milano, Italy

Aims: Dementia affects over 55 million people worldwide, with Alzheimer's Disease (AD) being the most represented form. These neurodegenerative diseases, called tauopathies, are characterized by aggregation and increased phosphorylation of the microtubule (MT)-associated protein tau, and up to now no drug is able to cure them. In pathological conditions, tau loses its physiological function, contributing to neurodegeneration. Our goal is to develop and apply methods able to identify polypharmacological drugs acting on tau aggregation and restoring the physiological tau/MT interaction.
Methods: We developed a multidisciplinary approach to monitor pathological changes of aggregation-prone human tau in living neurons and *in vitro*, as well as in patients-derived samples. This strategy served as a model to test potential drug candidates identified by drug design studies.
Results: We identified 2-phenyloxazole (PHOX) derivatives as polypharmacological small molecules able to interact with tau and to inhibit tau kinases. We found that the hit compound PHOX15 inhibits tau aggregation *in vitro*, *in cells* and *ex vivo*, it restores tau's physiological microtubule interaction, and reduces tau phosphorylation at pathology-associated sites.[1] Molecular dynamics simulations highlighted cryptic channel-like pockets crossing tau protofilaments and suggested that the binding of PHOX15 reduces the protofilament's ability to adopt a paired-helical filaments (PHF)-like conformation by modifying a key glycine triad.
Conclusions: Conclusions: Our data demonstrate that live-cell imaging of a tauopathy model enables screening of compounds able to modulate tau-microtubule interaction and allows identification of a promising polypharmacological drug that simultaneously inhibits tau aggregation and reduces tau phosphorylation. These results pave the way for a lead optimization of PHOX15, offering new possibilities to develop potential treatments for tauopathies. References: (1) Pinzi, L.; Conze, C.; Bisi, N. et al., *Nat Commun* **2024**, *15* (1), 1679.

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Virtual OO - 121

Virtual E-Posters and Oral On-Demand
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SUBJECT-LEVEL DETECTION OF CONVERGENT AND DIVERGENT NEURODEGENERATION PATTERNS USING SPATIOTEMPORAL CONNECTOMICS: TOWARDS ATROPHY CHARACTERIZATION IN PRECLINICAL ALZHEIMER'S DISEASE.

Cristina Sánchez Martín[1], Ibai Diez[2], Elisenda Bueichekú[3], Chan-Mi Kim[2], Michel J. Grothe[4], Pascual Sanchez-Juan[5], Jorge Sepulcre[3]
[1]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIIII, Neuroimaging, Madrid, Spain, [2]Gordon Center for Medical Imaging, Massachusetts General Hospital, Boston, United States of America, [3]Yale University, New Haven, United States of America, [4]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain, [5]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIIII, Madrid, Spain

Aims: Brain atrophy is a normal part of healthy aging, but it is aggravated by several neurodegenerative diseases. Previous studies have described heterogeneity in individual neurodegeneration patterns, but the network structure of these patterns at the individual level is not well understood. This study aimed to develop a novel spatiotemporal connectomic method based on graph theory applied to serial MRI measurements to describe subject-specific atrophy patterns in healthy aging at the single-subject level.
Methods: The study included 78 older cognitively normal participants from the Vallecas project, who underwent longitudinal T1 MRI scanning with 8 follow-up timepoints. Voxel-wise gray matter volumes were obtained, and a regression analysis was used to define the topology of atrophy of each subject. After that, gray matter values with 1% annual decrease were defined as accelerated atrophy measure. A graph theory approach based on the structural similarity of pairs of voxels with accelerated atrophy, considering, in turn, their similarity with the rest of the brain atrophy, was applied to identify general convergent or divergent behavior of accelerated atrophy.
Results: We identified different graph morphologies for each pair of voxels with accelerated atrophy, which could suggest a convergent or divergent behavior between them. Taking into account all the comparisons, we obtained individualized atrophy phenotypes with a predominantly convergent or divergent behavior of the structural changes In the brain of each subject.
Conclusions: We present a novel analytical tool for characterizing individualized atrophy phenotypes in healthy subjects based on graph theory and structural similarity analyses. This method may help to describe age-related neurodegeneration patterns at the individual level, which could be helpful for studying heterogeneity in neurodegeneration trajectories due to AD and other neurodegenerative diseases.

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Virtual OO - 122

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LONGITUDINAL CHANGES IN MEDIAL TEMPORAL LOBE TAU BURDEN OF INDIVIDUALS WITH AMYLOID-INDEPENDENT TAU UPTAKE ON POSITRON EMISSION TOMOGRAPHY

Tevy Chan[1], Joseph Therriault[1], Etienne Aumont[1], Yi-Ting Wang[1], Nesrine Rahmouni[1], Lydia Trudel[1], Arthur Macedo[1], Seyyed Ali Hosseini[1], Brandon Hall[1], Jaime Fernandez-Arias[1], Kely Quispialaya-Socualaya[1], Yansheng Zheng[1], Stijn Servaes[1], Gleb Bezgin[1], Serge Gauthier[2], Paolo Vitali[1], Tharick Pascoal[3], Pedro Rosa-Neto[1,2]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada, [3]University of Pittsburgh, Pittsburgh, United States of America

Aims: Primary age-related tauopathy (PART) describes neurofibrillary tangles in the absence of amyloid-β pathology. Amyloid-independent tau uptake on positron-emission tomography (PET), referred to as A-T+ PET status, might indicate underlying PART. This study aimed to assess longitudinal tau PET changes in the medial temporal lobe (MTL) of A-T+ individuals. Changes in MTL volumes and cognitive performance were also evaluated.
Methods: Longitudinal data from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort participants with at least 1 follow-up amyloid-β PET ([^{18}F]AZD4694) and tau PET ([^{18}F]MK6240) were included. MTL structures were segmented using the Automatic Segmentation of Hippocampal Subfields (ASHS) software. Individual participant and group average tau PET SUVR, MTL volumes, mini-mental state examination (MMSE), clinical-dementia rating (CDR), and CDR-sum of boxes (CDR-SOB) were plotted over time. Linear mixed models adjusted for age and sex compared longitudinal changes and the differences between A-T+ and A+T+ groups.
Results: A total of 22 participants with baseline A-T+ PET status (mean age 72.6 years) and 73 A+T+ were included (mean follow-up 2.39 years). In contrast to the A+T+ group, individuals with A-T+ did not show significant changes in their tau PET SUVR in the MTL during follow-up (Fig. 1). Some volume loss was noted in the entorhinal, transentorhinal and posterior hippocampal regions (Fig. 2). However, no significant changes in MMSE, CDR or CDR-SOB scores were observed (Fig.

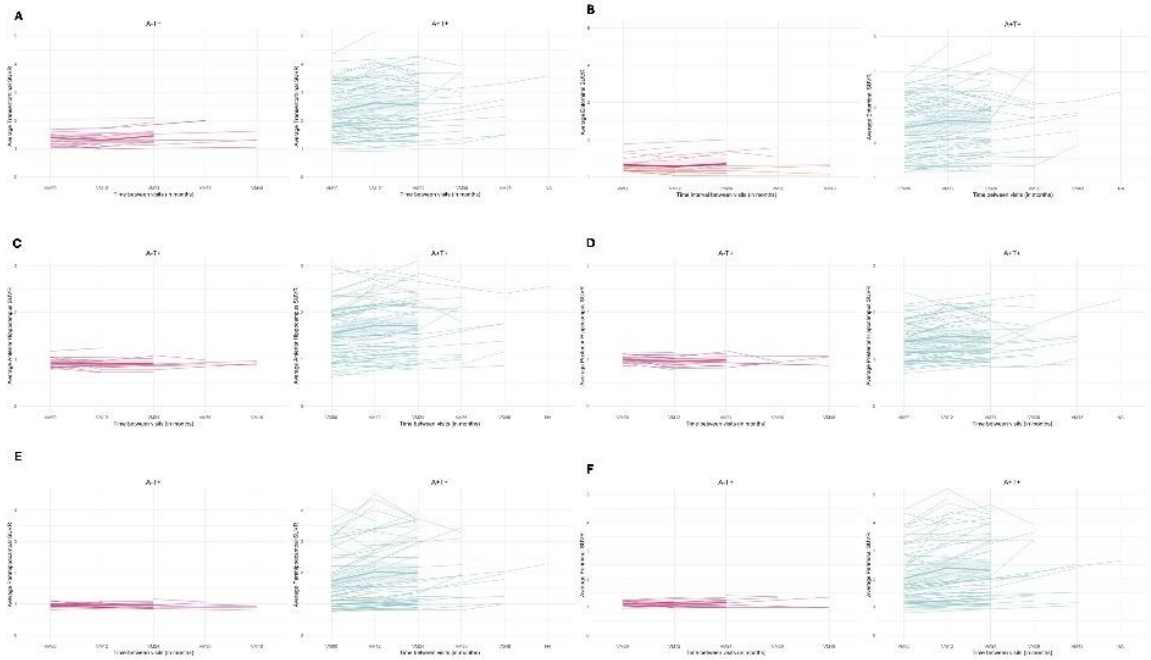

Fig. 1. Longitudinal changes in tau PET SUVR in A-T+ (pink) and A+T+ (green) groups in the entorhinal (A), transentorhinal (B), anterior hippocampal (C), posterior hippocampal (D), parahippocampal (E) and perirhinal (F) regions.

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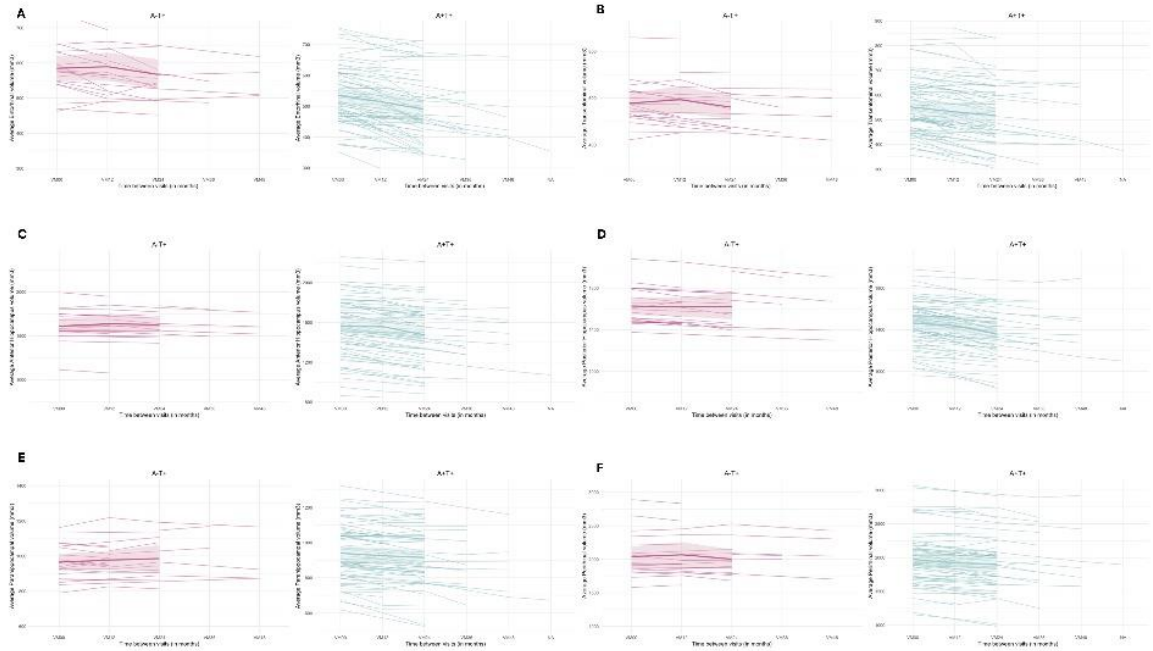

Fig. 2 Changes in medial temporal regional volumes over time in individuals with A-T+ (pink) and A+T+ (green) baseline PET status.

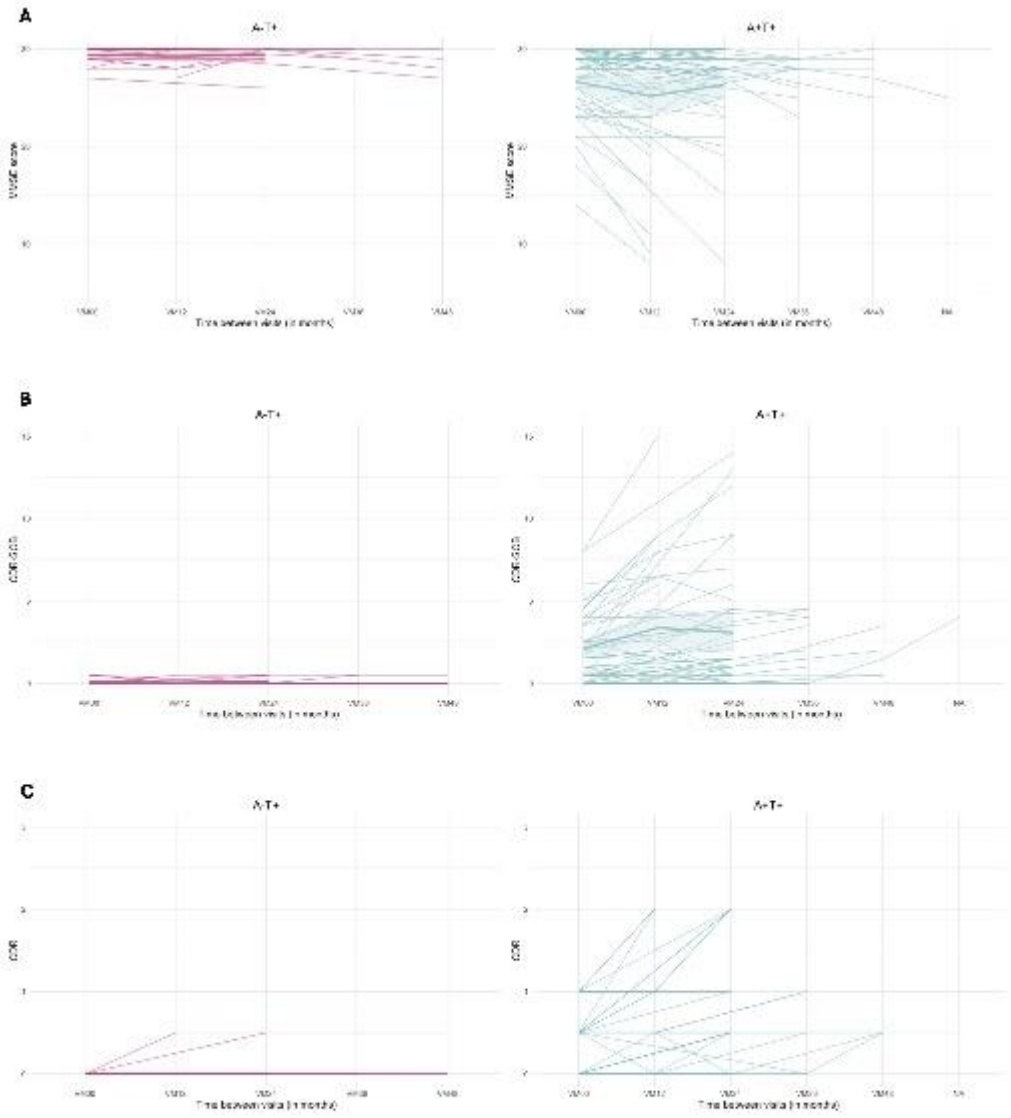

Fig. 3 Longitudinal changes in MMSE (A), CDR-SOB (B) and CDR (C) in A-T+ (pink) and A+T+ (green) groups. MMSE, mini-mental state examination . CDR clinical dementia rating, SOB sum of boxes.

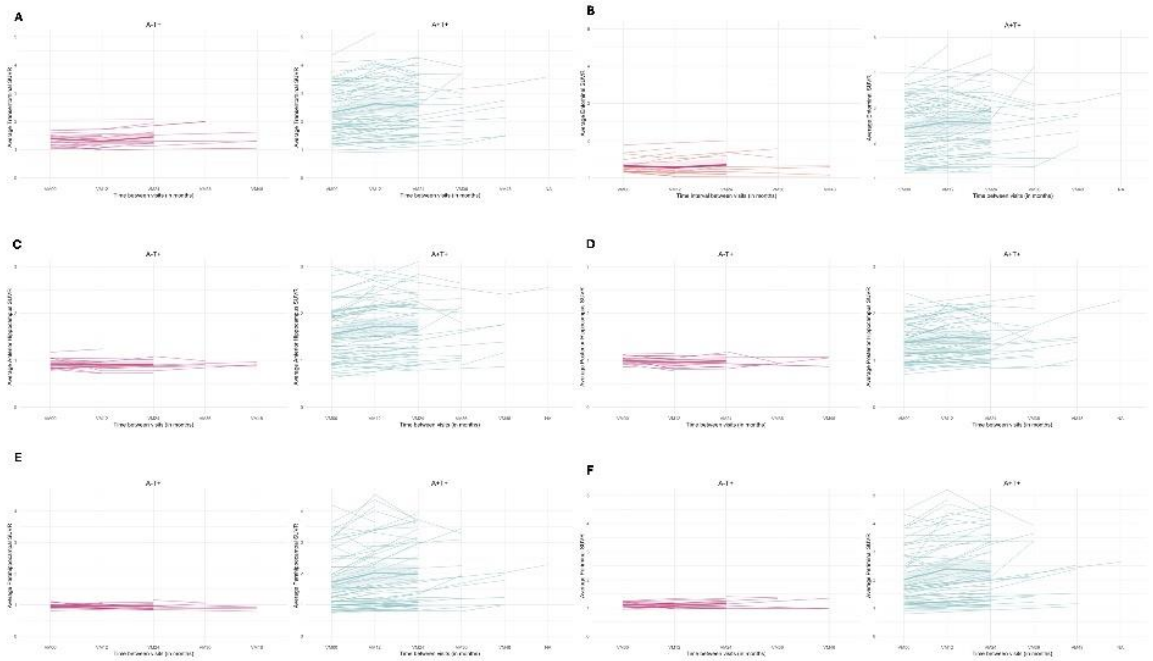

Fig. 1. Longitudinal changes in tau PET SUVR in A-T+ (pink) and A+T+ (green) groups in the entorhinal (A), transentorhinal (B), anterior hippocampal (C), posterior hippocampal (D), parahippocampal (E) and perirhinal (F) regions.

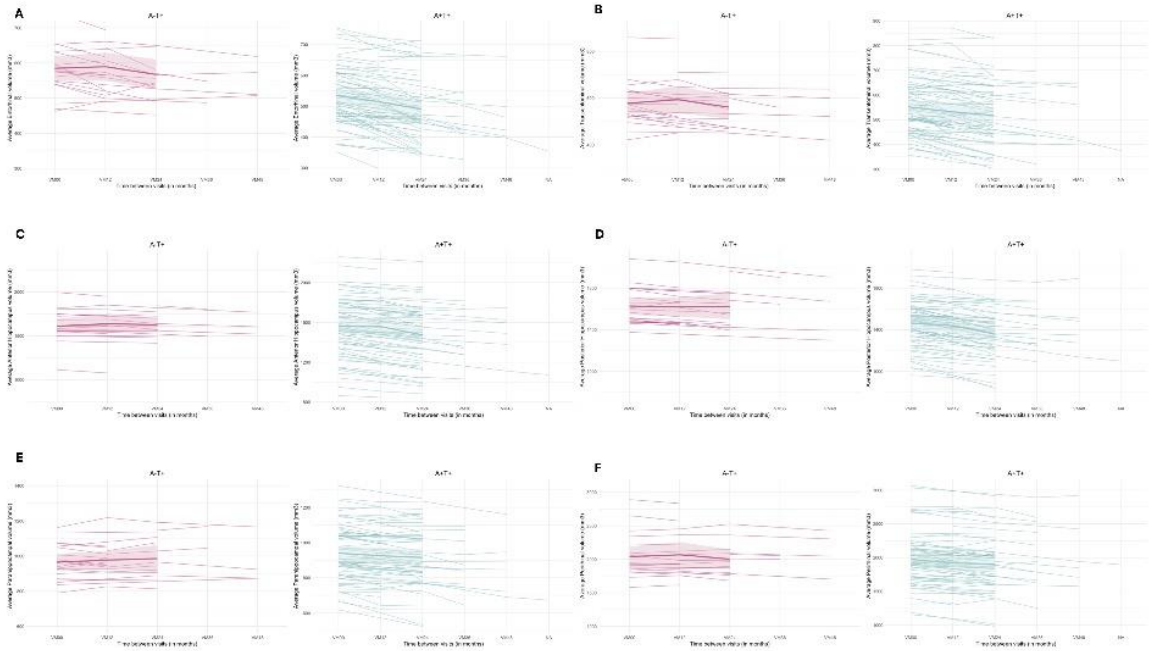

Fig. 2 Changes in medial temporal regional volumes over time in individuals with A-T+ (pink) and A+T+ (green) baseline PET status.

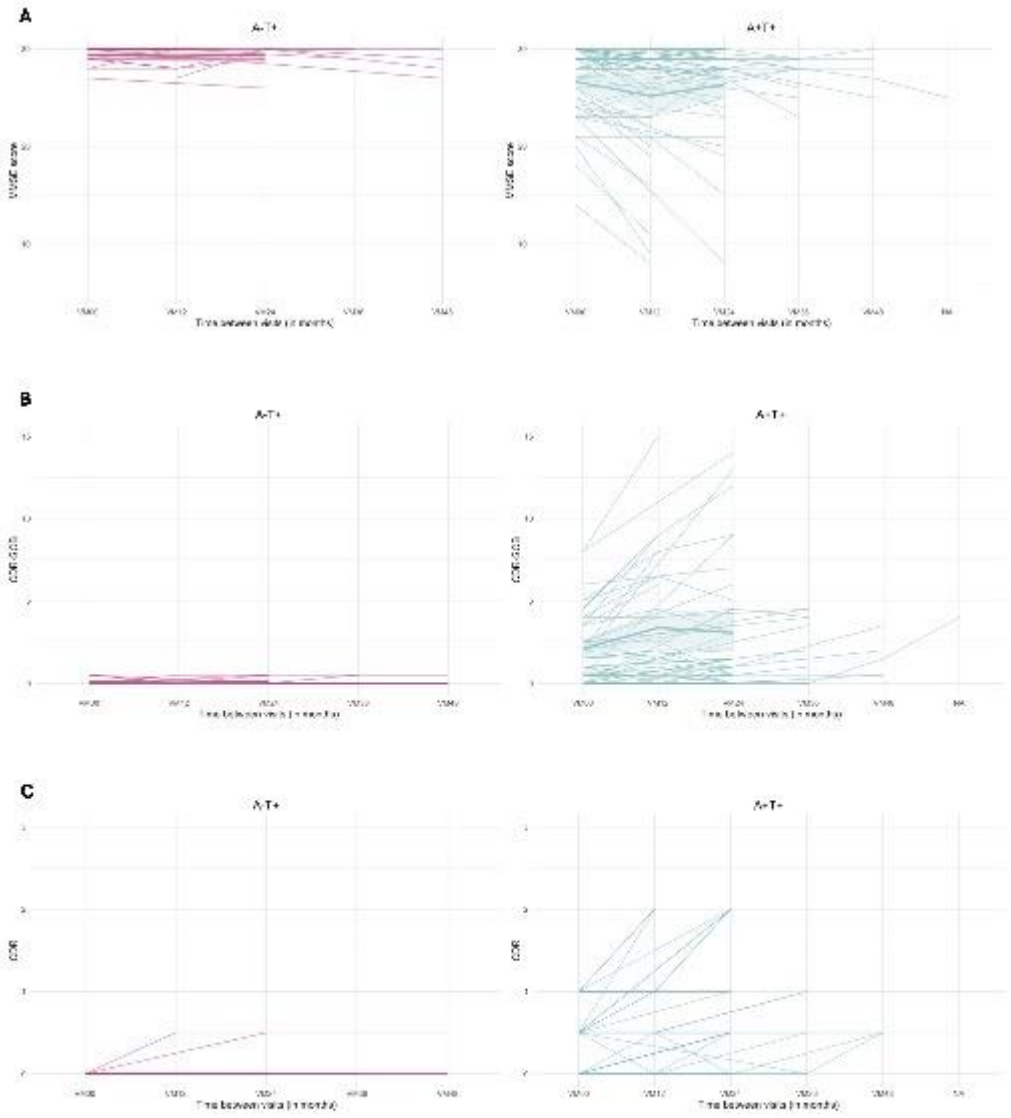

Fig. 3 Longitudinal changes in MMSE (A), CDR-SOB (B) and CDR (C) in A-T+ (pink) and A+T+ (green) groups. MMSE, mini-mental state examination . CDR clinical dementia rating, SOB sum of boxes.

Conclusions: Our data suggest that individuals with baseline A-T+ PET status have slower tau accumulation rates in the MTL as compared to A+T+ individuals, as well as slower rates of clinical disease progression. Prospective studies on tau accumulation and cognitive changes in these individuals could aid the prognostication of older adults with cognitive impairment.

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MAPPING INDIVIDUAL MOLECULAR CONNECTOMES IN ALZHEIMER'S DISEASE

Zhilei Xu[1], Mite Mijalkov[1], Yu-Wei Chang[2], Arianna Sala[3,4], Giovanni Volpe[2], Mattia Veronese[5,6], Sara Garcia-Ptacek[7,8], Joana Pereira[1,9]
[1]Karolinska Institutet, Department Of Clinical Neuroscience, Solna, Sweden, [2]University of Gothenburg, Department Of Physics, Gothenburg, Sweden, [3]University of Liege, Giga Consciousness, Liege, Belgium, [4]University Hospital of Liege, Centre Du Cerveau2, Liege, Belgium, [5]King's College London, Department Of Neuroimaging, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom, [6]University of Padua, Department Of Information Engineering, Padua, Italy, [7]Karolinska Institutet, Division Of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society, Huddinge, Sweden, [8]Karolinska University Hospital, Theme Inflammation And Aging, Stockholm, Sweden, [9]Lund University, Department Of Clinical Sciences, Malmö, Sweden

Aims: Mapping individual differences is a critical step towards improving personalized medicine approaches for Alzheimer's disease (AD). We aimed to develop a comprehensive analysis framework for mapping individual molecular connectome using longitudinal amyloid and tau positron emission tomography (PET) dataset and examine its superiority to previously proposed methodologies in tracking disease progression and cognitive decline along the AD continuum.
Methods: We construct individual molecular connectomes for amyloid-β (Aβ) positive subjects from the ADNI cohort using longitudinal amyloid-PET and tau-PET data through a statistical perturbation analysis on the partial Pearson correlation coefficient between the standardized uptake value ratios of Aβ and tau pathology for each pair of 68 cortical regions defined by the Desikan-Killiany atlas, while controlling for age, sex, and education. These individual molecular connectomes are fed into following analyses of connectome fingerprinting, linear mixed effects modeling, and machine-learning predictive modeling to examine its feasibility of personalized analysis and superiority to previously proposed methodologies.
Results: We demonstrate that the individual molecular connectomes constitute a unique fingerprint, allowing the identification of single individuals (accuracy rate: 83.6%-100.0%) and exhibiting significant vulnerability to disease progression across the AD continuum and over time ($P<0.005$). These connectomes could more accurately discriminate different diagnostic groups and predict longitudinal cognitive decline than previously proposed methodologies ($P<0.001$). Furthermore, genetic contribution to vulnerabilities of individual tau and amyloid connectomes are related to a common transcriptomic profile of apoptosis, whilst tau connectome is specifically related to pyrimidine metabolism, and amyloid connectome is specifically related to histone acetylation.
Conclusions: These results demonstrate individual molecular connectomes of significant clinical relevance to monitoring disease progression and evaluating the effectiveness of treatments across the AD continuum, which offers a promising avenue for personalized medicine strategies in AD.

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ALZHEIMER'S-ASSOCIATED INFLAMMATORY ALTERATIONS IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Patrick Lao, Seonjoo Lee, Anna Smith, Diana Guzman, Hannah Houlihan, Thairi Sanchez, Aubrey Johnson, Daniel Talmasov, Dina Dass, Ndubisi Chikwem, William Kreisl, Yasir Qureshi, James Noble, Scott Small
Columbia University, New York, United States of America

Aims: In Alzheimer's disease and related dementias (ADRD), microglia may promote pathology in the context of chronic sustained pro-inflammatory cues. We hypothesized that the Alzheimer's-associated inflammatory alterations, measured with TSPO PET, would be locally associated with amyloid, tau, and neurodegeneration as well as cognition.
Methods: Participants (21 controls, 24 individuals with ADRD) from the Longitudinal Imaging of Microglial Activation in Different Clinical Variants of Alzheimer's Disease study underwent amyloid PET (Florbetaben SUVR), tau PET (MK6240 SUVR), TSPO PET (ER176 SUVR), and structural MRI (gray matter volume). Amyloid positivity was determined by visual read. Cognitive assessment and consensus diagnosis (e.g., MCI, AD, PCA, FTD, LATE) were performed at the CUIMC ADRC. Separate models (e.g., amyloid, tau, neurodegeneration, cognition) tested for associations with TSPO across 13 regions, adjusting for TSPO binding affinity.
Results: In the inferior parietal and prefrontal cortices, greater TSPO was associated with greater tau alone. In the fusiform gyrus, greater TSPO was associated with lower gray matter volume alone. In the amygdala, hippocampus, inferior and superior parietal cortex, and middle inferior temporal gyrus, greater TSPO was associated with greater tau and lower gray matter volume. Regionality depended on amyloid positivity, with hippocampal TSPO-tau associations for amyloid-negative individuals, driving an overall negative TSPO-amyloid association (i.e., amyloid-negative individuals with ADRD had greater TSPO, tau, and neurodegeneration). Greater TSPO was associated with lower episodic memory, working memory, fluency, and visuospatial ability z-scores.

	TSPO~amyloid	TSPO~tau	TSPO~neurodegeneration
Prefrontal Cortex	0.03 [-0.2,0.25] p=1	**0.04 [0,0.09] p=0.05**	-0.004 [-0.01,0.001] p=0.33
Insula	-0.02 [-0.29,0.26] p=1	0.03 [-0.07,0.14] p=1	-0.02 [-0.07,0.02] p=0.82
Cingulate Gyrus	0.03 [-0.19,0.25] p=1	0.05 [-0.03,0.12] p=0.61	0.02 [-0.01,0.05] p=0.7
Fusiform Gyrus	0.13 [-0.17,0.43] p=0.95	0.04 [-0.02,0.1] p=0.42	**-0.09 [-0.16,-0.02] p=4e-03**
Lingual Gyrus	0.15 [-0.19,0.49] p=0.95	0.03 [-0.01,0.08] p=0.22	-0.04 [-0.09,0.01] p=0.14
Entorhinal Cortex	0.2 [-0.3,0.7] p=0.98	0.06 [-0.01,0.14] p=0.11	-0.16 [-0.35,0.03] p=0.18
Middle Inferior Temporal Gyrus	0.16 [-0.11,0.44] p=0.67	**0.05 [0,0.1] p=0.03**	**-0.02 [-0.04,0] p=4e-03**
Superior Temporal Cortex	0.05 [-0.23,0.32] p=1	0.04 [-0.02,0.11] p=0.48	-0.02 [-0.06,0.02] p=0.83
Inferior Parietal Cortex	0.12 [-0.12,0.36] p=0.89	**0.04 [0.01,0.07] p=5e-03**	-0.01 [-0.03,0.002] p=0.12
Superior Parietal Cortex	0.13 [-0.11,0.37] p=0.8	**0.04 [0.01,0.07] p=5e-03**	**-0.02 [-0.04,0] p=0.01**
Amygdala	-0.05 [-0.5,0.39] p=1	**0.13 [0.06,0.19] p=2e-07**	**-0.48 [-0.63,-0.32] p=2e-15**
Hippocampus	**-0.7 [-1.2,-0.18] p=1e-03**	**0.38 [0.19,0.58] p=3e-07**	**-0.29 [-0.39,-0.2] p=6e-16**
Striatum	-0.03 [-0.35,0.28] p=1	0.02 [-0.29,0.34] p=1	-0.02 [-0.08,0.03] p=0.93

Table 1. Associations between TSPO and amyloid, tau, and neurodegeneration. Each column represents a single model across 13 brain regions.

	TSPO~amyloid	TSPO~tau	TSPO~neurodegeneration
Prefrontal Cortex	0.03 [-0.2,0.25] p=1	**0.04 [0,0.09] p=0.05**	-0.004 [-0.01,0.001] p=0.33
Insula	-0.02 [-0.29,0.26] p=1	0.03 [-0.07,0.14] p=1	-0.02 [-0.07,0.02] p=0.82
Cingulate Gyrus	0.03 [-0.19,0.25] p=1	0.05 [-0.03,0.12] p=0.61	0.02 [-0.01,0.05] p=0.7
Fusiform Gyrus	0.13 [-0.17,0.43] p=0.95	0.04 [-0.02,0.1] p=0.42	**-0.09 [-0.16,-0.02] p=4e-03**
Lingual Gyrus	0.15 [-0.19,0.49] p=0.95	0.03 [-0.01,0.08] p=0.22	-0.04 [-0.09,0.01] p=0.14
Entorhinal Cortex	0.2 [-0.3,0.7] p=0.98	0.06 [-0.01,0.14] p=0.11	-0.16 [-0.35,0.03] p=0.18
Middle Inferior Temporal Gyrus	0.16 [-0.11,0.44] p=0.67	**0.05 [0,0.1] p=0.03**	**-0.02 [-0.04,0] p=4e-03**
Superior Temporal Cortex	0.05 [-0.23,0.32] p=1	0.04 [-0.02,0.11] p=0.48	-0.02 [-0.06,0.02] p=0.83
Inferior Parietal Cortex	0.12 [-0.12,0.36] p=0.89	**0.04 [0.01,0.07] p=5e-03**	-0.01 [-0.03,0.002] p=0.12
Superior Parietal Cortex	0.13 [-0.11,0.37] p=0.8	**0.04 [0.01,0.07] p=5e-03**	**-0.02 [-0.04,0] p=0.01**
Amygdala	-0.05 [-0.5,0.39] p=1	**0.13 [0.06,0.19] p=2e-07**	**-0.48 [-0.63,-0.32] p=2e-15**
Hippocampus	**-0.7 [-1.2,-0.18] p=1e-03**	**0.38 [0.19,0.58] p=3e-07**	**-0.29 [-0.39,-0.2] p=6e-16**
Striatum	-0.03 [-0.35,0.28] p=1	0.02 [-0.29,0.34] p=1	-0.02 [-0.08,0.03] p=0.93

Table 1. Associations between TSPO and amyloid, tau, and neurodegeneration. Each column represents a single model across 13 brain regions.

Conclusions: Across ADRD diagnoses that have different underlying brain pathologies (i.e., different brain microenvironments), greater microglia density was associated with greater tau burden, neurodegeneration, and cognitive impairment, but was present with or without amyloid positivity. Glia may represent an interesting target for intervention strategies in ADRD-associated tau and neurodegeneration.

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DO EDUCATION AND PREMORBID INTELLIGENCE PREDICT COGNITIVE DECLINE OVER ONE YEAR IN RURAL PATIENTS WITH DEMENTIA?

Diego Diaz, Andrew Kirk, Megan O'Connell, Debra Morgan
University of Saskatchewan, Saskatoon, Canada

Aims: Education and premorbid intelligence have been used to predict disease trajectory in dementia. However, there is conflicting evidence regarding their independent predictive ability. This study aims to investigate whether education and premorbid intelligence predict cognitive and functional decline in rural dementia patients over a one-year span.
Methods: Data from 614 rural patients was analyzed for the association between a) years of education and b) premorbid intelligence [Premorbid Verbal IQ] and cognitive function through linear regression analysis as an overall group sample, and stratified into 4 groups [Subjective Cognitive Impairment: N=168, Mild Cognitive Impairment: N=98, Alzheimer's Disease-Dementia: N=249, Non-Alzheimer's Disease Dementia: N=99] according to dementia type. Premorbid verbal IQ was quantified using the Weschler Adult Reading Test & Wide Range Achievement Test 4th Edition, after norming each were scored on a scale of 100 [SD=15].
Results: A higher Premorbid Verbal IQ score predicted a smaller decline in cognition in the overall group sample [Clinical Dementia Rating Regression Coefficient= -0.048 + 0.021, P= 0.023] and reduced caregiver dependence in the Non-AD dementia group [Functional Activities Questionnaire Regression Coefficient= -0.286 + 0.133, P= 0.038] one-year post-diagnosis. Education was not a statistically significant predictive factor of cognition in the overall sample or within each individual diagnostic group one-year post-diagnosis.
Conclusions: Higher premorbid verbal IQ score predicts less cognitive decline and reduced caregiver dependence one-year post-diagnosis in rural patients. Additionally, we found no association between years of education and measures of cognition one-year post-diagnosis. Premorbid intelligence is shown to be predictive of cognition and function one-year post-diagnosis in rural patients and may be useful for determining prognosis and guiding treatment planning.

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COMBINING PLASMA P-TAU 181 AND AB42/40 RATIO FOR ENHANCED ALZHEIMER'S DISEASE DIAGNOSIS

Emilien Boyer, Louise Deltenre, Marion Dourte, Lise Colmant, Bernard Hanseeuw, Pascal Kienlen-Campard
UCLouvain, Institute Of Neurosciences, Brussels, Belgium

Aims: One of the main current research directions aims to facilitate the identification of Alzheimer's disease patients at preclinical stages (PC-AD). Hallmark proteins pathogenic in AD, amyloid and tau, can now be quantified in plasma samples using single-molecule array (Simoa) to facilitate PC-AD diagnosis. We aimed to compare the performance of p-tau181 to the plasma ratio Aβ42/40 for predicting tau deposition and amyloid deposition in the brain, as evaluated by PET scanner, and to determine whether combining their measurements could increase test accuracy in a non-demented population.
Methods: Plasma samples were obtained in non-demented participants who underwent AD biological staging with CSF analysis or ^{11}C-PIB / ^{18}F-Flutemetamol-PET and ^{18}F MK-6240-PET examination (N=101). Quantification of amyloid 42-40 peptides and p-tau181 protein was achieved with Simoa analysis. Patients were classified as A+ (n=41) or A-(n=66), T+ (n=35) or T- (n=71), and A+T+ (n=31) or A+T-(62). Test accuracy was calculated with ROC analysis.
Results: We observed that plasma p-tau181 identified better amyloid status of non-demented participants than ratio Aβ42/40 (AUC=0.79 vs 0.72). The same conclusion was found for T+ identification (for p-tau181 AUC=0.79, for Aβ42/40 AUC=0.68). The best AUC was found when plasma p-tau181 was associated with ratio Aβ42 to predict A+T+ status (AUC=0.84) and A+ status (AUC=0.82). No changes were foud for T+ status prediction (AUC=0.79).
Conclusions: In a non-demented population, plasma p-tau181 was a better indicator of amyloid deposition in the brain than ratio Aβ42/40 alone, but their combination increased the prediction of amyloid PET positivity. The best candidate for tau deposit detection was plasma p-tau181 alone and to diagnose AD status (A+T+) the best was to use the association of both markers.

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CSF P-TAU198 AND P-TAU356 AS ANTEMORTEM BIOMARKERS FOR EARLY AD DIAGNOSIS

Ling Wu[1], Hibat Gindeel[2], Nailya Gilyazova[2], John Ervin[3], Andy Liu[4], Jerry Wang[5], Bin Xu[1]
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Aims: Alzheimer's disease (AD) is characterized by a long preclinical phase. Although late-stage AD may be robustly differentiated from cognitively normal (CN) individuals by means of a clinical evaluation, PET imaging, and established biofluid biomarkers, disease differentiation between cognitively normal and mild cognitive impairment (MCI) remains a challenging task. Differential biomarkers for early-stage AD diagnosis with accessible biofluid samples are urgently needed.
Methods: From a systematic screen of site-specific phospho-tau antibodies targeting over two-dozen phosphorylation sites that showed high frequencies in AD patients, we identified two novel epitopes p-tau198 and p-tau356.
Results: P-tau198 and p-tau356 were not only highly capable to differentiate AD from cognitively normal (CN) brains, but also discriminate MCI from CN brains with outstanding differentiation powers that rival or outcompete p-tau181, p-tau217 and p-tau231: p-tau198 has an AUC of 0.85 (95% CI = 0.70-0.99) and p-tau356 has an AUC of 0.93 (95% CI = 0.79-1.00). We further validated p-tau198 and p-tau356 using immunohistochemistry staining of MCI and CN postmortem brains of CA1-CA4 hippocampal areas, entorhinal cortex and adjacent regions. We discovered that p-tau356 epitope as a marker of tau burden in the superior temporal cortex showed significantly better correlation with Braak stages of MCI subjects (r=0.83) compared to neuropathological reference AT8 epitope (p-tau202/205; r=0.67). We developed homebrew ultrasensitive single molecular array (Simoa) tests for cerebrospinal fluid (CSF) detection and quantification. Our results showed significantly elevated p-tau198 and p-tau356 concentrations in a cohort of CSF samples from MCI patients compared to those from CN subjects.
Conclusions: Our discoveries provide new diagnostic tools for early AD diagnosis in translational medicine.

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CONNECTOMICS AND NEUROTRANSMITTER RECEPTOR PROFILE EXPLAIN REGIONAL TAU PATHOLOGY IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) tau pathology spreads through neuronal pathways and synaptic connections. Alteration in synaptic activity facilitates tau spreading. Multiple neurotransmitter systems are shown to be implicated in AD, but their influence on the trans-synaptic spread of tau is not well understood. Here, I aimed to combine resting-state fMRI connectomics, neurotransmitter receptor profiles, and tau-PET data to explain the regional susceptibility to tau accumulation.
Methods: The tau-PET imaging data of 161 Aβ-negative cognitively unimpaired (CU) participants as control and 259 Aβ-positive subjects were recruited from ADNI. Furthermore, normative resting-state fMRI connectomes of CU participants and 19 neurotransmitter receptor densities of more than 1200 healthy individuals were obtained.
Results: Linear regression analysis revealed that a higher tau-PET z-score is associated with a lower density of nine receptors in the serotonin, dopamine, GABA, Acetylcholine, and glutamate systems. Furthermore, adding four neurotransmitter receptor density z-scores significantly increased the proportion of explained variance by 3% to 7% compared to the epicenter-connectivity distance model in the group-level analysis. Also, adding nine neurotransmitter receptor density z-score to the epicenter-connectivity distance model increased the explanatory power of variability in individual levels of tau-PET z-score by 3% to 8%. Moreover, Adding the Aβ-PET z-score the the previous model increased the proportion of explained variance of the tau-PET z-score by an additional 4% to 10% at the individual level.
Conclusions: In conclusion, I found that micro-architectural measures, Aβ, and connectomic vulnerability jointly shape the tau pathology pattern. The current study demonstrated the additive value of atlas-based neurotransmitter receptor mapping and individual-level Aβ-PET scans to enhance the connectivity-based explanation of tau accumulation.

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LONGITUDINAL CREATININE TRAJECTORIES IDENTIFY SUB-POPULATIONS WITH DIFFERENT BURDEN OF ALZHEIMER'S DISEASE RELATED BIOMARKERS IN A COMMUNITY-BASED COHORT

Vrinda Kalia[1], Hanisha Udhani[2], Saurabh Dubey[2], Renu Nandakumar[2], Dolly Reyes-Dumeyer[3], Yian Gu[4], Lawrence Honig[3,5], Richard Mayeux[5], Gary Miller[1], Badri Vardarajan[6]
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Aims: We investigated the influence of kidney function on metabolites associated with Alzheimer's disease (AD) by leveraging longitudinal measurements of creatinine.
Methods: Plasma metabolomic profiles were generated in 653 individuals at three different time points (98 incident clinical AD cases) using liquid-chromatography coupled high-resolution mass spectrometry. Plasma biomarkers, P-tau181, NfL, GFAP, and ß-amyloid, were measured too. A latent class mixed model (LCMM) identified two distinct creatinine trajectories: one increasing and another stable over time. The difference in the metabolomic and biomarker profiles, and incidence of AD between the two clusters was determined, adjusting for age, sex, ethnicity, and follow-up time.
Results: The average follow-up time between visits was ~5 years (min = 1.4, max = 22.9). LCMM classified the sample population into two clusters, one with stable creatinine levels (cluster1, n = 341), the other with increasing creatinine levels (cluster2, n = 312). Cluster2 membership was associated with higher levels of renal function related metabolites and lower levels of lipid metabolites including linolenic acid (p = 8.1E-04) and long chain lysophosphatidylcholines. People in cluster2 had higher levels of P-tau181 (p = 2.8E-07), NfL (p = 4.5E-09), GFAP (p = 4.3E-04) but $Aß_{42}/Aß_{40}$ (p = 0.06) was not different. There were more incident P-tau181-supported AD cases in cluster 2 who had higher levels of renal function related metabolites and higher levels of features annotated as food derived metabolites.
Conclusions: Longitudinal creatinine trajectories were used to classify people into two clusters, one with declining renal function and the other with stable renal function, as might be expected in a community-based cohort. People classified with declining renal function had a higher burden of AD-related biomarkers and higher proportion were diagnosed with P-tau181-supported AD.

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ULTRA HIGHEST PLEX SPATIAL MULTIOMICS REVEALS DISTINCT TRANSCRIPTOMIC AND PROTEOMIC SENESCENCE CELL BIOLOGY IN ALZHEIMER'S DISEASE

Alyssa Rosenbloom[1], Miranda Orr[2], Tim Orr[2], Hiromi Sato[1], Erin Piazza[1], Brian Filanoski[1], Lori Hamanishi[1], Joseph Beechem[1]
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Aims: The advancement of spatially resolved, multiplex proteomics and transcriptomics has revolutionized and redefined the approaches to complex biological questions pertaining to tissue pathology and cellular interactions. Therefore, more holistic, ultra-high-plex multiomic measurement of RNA and protein simultaneously within a single tissue section with distinct spatial context is critical to a more complete biological understanding of cellular interactions and activities; in particular, senescence cell biology and the role of phosphorylated microtubule associated protein tau species in Alzheimer's disease (AD) pathology.
Methods: Tau neuropathology includes intraneuronal deposition of heavily phosphorylated tau as neurofibrillary tangles (NFTs), which closely correlates with neuron loss and cognitive decline. A Digital Spatial Profiler platform is uniquely suited to support high-plex multiomics from discrete regions of interest (ROIs) in FFPE tissue sections while preserving spatial context. The assays use antibodies and ISH probes coupled to photocleavable DNA barcodes readout with NGS sequencing.
Results: We used the Human Immuno-Oncology Proteome Atlas (IPA), a 570+ antibody-based proteomic discovery panel, coupled with a novel ultra-high-plex neural proteomic discovery panel and a Whole Transcriptome RNA panel, as a highest plex spatial multi-omics solution to explore the role of specific phospho tau species on cellular senescence and disease progression in human AD positive neural samples, comparing neuritic and non-neuritic plaque pathologies. We observed distinct RNA and protein expression profiles based on plaque pathology and cellular proximity of tangles, including distinct tau hyperphosphorylation profiles.
Conclusions: Presence of neurofibrillary tangles are closely correlated with neuron loss and observed cognitive decline. Ultra highest plex multiomics offer a unique solution to identify distinct RNA and proteomic profiles of tau tangles and surrounding pathology, aiding in discovery of potential targets for therapeutic interventions in Alzheimer's disease, aging, and cellular senescence.

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TRANSCRIPTIONAL PROGRAMS MEDIATING NEURONAL TOXICITY AND ALTERED GLIAL–NEURONAL SIGNALING IN A DROSOPHILA KNOCK-IN TAUOPATHY MODEL

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Aims: Missense mutations in the gene encoding the microtubule-associated protein TAU (current and approved symbol is MAPT) cause autosomal dominant forms of frontotemporal dementia. Multiple models of frontotemporal dementia based on transgenic expression of human *TAU* in experimental model organisms, including *Drosophila*, have been described. These models replicate key features of the human disease but do not faithfully recreate the genetic context of the human disorder. Here we use CRISPR-Cas-mediated gene editing to model frontotemporal dementia caused by the TAU P301L mutation by creating the orthologous mutation, P251L, in the endogenous *Drosophila tau* gene. Flies heterozygous or homozygous for Tau P251L display age-dependent neurodegeneration, display metabolic defects, and accumulate DNA damage in affected neurons.
Methods: To understand the molecular events promoting neuronal dysfunction and death in knock-in flies, we performed single-cell RNA sequencing on approximately 130,000 cells from brains of Tau P251L mutant and control flies.
Results: We found that expression of disease-associated mutant *tau* altered gene expression cell autonomously in all neuronal cell types identified. Gene expression was also altered in glial cells, suggestive of non-cell-autonomous regulation. Cell signaling pathways, including glial–neuronal signaling, were broadly dysregulated as were brain region and cell type–specific protein interaction networks and gene regulatory programs.
Conclusions: In summary, we present here a genetic model of tauopathy that faithfully recapitulates the genetic context and phenotypic features of the human disease, and use the results of comprehensive single-cell sequencing analysis to outline pathways of neurotoxicity and highlight the potential role of non-cell-autonomous changes in glia.

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SELECTIVE TARGETING OF PATHOGENIC TDP-43 WITH MISFOLDING-SPECIFIC MONOCLONAL ANTIBODIES AND INTRABODIES AGAINST A PATHOGENIC LOSS-OF-STRUCTURE EPITOPE IN THE N-TERMINAL DOMAIN

Neil Cashman[1], Beibei Zhao[1], Juliane Coutts[2], Sarah Louadi[2], Ebrima Gibbs[2], Anke Djikstra[3], Ian Mackenzie[4], Megan Huang[5], Stefan Aigner[5], Eugene Yeo[5], Johanne Kaplan[1]
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Aims: TAR DNA-binding protein 43 (TDP-43) is associated with the pathogenesis of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD). Normally TDP-43 is predominantly localized in the nucleus, and regulates RNA splicing, transport, and stability. In disease, it is mislocalized to the cytoplasm and forms aggregates, which contribute to neurotoxicity and cell-to-cell propagation of pathogenic TDP-43. Development of effective immunotherapeutic agents requires stringent selectivity for misfolded TDP-43 in order to maintain the essential physiological functions of the normal isoform. The objective was to generate and evaluate the activity of monoclonal antibodies (mAbs) and intrabodies against an N-terminal domain (NTD) epitope only exposed when the protein is misfolded in disease (Pokrishevsky et al JBC 2024).
Methods: Monoclonal antibodies (mAbs) were characterized by surface plasmon resonance (SPR), immunocytochemistry (ICC) in cell lines, and immunohistochemistry (IHC) of human diseased CNS. Antibodies were tested for inhibition of misfolded TDP-43 aggregate propagation by western blotting on recipient human HEK293T cells. Intrabodies were tested for effects on TDP-43 cytoplasmic aggregates in human induced pluripotent stem cell-derived motor neuron (iPSC-MN) and HEK293T cells.
Results: Our mAbs displayed subnanomolar affinity against the NTD epitope by SPR, and selectively reacted with pathological TDP-43 in post-mortem tissues from ALS, FTD, and AD patients. In HEK293T cells, mAbs and corresponding intrabodies specifically reacted with cytoplasmic aggregates of transfected misfolded TDP-43 lacking the nuclear localization signal, TDP-43^{DNLS}. Functionally, mAbs inhibited cell-to-cell transmission of TDP-43^{DNLS}. Intrabodies promoted the degradation of intracellular aggregates of TDP-43 in HEK293T cells and in iPSC-MNs from ALS patients.
Conclusions: The results provide proof-of-concept evidence that supports selective targeting of misfolded toxic aggregates of TDP-43 as a potentially safe and effective avenue to treat neurodegenerative diseases associated with TDP-43 proteinopathy.

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VALIDATION OF A NOVEL IMMUNOASSAY DETECTING THE FOURTH CNS INTERMEDIATE FILAMENT TYPE IV: ALPHA-INTERNEXIN

Francisco Meda[1], Camilla Johansson[2], Karin Palm[2], Gunnar Brinkmalm[1], Ulf Andreasson[1,2], Kaj Blennow[1,2], Hlin Kvartsberg[1,2], Henrik Zetterberg[1,2,3,4,5]
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Aims: Background: Alpha-internexin (AINX) is a type IV intermediate filament alongside the neurofilament triplet proteins. Because of a lack of previously published studies quantifying AINX in cerebrospinal fluid (CSF), and its high sequence similarity with other neurofilaments, the objective of this project was to validate an in-house immunoassay that specifically detects AINX and assess its biomarker capabilities.
Methods: AINX in-house antibodies (B15 and Ina1), were used to detect AINX in CSF using the ultrasensitive Simoa platform. An in-house recombinant AINX protein was used as calibrator and pools of CSF with high and low concentrations of AINX used as quality controls for the validation experiments. Immunoprecipitation followed by mass spectrometry (IP-MS), was also performed to evaluate antibody binding and specificity. Validation parameters were assessed according to the literature (Andreasson et al., 2015).
Results: IP-MS results on SDS brain extracts revealed good sequence coverage of AINX for both antibodies (56% for B15 and 85% for Ina1). The Simoa immunoassay was validated for CSF with repeatability and intermediate precision of <3,4% and <10.4%, respectively. Average spike recovery range between 93-102%, measurement range 14-0,014 pg/mL and dilution linearity up until 32-fold. Samples were stable for up to 5 freeze/thaw cycles both at room temperature and 4°C for up to a week. Preliminary results showed varying correlations of AINX with NfL showcasing the possibilities of using this protein as a biomarker for neurodegeneration, independently of NfL.
Conclusions: Conclusion: In this study we demonstrate robust performance of a novel assay for accurately detection of AINX in CSF. In the future we will focus on further evaluating its biomarker potential in different neurodegenerative diseases and acute conditions such as stroke or traumatic brain injury.

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EXPLORING RISK FACTORS FOR CEREBRAL AMYLOID ANGIOPATHY

Liwei Ma[1,2], Yihan Wang[1,2], Andrew Huynh[3,4], Sanka Amadoru[3,4], Scott Wrigley[3], Paul Yates[3,4], Colin Masters[2], Benjamin Goudey[2], Liang Jin[1,2], Yijun Pan[1,2]
[1]The University of Melbourne, Florey Department Of Neuroscience And Mental Health, Parkville, Australia, [2]The Florey Institute of Neuroscience and Mental Health, Parkville, Australia, [3]Austin Health, Department Of Aged Care, Heidelberg, Australia, [4]Austin Health (The University of Melbourne), Department Of Medicine, Heidelberg, Australia

Aims: To identify the risk factors for cerebral amyloid angiopathy (CAA) and develop a predictive algorithm for detecting individuals at high risk of CAA
Methods: We conducted a secondary analysis using data from 2,118 dementia-free participants at baseline from the Religious Orders Study (ROS), Memory and Aging Project (MAP), and Minority Aging Research Study (MARS), all with clinical and neuropathology data. We assessed cross-sectional associations between neuropathological changes and CAA and examined longitudinal relationships between potential risk factors and CAA. The identified risk factors were then used to develop a machine learning prediction model.
Results: In the cross-sectional analysis, Aß plaque, neuritic plaque, and neurofibrillary tangles were associated with increased odds of cerebral amyloid angiopathy (CAA), with the association strength rising with increased CAA severity. The correlation between Alzheimer's disease neuropathological changes (ADNC) and CAA was especially pronounced among females, non-Caucasians, smokers, individuals with stroke/head injury/memory complaints, APOE-ε4 carriers, and those free from diabetes or heart conditions. Factors such as education, smoking, diabetes, and heart conditions emerged as potential modifiers of the ADNC-CAA link. Longitudinally, increased CAA risk was noted in males, older individuals, smokers, and those with diabetes, heart conditions, lower visual acuity, lower MMSE scores, and APOE-ε4 carriers. Employing these risk factors, our machine learning model attained a ROC-AUC of 0.63 in predicting CAA.
Conclusions: Our research pinpointed risk factors for CAA, providing insights that can guide prevention strategies. AD patients at high risk for CAA may need closer monitoring for amyloid-related imaging abnormalities when treated with monoclonal antibodies.

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LONGITUDINAL BIOPHYSICAL MODEL OF TAU SPREAD IN INDIVIDUALS

Robin Sandell[1], Justin Torok[2], Daren Ma[3], Ashish Raj[3]
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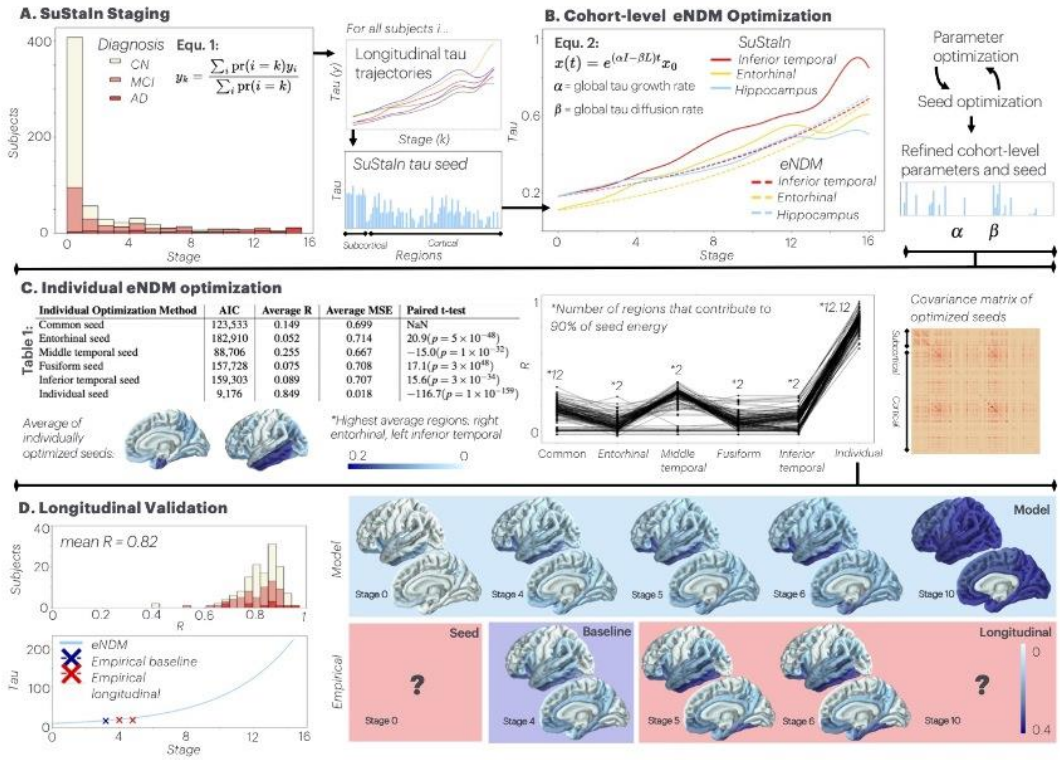
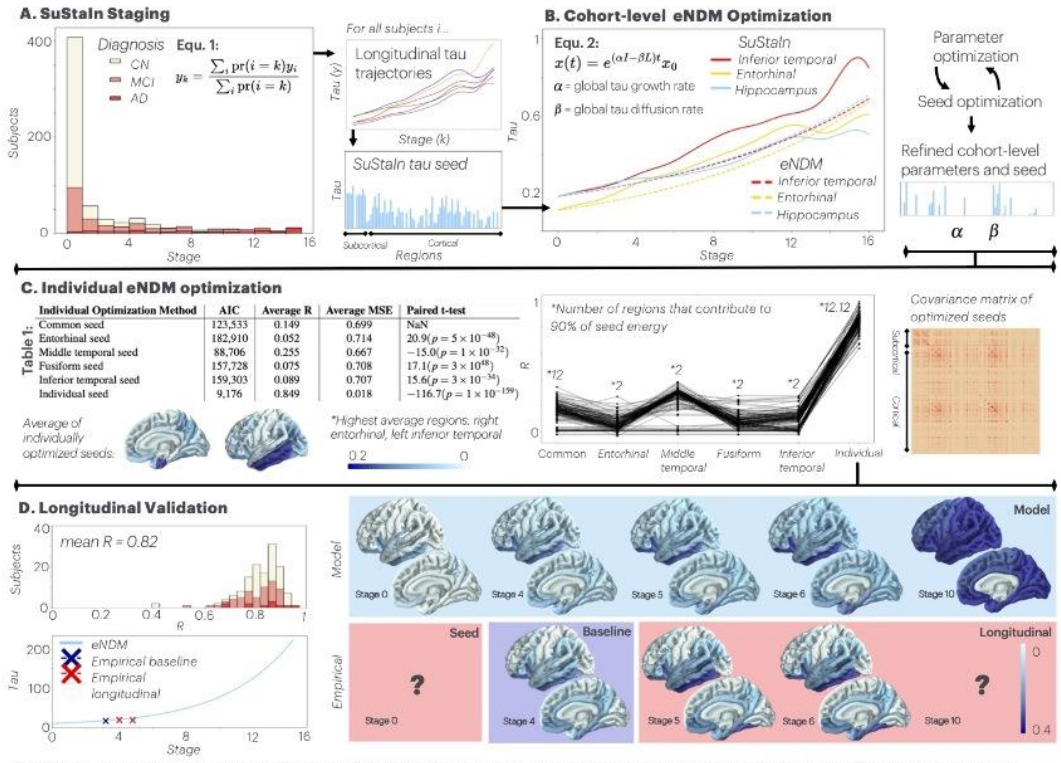
Aims: This study models tau neurofibrillary tangle spread in Alzheimer's Disease (AD) using machine learning and biophysical modeling techniques. We aimed to create predictive models of individuals' spatiotemporal tau, explore between-subject heterogeneity, and impart biophysical relevance to prior statistical approaches.
Methods: We employed Subtype and Stage Inference algorithm (SuStaIn) to probabilistically stage 650 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) based on cross-sectional biomarker data, from which we interpolated a longitudinal tau trajectory for the cohort. We then optimized a biophysical network diffusion model (eNDM) to fit both the cohort-level trajectory and individual tau-PET at each subject's SuStaIn stage. eNDM treats the dynamics of tau spread as a diffusive process between connected brain regions originating from a seed vector.
Results: Iterations between model parameter and seed vector optimization produced refined cohort-level parameters and seed. Individual seed optimization with fixed cohort-level parameters (mean R = 0.84) dramatically outperformed individual parameter optimization with a fixed cohort-level seed (mean R= 0.14), as well as binary seeds corresponding to four 'tau epicenters' identified by Vogel et al. (2018). The superior fit of individually optimized seeds suggests that heterogeneity between subjects largely derives from unique seed patterns. We validated our approach by correlating eNDM's prediction to longitudinal tau-PET for each subject at corresponding stages (mean R= 0.81).



A. Histogram of SuStaIn stage assignment aligns with diagnostic categories. Based on the probability distribution for each subject across stages, we interpolated regional tau trajectories (equ.1). T=0 from SuStaIn initialized eNDM. **B**. eNDM optimized to fit the tau trajectories from SuStaIn across stages and regions (equ.2). Iterative optimization of global parameters and seed refined the model fit. **C**. Comparison of optimization methods of eNDM to individuals' tau, including common seed + individual parameters, binary 'tau epicenters' identified by Vogel et al. (2018), and individually optimized seeds + common parameters (table 1 and ladder graph of Pearson's R across methods). Highest average seed regions across subjects plotted on the brain. Covariance matrix of optimized seeds across subjects indicates substantial heterogeneity. **D**. Histogram of R between empirical longitudinal tau and eNDM's prediction for each subject. eNDM prediction, empirical baseline, and longitudinal follow-ups for a single subject (total tau plot and plotted onto the brain).



A. Histogram of SuStaIn stage assignment aligns with diagnostic categories. Based on the probability distribution for each subject across stages, we interpolated regional tau trajectories (equ.1). T=0 from SuStaIn initialized eNDM. **B**. eNDM optimized to fit the tau trajectories from SuStaIn across stages and regions (equ.2). Iterative optimization of global parameters and seed refined the model fit. **C**. Comparison of optimization methods of eNDM to individuals' tau, including common seed + individual parameters, binary 'tau epicenters' identified by Vogel et al. (2018), and individually optimized seeds + common parameters (table 1 and ladder graph of Pearson's R across methods). Highest average seed regions across subjects plotted on the brain. Covariance matrix of optimized seeds across subjects indicates substantial heterogeneity. **D**. Histogram of R between empirical longitudinal tau and eNDM's prediction for each subject. eNDM prediction, empirical baseline, and longitudinal follow-ups for a single subject (total tau plot and plotted onto the brain).

Conclusions: We present a new method to predict past and future tau for any subject based only on cross-sectional data that combines SuStaIn and network diffusion modeling. Our analysis builds on prior work by exploring heterogeneity on an individual instead of a group level and by imparting biophysical relevance to SuStaIn. Our insight into individual tau spread patterns could potentially inform more precise disease prediction and AD treatment development.

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ACTIVATION OF ENDOLYSOSOMAL NEURONAL DEGRADATIVE MECHANISMS TO AMELIORATE PRION DISEASE

Sandra Encalada[1,2], Tai Chaiamarit[3], Yin Wu[1], Delany Rodriguez Lara[1], Sammy Weiser Novak[4], Leonardo Andrade[4], Uri Manor[5], Rachel Botham[6], Leonard Yoon[6], Jeffery Kelly[6]
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Aims: Intra-axonal accumulations of misfolded protein aggregates inside dystrophic axons are a hallmark of virtually all neurodegenerative disorders. These swellings are observed in brains at early disease stages and are tied to neuronal impairment. How these swellings containing aggregates form in axons and the mechanisms of neuronal toxicity are not well understood.
Methods: Using a combination of high-resolution fluorescence and electron microscopy imaging, genetics, and biochemical approaches,
Results: We identified an endolysosomal trafficking pathway that regulates the formation of toxic aggregates formed by mutant prion proteins (PrP) specifically along mammalian axons. In this **a**xonal **r**apid **e**ndosomal **s**orting and **t**ransport-dependent **a**ggregation (ARESTA) pathway, misfolded mutant PrP traveling inside post-Golgi membrane endosomes, translocate into the axon via active kinesin, where they fuse to other vesicles to generate very large endolysosomes where mutant PrP aggregates form. We termed these newly identified large membrane-delimited endolysosomal aggregate structures "endoggresomes" (aggregates within endosomes). Endoggresomes impair neuronal calcium dynamics, disrupt subcellular trafficking, remodel critical organelles such as endosomes and mitochondria along axons, and result in reduced neuronal viability. Genetic reduction of ARESTA pathway components in cultured neurons as well as in the brains of AAV mouse models of mutant prion disease inhibits mutant PrP endoggresome formation as well as pathological lesions, restoring neuronal function. Moreover, pharmacologically activation of lysosomal flux/autophagy with newly identified small molecules efficiently clears endoggresomes in axons of cultured neurons, circumventing neuronal toxicity and neuronal cell death. Importantly, these autophagy activators also efficiently reduce mutant PrP aggregates and brain pathological lesions in our AAV-generated mouse models of mutant PrP disease.
Conclusions: These data strongly suggest that ARESTA pathway and the autophagy/lysosomal trafficking pathways are anti-aggregation targets amenable to therapeutic modulation in the prionopathies.

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EARLY MITOCHONDRIAL METABOLISM ALTERATIONS AND OXIDATIVE STRESS DEVELOP IN A GENETIC FORM OF ALZHEIMER'S DISEASE

Simona Lanzillotta, Antonella Tramutola, Fabio Di Domenico, Marzia Perluigi, Eugenio Barone
Sapienza University of Rome, Rome, Italy

Aims: Down Syndrome (DS) is a genetic form of Alzheimer's disease (AD) caused by the presence of an extra copy of chromosome 21. A critical feature of DS brain is the elevated oxidative stress (OS) levels, which exacerbate neurodevelopmental processes and contribute to AD-like neurodegeneration. Mitochondria play a crucial role in cellular energy metabolism, and their impairment is one of the major causes of cellular OS. This study aims to investigate the trajectory of mitochondrial proteostasis alterations and their impact during brain development and the onset of AD-like neurodegeneration in DS.
Methods: Mitochondrial Unfolded Protein Response (UPRmt), mitochondrial protein quality control (MQC) markers, OXPHOS chain protein levels, and activity along with OS markers were evaluated in frontal cortex samples from Ts2Cje and euploid mice at P0, 1M, and 6M. In parallel, AD neuropathological hallmarks (Aβ and Tau), as well as cognitive tasks, were assessed. Multiple variable analyses were used to build a model highlighting the link between observed alterations.
Results: Our results show significant alterations in UPRmt markers, particularly at postnatal day 0 (P0) and 1 month (1M). Defects in MQC, including disrupted biogenesis and dynamics, were evident. Impaired UPRmt and MQC correlate with decreased mitochondrial activity and altered OXPHOS complex expression. Elevated OS markers were observed, linking mitochondrial dysfunction to increased oxidative damage. Remarkably, mitochondrial alterations paralleled cognitive dysfunction and preceded the accumulation of AD hallmarks in Ts2Cje mice.
Conclusions: Our findings underscore the critical role of mitochondrial metabolism, showing how its alterations significantly impact the development of AD-like neuropathology in DS brain. These results provide new insights into early alterations driving neurodegeneration, which may also apply to the aging process and AD development in the general population.

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THE THERAPEUTIC POTENTIAL OF GEROPROTECTIVE AGENTS IN RESCUING COGNITIVE DEFICITS IN HUNTINGTON'S DISEASE

Bindu Paul[1], Sunil Jamuna Tripathi[2], Suwarna Chakraborty[2], Edwin Vázquez-Rosa[3], Dunja Petrovic[4], Emilia Kourossis[4], Andrew Pieper[5], Milos Filipovic[4], Solomon Snyder[1]
[1]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, JHMI, The Solomon H. Snyder Department of Neuroscience, JHMI,Lieber Institute for Brain Development, Baltimore, United States of America, [2]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, United States of America, [3]Brain Health Medicines Center, Harrington Discovery Institute, Dept. of Psychiatry, Case Western Reserve University, Geriatric Psychiatry, GRECC, Louis Stokes VA MC, Institute for Transformative Molecular Medicine, School of Medicine, CWRU, Cleveland, United States of America, [4]Leibniz-Institut für Analytische Wissenschaften - ISAS, Dortmund, Germany, [5]Brain Health Medicines Center, Harrington Discovery Inst., Dept. of Psychiatry, Case Western Reserve University, Geriatric Psychiatry, GRECC, Louis Stokes VA MC, Inst. for Transformative Molecular Medicine, CWRU, Dept. Pathology, Dept. Neurosciences, CWRU, Cleveland, United States of America

Aims: Although Huntington's disease is considered to predominantly affect motor functions, cognitive dysfunction is also an important facet of the disease. In this study, we have investigated the effect of the gaseous signaling molecule, hydrogen sulfide, on cognitive functions and neuroprotective processes in Huntington's disease.
Methods: Using cell culture (striatal progenitor cell lines) and mouse models of HD, including R6/2 and zQ175, and using sulfhydration, a post-translational modification mediated by hydrogen sulfide donors, as a readout, we identify signaling pathways that are derailed in HD and which are corrected by hydrogen sulfide donors and boosters such as sodium hydrogen sulfide (NaHS) and monensin, A Golgi stressor. We utilized the dimedone-switch assay, which specifically detects sulfhydration (conversion of the -SH group of cysteine residues to –SSH or persulfide group) to detect differential sulfhydration in HD.
Results: We have identified irreversible cysteine oxidation and diminished sulfhydration leading to protein aggregation as a pathogenic event in HD. We also report that the integrated stress response pathway central to amino acid homeostasis, Golgi stress response and heme metabolism are disrupted in HD. Restoring H_2S metabolism prevents these abnormalities and prevents both motor and cognitive decline in mouse models of HD.
Conclusions: Our results are also relevant to other neurodegenerative conditions involving disrupted sulfhydration, such as Alzheimer's and Parkinson's disease. Accordingly, agents that restore sulfhydration balance may confer therapeutic benefits.

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IN VIVO CRISPR/CAS9 SCREEN IDENTIFY TNFA-NFKB-P53 AXIS THAT RESTRICTS HUMAN PSC-DERIVED DOPAMINE NEURON SURVIVAL IN GRAFT

Tae Wan Kim[1], So Yeon Koo[2], Lorenz Studer[3]
[1]DGIST, Department Of Interdiciplanary Engineering, Daegu, Korea, Republic of, [2]Sloan-Kettering Institute for Cancer Research, The Center For Stem Cell Biology,, New York, United States of America, [3]Memorial sloan kettering cancer center, Center For Stem Cell Biology; Developmental Biology Program,, New York city, United States of America

Aims: Ongoing, first-in-human clinical trials illustrate the translational potential of human pluripotent stem cell (hPSC)-based cell therapies in Parkinson's disease (PD). However, an unresolved challenge is the extensive cell death following transplantation and the need for developing the elimination of potential off-target cell types in long-term grafts. We aim to define factor(s) that restrict the *in vivo* survival of human PSC-derived postmitotic dopamine neurons following transplantation.
Methods: We performed an *in vivo* pooled CRISPR/Cas9 screen to identify mechanisms of dopamine neuron death upon transplantation. As a translationally relevant strategy to purify postmitotic dopamine neurons, we performed a cell surface marker screen that enables purification without genetic reporters.
Results: We identified p53-mediated apoptotic cell death as a major contributor to dopamine neuron loss and uncovered a causal link of TNFa-NFκB signaling in limiting cell survival. Additionally, we defined cell surface markers to purify postmitotic dopamine neurons. Combining cell sorting and treatment with adalimumab, a clinically approved TNFa inhibitor, enabled efficient engraftment of postmitotic dopamine neurons with extensive re-innervation and functional recovery in a preclinical PD mouse model.
Conclusions: Our work addresses the mechanism underlying postmitotic dopamine neuron death at grafting and establishes a strategy for enhancing dopamine neuron survival that should be applicable to PD cell-based therapies.

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A STEROID SULFATASE INHIBITOR, ONESTX-01, AS A NOVEL TREATMENT FOR NEURODEGENERATIVE DISEASES: EFFECT IN PROGRESSION IN HUNTINGTON DISEASE MODELS

Juan Fernández-Cabrera[1,2], Elena Rodríguez-Sandoval[2], Almudena Ramos-Pozo[3], Mercedes Pérez-Jiménez[3], Javier Valle-Galisteo[2,3], Cristina García-Gutiérrez[3], Antonio Aires[2,4], Sandra Gavaldá[2], Viñas Andrés-Simón[2], Ángel Cebolla-Ramírez[2], Manuel Muñoz-Ruiz[3], Ángel Carrión-Rodríguez[1]
[1]University Pablo de Olavide, Physiology, Anatomy And Cellular Biology, Sevilla, Spain, [2]Olavide Neuron STX SL, Onestx, Sevilla, Spain, [3]University Pablo de Olavide, CABD, CSIC, JA, Sevilla, Spain, [4]Biomedal SL, Sevilla, Spain

Aims: ONESTX-01 (formerly Irosustat) is a small molecule that blocks steroid sulfatase (STS), increasing the ratio of sulfated to free steroids in both animals and humans. This compound has demonstrated good safety and tolerability in numerous Phase I and II cancer trials. Additionally, ONESTX-01 extends the lifespan of model organisms and alleviates symptoms in neurodegenerative disease models by improving cognitive impairment. It also seems to improve other hallmarks of agings that appear exacerbated in neurodegenerative diseases such as reduced adult neurogenesis and neuroinflammation, indicating a broad action of certain sulfated steroids. In a C. elegans Huntington Disease (HD) model, ONESTX-01 diminished protein aggregates linked to HD. In this study, we explored the effects of oral ONESTX-01 on motor and cognitive decline associated with aging in the R6/1 mouse model of HD.
Methods: The R6/1 HD mice model (twelve-week-old) was subjected to continuous oral administration of ONESTX-01 to observe its effects on the age-related progression of motor and cognitive symptoms associated with HD. The disease progression was monitored using rotarod and object recognition memory tests. Analysis of biomarkers of the ONESTX-01 activity was also performed as the steroid profile in treated and untreated animals.
Results: During the treatment time, the R6/1 mice could show significant cognitive recovery, and a moderate improvement in motor coordination. Histological and biochemical changes in the treated and untreated mice will be showed in the meeting.
Conclusions: Preliminary data suggest ONESTX-1 treatment could be a new approach to reversing or alleviating key symptoms in HD patients. The beneficial effect of ONESTX-01 in proteinopathies may be conserved accross evolutionary distant animal models.

Virtual OO - 143

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DUAL DECLINE IN COGNITION AND GAIT SPEED: ASSOCIATIONS WITH MYELINATION

Zhaoyuan Gong, Jonghyun Bae, Noam Fox, Nathan Zhang, Alex Guo, John Laporte, Luigi Ferrucci, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

Aims: Gait speed and cognitive processing speed are essential indicators of aging, with declines linked to adverse outcomes. Dual decline, where both functions deteriorate simultaneously, is a strong predictor of morbidity and mortality. However, its relationship with white matter integrity, especially myelination as measured by myelin water fraction (MWF), has not been established. This study investigates the association between dual decline and myelin content in aging individuals.
Methods: 137 cognitively unimpaired participants underwent MRI to quantify MWF. Cognitive and gait assessments were conducted at visits before and concurrent with MRI scans, measuring processing speed (445 visits) and usual gait speed (437 visits) (Figure 1). Linear mixed-effects models with random slopes and intercepts estimated the rate of decline for each subject. Participants were categorized into non-decliners, single decliners, and dual decliners. We conducted Wilcoxon Rank Sum tests to compare MWF among these groups and performed multiple linear regression to assess the association between regional MWF and decline type, adjusting for age at MRI, age × type, age^2, age^2 × type, and sex.

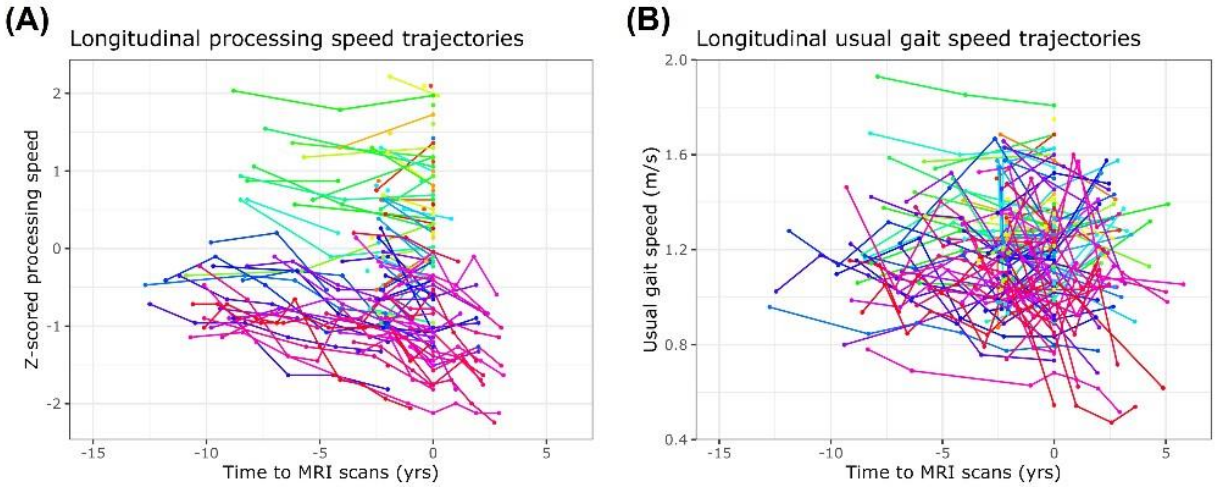

Figure 1. Panel A displays the longitudinal trajectory of processing speed for individual subjects. Panel B illustrates the longitudinal trajectory of the usual gait speed for individual subjects. The rate of decline for each subject was estimated using linear mixed-effects models with both random slopes and intercepts. The individual rate of decline reflects the sum of both the fixed effects and the random effects.

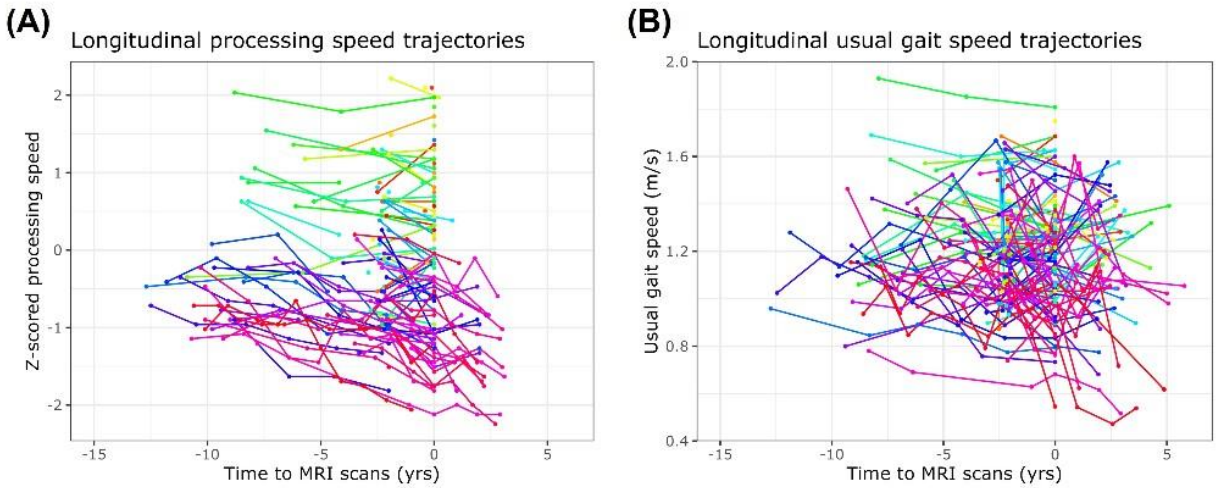

Figure 1. Panel A displays the longitudinal trajectory of processing speed for individual subjects. Panel B illustrates the longitudinal trajectory of the usual gait speed for individual subjects. The rate of decline for each subject was estimated using linear mixed-effects models with both random slopes and intercepts. The individual rate of decline reflects the sum of both the fixed effects and the random effects.

Results: Figure 2A illustrates the categorization into decline types, with significant differences in MWF observed across groups (Figure 2B). Table 1 summarizes the regression results, showing that both single and dual decliners are significantly associated with lower MWF values, with dual decliners exhibiting stronger associations in most regions except the occipital lobe.

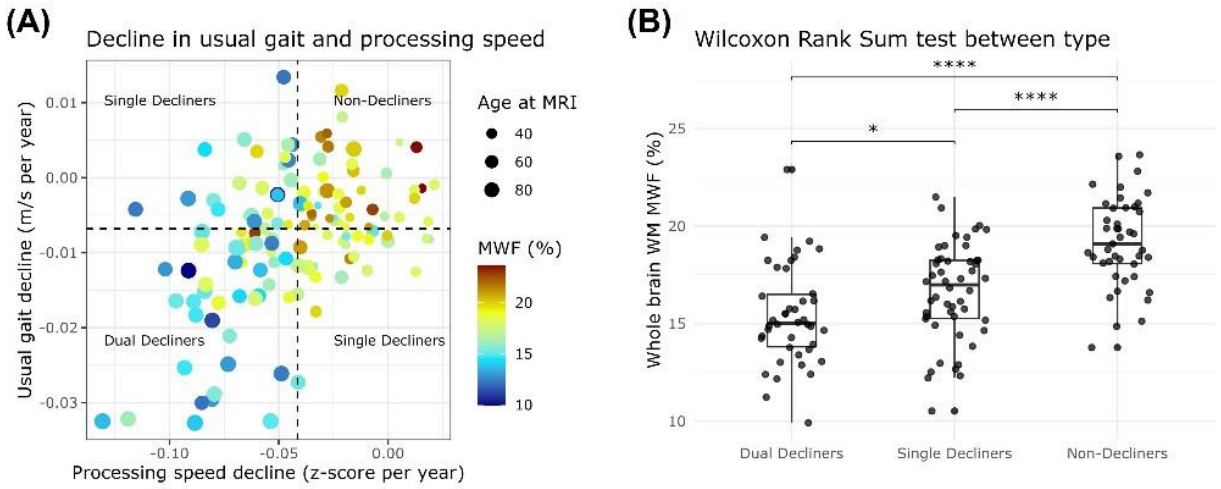

Figure 2. Panel A shows the distribution of subjects based on their annual rates of decline in processing speed (X-axis) and usual gait speed (Y-axis). Contrary to previously reported cut-off points of decline in gait speed (e.g., 0.05 m/s), our healthy aging cohort is categorized into four quadrants based on median values of the decline rates. These quadrants are labeled as dual decliners, single decliners, and non-decliners. We categorize those four quadrants as dual decliners, single decliners and non-decliners. Whole brain white matter myelin water fraction (WM MWF) is indicated by color, and age at MRI by point size. Panel B displays the results of a Wilcoxon Rank Sum test, showing significant differences in MWF across the three types. * indicates p-value < 0.05, and **** indicates p-value < 0.0001.

ROI \ Type	Single Decliner		Dual Decliner	
	Estimate	P-value	Estimate	P-value
Whole Brain WM	-2.71E-02	1.31E-03	-3.21E-02	4.55E-04
Frontal lobe WM	-2.42E-02	5.75E-03	-3.19E-02	8.29E-04
Temporal lobe WM	-3.18E-02	8.62E-04	-3.30E-02	1.35E-03
Occipital lobe WM	-3.42E-02	8.02E-04	-3.16E-02	3.92E-03
Parietal lobe WM	-2.82E-02	1.62E-03	-3.16E-02	1.10E-03
Cerebellum WM	-2.51E-02	5.01E-03	-2.78E-02	4.10E-03

Table 1. Linear regression results for different ROI MWF values indicate that both single decliners and dual decliners are significantly associated with lower MWF values. The association is stronger in dual decliners across all ROIs except for the occipital lobe.

Conclusions: Dual decline in processing speed and gait speed is linked to reduced white matter integrity, suggesting higher susceptibility to myelin damage which could lead to subsequent neurodegeneration.

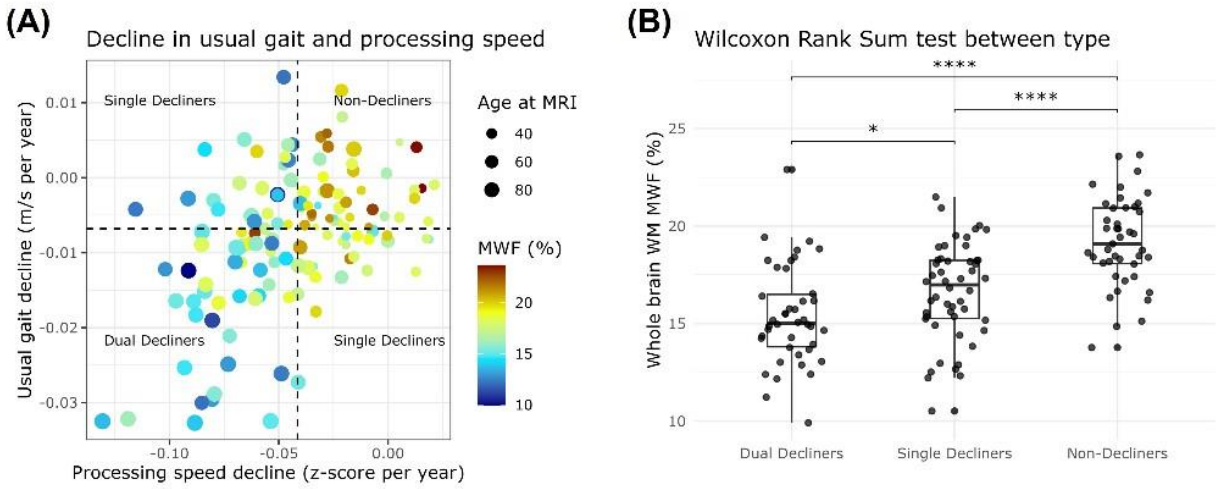

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Table 1. Linear regression results for different ROI MWF values indicate that both single decliners and dual decliners are significantly associated with lower MWF values. The association is stronger in dual decliners across all ROIs except for the occipital lobe.

Conclusions: Dual decline in processing speed and gait speed is linked to reduced white matter integrity, suggesting higher susceptibility to myelin damage which could lead to subsequent neurodegeneration.

These findings highlight the need to monitor both cognitive and physical declines to identify aging individuals at higher risk for brain microstructural changes.

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NEURONAL BRAIN IRON ACCUMULATION IN A SOUTH INDIAN COHORT-CLINICO-RADIOLOGICAL AND GENETIC CORRELATIONS

Divya Kalikavil Puthanveedu[1], Ajith Cherian[2]
[1]SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, Neurology, Thiruvananthapuram, India, [2]SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, Thiruvananthapuram, India

Aims: To investigate the clinical features, magnetic resonance imaging (MRI) findings, and genetic mutations in patients diagnosed with Neurodegeneration with brain iron accumulation (NBIA) and to establish genotype-phenotype correlations within this cohort.
Methods: Eighteen patients from a single center in South India were included, who had extra pyramidal features, spasticity, seizures and neuropsychiatric abnormalities in varying combinations. All patients exhibited MRI evidence of iron deposition.A range of ancillary tests were performed, including serum ceruloplasmin, ferritin levels, hormonal profiles, and neuropsychological assessments.Targeted gene sequencing was conducted for the ten known NBIA-related genes.
Results: The cohort consisted of 11 males(mean age 23.94 [range-2-63]). Seven patients were born to consanguineous parents, and 5 had a family history of similar disorders.Initial symptom was dystonia in 13,while parkinsonism was the first symptom in 3, chorea in 1,and ataxia in 1.Over the course of the disease,16 developed dystonia,8 exhibited parkinsonism,and other symptoms included ataxia,myoclonus,chorea,hand stereotypies. Oculomotor abnormalities were the most prevalent associated features (11-slow saccades,2-apraxia of eyelid opening).Neuropsychiatric symptoms was seen in 4, pyramidal signs in 3, optic disc pallor in 2, seizures in 2, and retinal pigmentary degeneration in 1. MRI showed iron deposition in the globus pallidus for all patients, with 9 showing blooming in the substantia nigra and 3 displaying combined involvement of the red nucleus, dentate nucleus, and striatum.Two patients exhibited the classic "eye of the tiger" sign,while 3 had bilateral white matter hyperintensities. Genetic analysis revealed mutations in *PANK2* (2 patients),*PLA2G6* (2),*WDR45* (1),*FA2H* (1),*ATP13A2* (1),*DCAF17* (2),and ceruloplasmin (1). Nine patients tested negative for known mutations,but clinical exome sequencing identified mutations in *KMT2B*, *XPR2*, and *SNCB* in three individuals.
Conclusions: This case series expands the genetic spectrum of NBIA and provides valuable insights into genotype-phenotype correlations.

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COMPREHENSIVE ASSESSMENT OF AUTONOMIC DYSFUNCTION IN PARKINSON'S DISEASE

Yogesh Kumar[1], Gunjan Kumar[2]
[1]AIIMS PATNA, PATNA, India, [2]PMCH Patna, Neurology, Patna, India

Aims: To comprehensively assess autonomic dysfunction in Parkinson's Disease (PD) patients, focusing on sudomotor, cardiovagal, and adrenergic functions, and to investigate the correlation between autonomic dysfunction and disease severity, as well as the effects of dopaminergic medication on autonomic function.
Methods: Sixty PD patients and thirty age- and sex-matched healthy controls underwent autonomic function tests including deep breathing, Valsalva maneuver, and head-up tilt test. Heart rate variability (HRV), baroreflex sensitivity (BRS), and blood pressure changes were analyzed. PD patients were assessed in both ON and OFF medication states.
Results: PD patients showed significant impairment in all autonomic parameters compared to controls ($p<0.001$). HRV negatively correlated with UPDRS III scores ($r=-0.52$, $p<0.001$), and BRS negatively correlated with Hoehn and Yahr stage ($r=-0.48$, $p<0.001$). Systolic blood pressure drop on tilt positively correlated with disease duration ($r=0.43$, $p<0.001$). Dopaminergic medication showed modest improvement in HRV ($p=0.032$) and BRS ($p=0.041$) in the ON state compared to the OFF state.
Conclusions: This study demonstrates significant and widespread autonomic dysfunction in PD, correlating with disease severity. The modest effect of dopaminergic medication on autonomic function suggests a complex interplay between dopaminergic systems and autonomic regulation. These findings emphasize the importance of comprehensive autonomic assessment in PD and suggest autonomic parameters as potential markers of disease progression.

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PARKINSON'S DISEASE: CAN WE SAVE MONEY THANKS TO EARLY DETECTION TOOLS BASED ON AI?

Dimitri Scronias[1], Jacopo Lot[2], Berengère Davin[1], Octave Guinebretiere[3], Thomas Nedelec[3], Bruno Ventelou[2]
[1]ORS PACA, Marseille, France, [2]AMU, Aix-marseille School Of Economics, Marseille, France, [3]Paris Brain Institute, Icm, Paris, France

Aims: To study the amount of medical expenses potentially saved by the French National Healthcare Insurance (NHI) by adopting early detection test of Parkinson disease (PD) using an Artificial Intelligence tool in an outpatient setting.
Methods: We built a cohort of 26,274 patients over 50 newly diagnosed with PD in 2016 using French medical administrative data. Using dynamic microsimulation Markovian modeling, we simulated the long-term evolution of PD severity on our PD cohort, and its costs to NHI, until 2080 (scenario S0). We also evaluate how these would behave under the hypothesis of earlier detection and slower evolution of the disease due to early diagnosis (scenario S1).
Results: Compared to non-PD individuals, PD patients incur average per year extra costs of 4,092€ for mild patients or 10,793€ for severe patients. A male patient with PD, diagnosed in his fifties, will cost on average 103,289€ to the NHI over their lifetime (S0). Supposing an early detection that leads to decreased probabilities of moving to severe stages of PD (S1), a male patient can expect to live 1.75 year longer, and will cost on average 8,690€ more than without the early detection at the end of his lifetime (sum not discounted). This valuation of 8,690€ is the result of two opposite effects: lower costs occur through slower transition to advanced stages of PD, but higher costs are incurred through earlier detection and decrease in mortality.
Conclusions: Early detection of PD using AI may lead to higher spending by the NHI over the lifetime of patients. Nevertheless, this finding must be counterbalanced by higher quality of life, decreases in mortality and potential gains in productivity offered by early treatment of PD.

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BIOMARKERS OF STRUCTURAL DEGENERATION OF THE LOCUS COERULEUS ARE ASSOCIATED WITH MORE RAPID AGE-RELATED COGNITIVE DECLINE

Jonghyun Bae, Zhaoyuan Gong, Caio Mazucanti, Murat Bilgel, John Laporte, Mary Faulkner, Josephine Egan, Susan Resnick, Christopher Ramsden, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

Aims: The locus coeruleus (LC) is a critical brain region linked to neurodegenerative disease, such as Alzheimer's disease. Previous studies identified the LC as the initial site of tau accumulation in the early stages of disease progression. While monitoring the structural changes in the LC may provide more insights on disease progression and pathophysiology, current studies are limited to less quantitative methods. In this study, we aim to investigate the association of quantitative MRI (qMRI) biomarkers, reflecting microstructural changes of the LC, with cognitive decline.
Methods: Our final study cohort included 115 individuals between 22 to 94 years of age. Each participants underwent our BMC-mcDESPOT imaging protocol to measure qMRI biomarkers, namely relaxation rates (R_1, R_2) and myelin water fraction (MWF), to probe changes in microstructural integrity and myelination level of the LC. We investigated both age-related changes of qMRI biomarkers in the LC as well as its association with cross-sectional and longitudinal changes in cognitive performance obtained retrospectively over several years.
Results: We found a significant negative age-related decline in LC myelin content and microstructural integrity (Fig. 1). Our cross-sectional analysis revealed significant correlations between lower relaxation rates and myelin content and lower in memory and verbal fluency (Fig. 2). Furthermore, our longitudinal analysis results suggest that these MRI biomarkers are significantly associated with steeper longitudinal changes in multiple cognitive domains, such as memory, verbal fluency, processing speed and executive function (Fig.

Figure 1

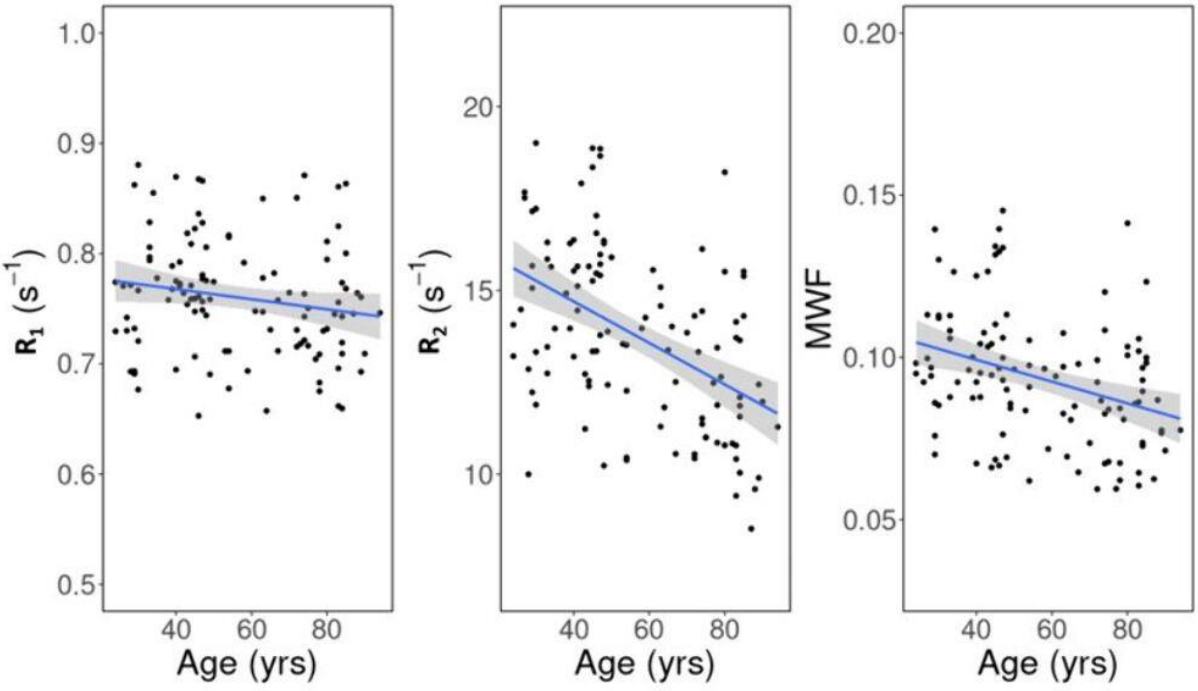

Figure 1. Age-related associations of locus coeruleus quantitative MRI metrics, adjusted for sex, race, and years of education. Significant negative correlations were found between age and both R_2 and MWF.

3).

Figure 2

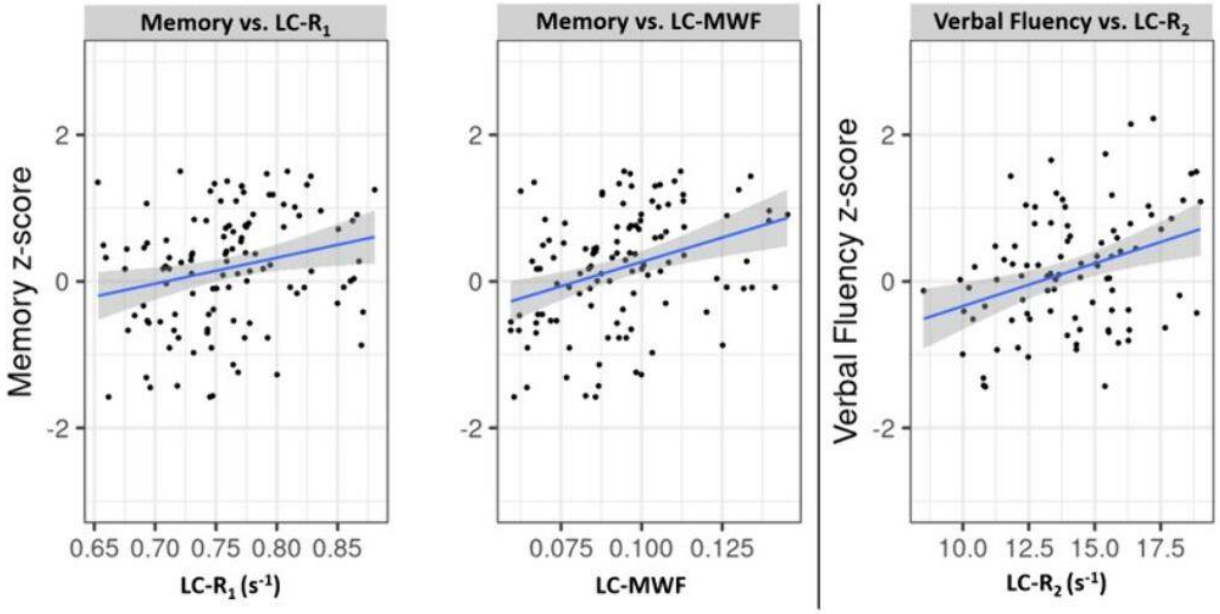

Figure 2. Correlation plots demonstrating the relationships between qMRI metrics of the locus coeruleus and z-scored cognitive assessments from the cross-sectional analysis. We found strong positive associations between R_1 and memory, MWF and memory, and R_2 and verbal fluency. These findings suggest that qMRI metrics are linked to specific cognitive domains.

Figure 3

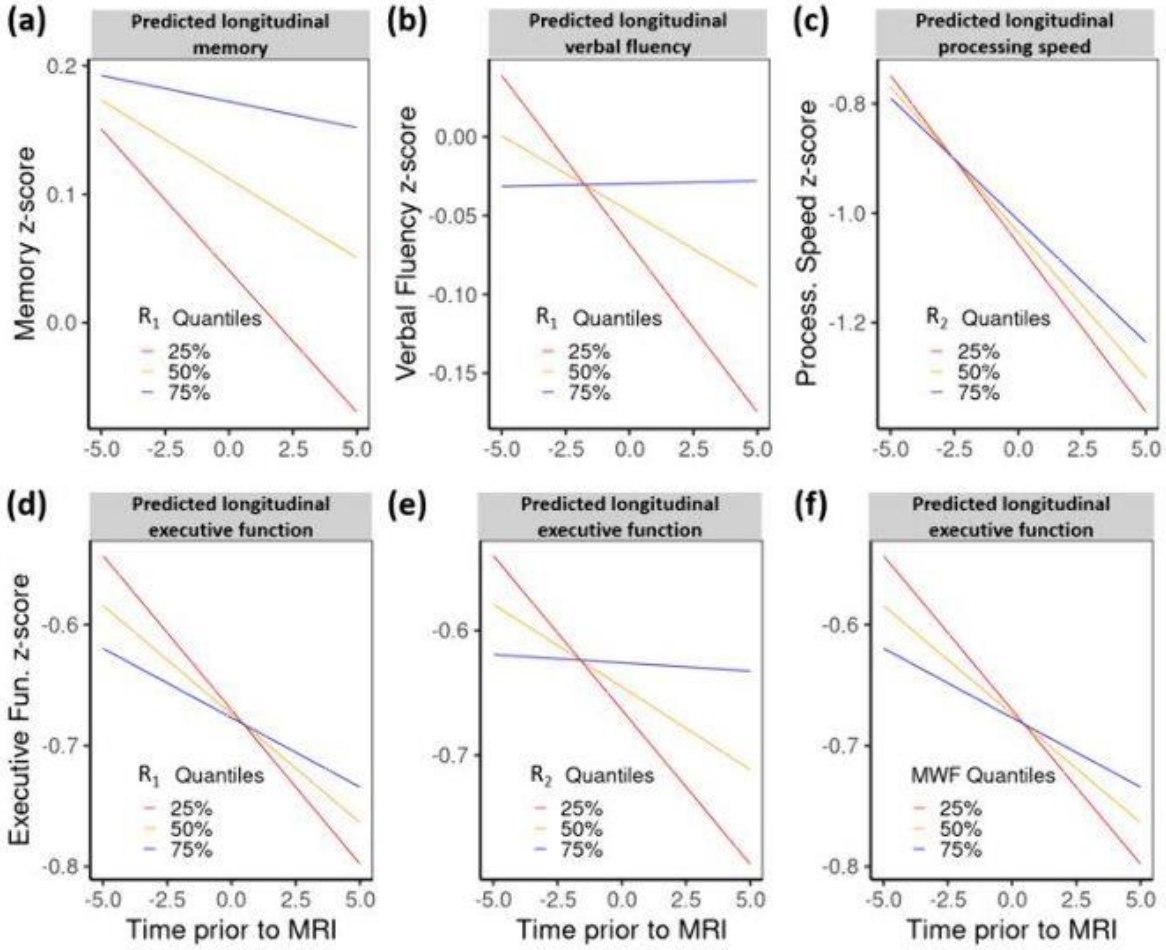

Figure 3. Predicted longitudinal cognitive trajectories estimated from linear mixed-effects regression models at different quantiles of Locus Coeruleus quantitative MRI (qMRI) metrics (red, orange, and blue lines represent the 25th, 50th, and 75th percentiles, respectively). The results show significant differences in the rate of cognitive decline across various domains, including (a) memory, (b) verbal fluency, and (d) executive function, for R_1. Additionally, R_2 showed significant associations with longitudinal changes in (c) processing speed and (e) executive function, while MWF showed significant associations with longitudinal changes in executive function (f). These findings suggest that individual differences in qMRI metrics are linked to distinct patterns of cognitive aging.

Figure 1

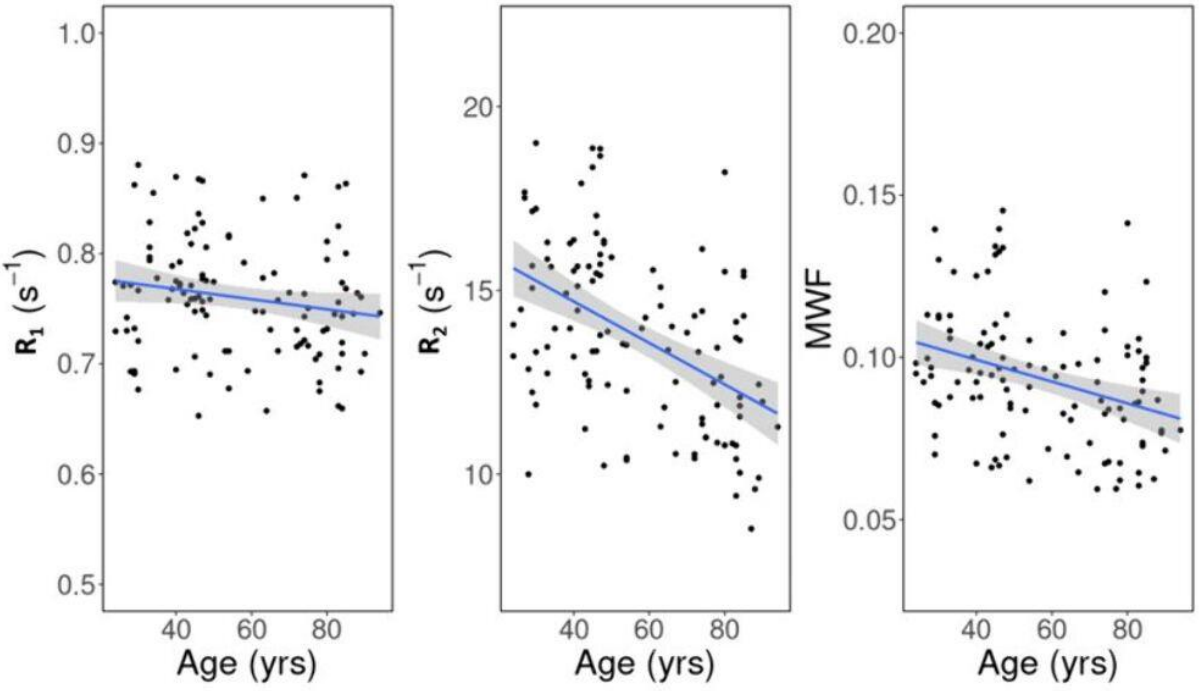

Figure 1. Age-related associations of locus coeruleus quantitative MRI metrics, adjusted for sex, race, and years of education. Significant negative correlations were found between age and both R_2 and MWF.

Figure 2

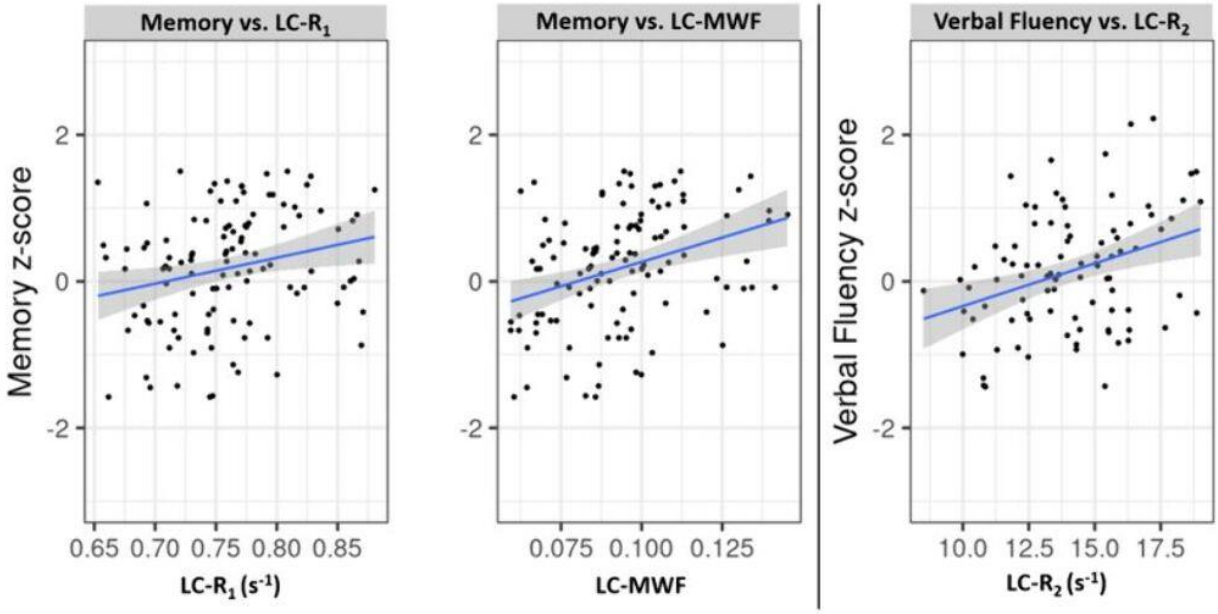

Figure 2. Correlation plots demonstrating the relationships between qMRI metrics of the locus coeruleus and z-scored cognitive assessments from the cross-sectional analysis. We found strong positive associations between R_1 and memory, MWF and memory, and R_2 and verbal fluency. These findings suggest that qMRI metrics are linked to specific cognitive domains.

Figure 3

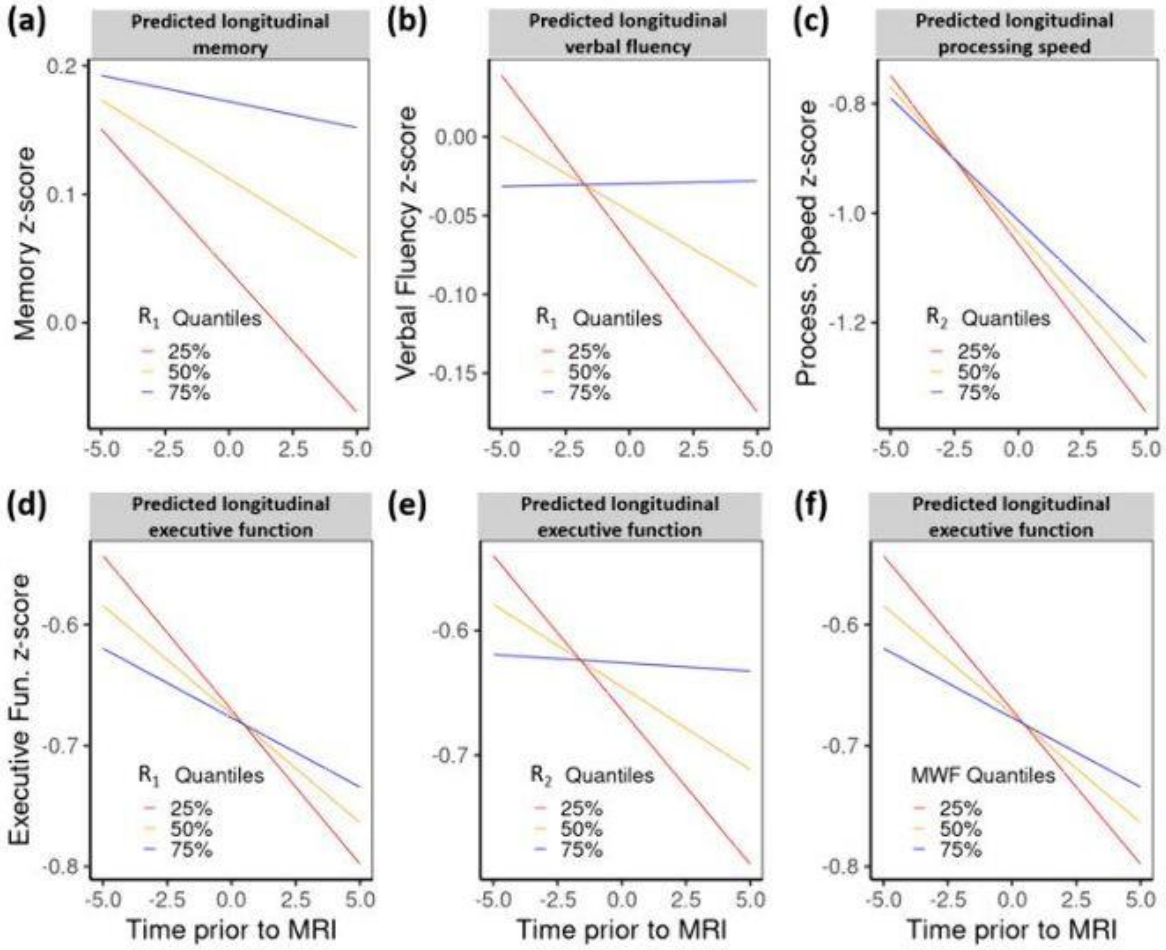

Figure 3. Predicted longitudinal cognitive trajectories estimated from linear mixed-effects regression models at different quantiles of Locus Coeruleus quantitative MRI (qMRI) metrics (red, orange, and blue lines represent the 25th, 50th, and 75th percentiles, respectively). The results show significant differences in the rate of cognitive decline across various domains, including (a) memory, (b) verbal fluency, and (d) executive function, for R_1. Additionally, R_2 showed significant associations with longitudinal changes in (c) processing speed and (e) executive function, while MWF showed significant associations with longitudinal changes in executive function (f). These findings suggest that individual differences in qMRI metrics are linked to distinct patterns of cognitive aging.

Conclusions: Results from our study suggest that structural degeneration of the LC is associated with lower cognitive scores cross-sectionally and further predicts more pronounced cognitive decline longitudinally. These *in-vivo* qMRI biomarkers provide quantitative biomarkers for LC structure, that can serve as potential biomarkers for monitoring neurodegeneration processes.

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TARGETED SPATIAL TRANSCRIPTOMICS FOR THE VALIDATION OF MYELIN WATER FRACTION IMAGING USING BMC-MCDESPOT

Jonghyun Bae[1], Zhaoyuan Gong[1], Alex Guo[1], Noam Fox[2], Nathan Zhang[1], John Laporte[1], Mustapha Bouhrara[1]
[1]National Institute on Aging, Baltimore, United States of America, [2]National Institutes of Health, National Institute On Aging, Baltimore, United States of America

Aims: Demyelination has been identified as a cardinal feature of aging and has been linked to cognitive decline. While myelin water fraction (MWF) imaging facilitates assessing myelin integrity and changes with aging, validating the specificity of this neuroimaging markers remains challenging. Therefore, in this study, we aim to use transcriptomics to investigate the correlation between myelin basic protein gene expression and imaging-derived MWF measurements.
Methods: MWF Imaging: We selected longitudinal studies (BLSA and GESTALT) with participants under 60 to exclude aging effects on myelination. The cohort included 77 cognitively unimpaired individuals (ages 22-59; M/F=42/35). MWF maps were generated using the BMC-mcDESPOT protocol and registered to the MNI template. Mean MWF values from various white matter and deep gray matter regions were extracted using the JHU atlas. Transcriptomics: Microarray data from the Allen Human Brain Atlas included gene expression from six healthy adults. Probes for the myelin basic protein (MBP) gene were identified, normalized, and aggregated across subjects. Gene expression was mapped to MNI coordinates for different ROIs, and correlations with MWF values were analyzed to explore their relationship.
Results: Figure 1(a) displays high-resolution MWF maps and corresponding MWF values for various brain ROIs (Figure 1(b)), highlighting higher myelination levels in white matter compared to subcortical gray matter. Figure 2(a) illustrates the spatial gene expression of MBP, with sample quantification in Figure 2(b). Lastly, Figure 3 demonstrates a strong and significant positive correlation between MBP gene expression and MWF measurements.

Figure 1

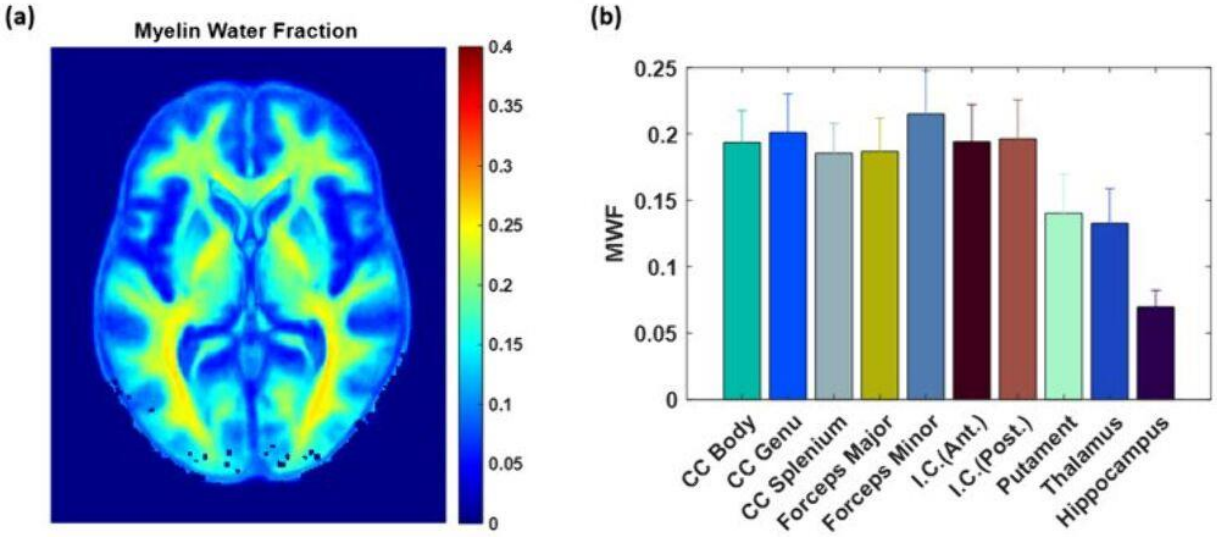

Figure1. (a) The averaged myelin water fraction (MWF) maps from our study participants (n=77, age=22-59, M/F=42/35) (b) The mean and standard deviation of MWF values at different brain regions. Note that subcortical gray matter region (i.e. putamen, thalamus and hippocampus) exhibit much lower levels of myelination compared to heavily myelinated white matter tracts (corpus callosum (CC), Internal Capsule (I.C.), Forceps major/minor).

Figure 2

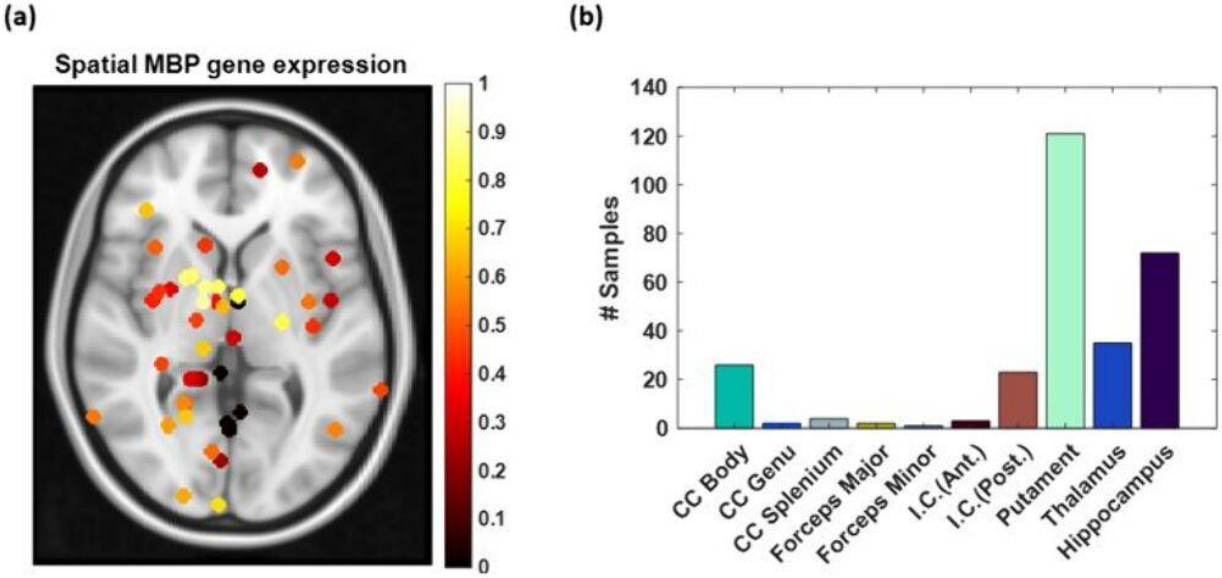

Figure 2. (a) Spatial representation of gene expression of myelin basic protein from Allen Human Brain Atlas microarray dataset. (b) Quantification of number of total samples obtained at different regions of the brain, including several white matter tracts and subcortical gray matter.

Figure 3

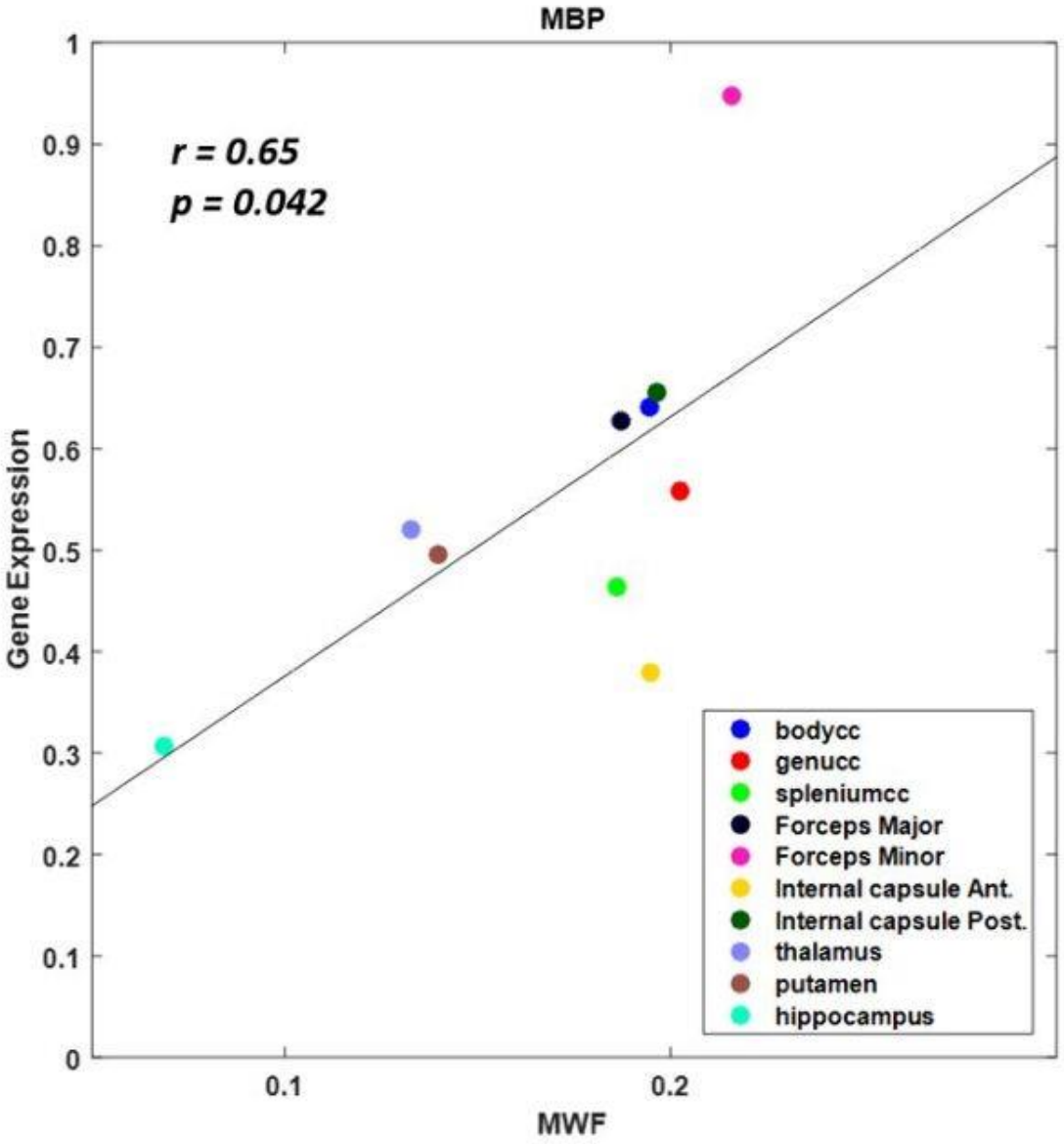

Figure 3. A correlation plot between the gene expression for myelin basic protein and measured myelin water fraction (MWF) values at different brain regions. We found a strong and significant positive correlation between these measures, suggesting high specificity of MWF.

Figure 1

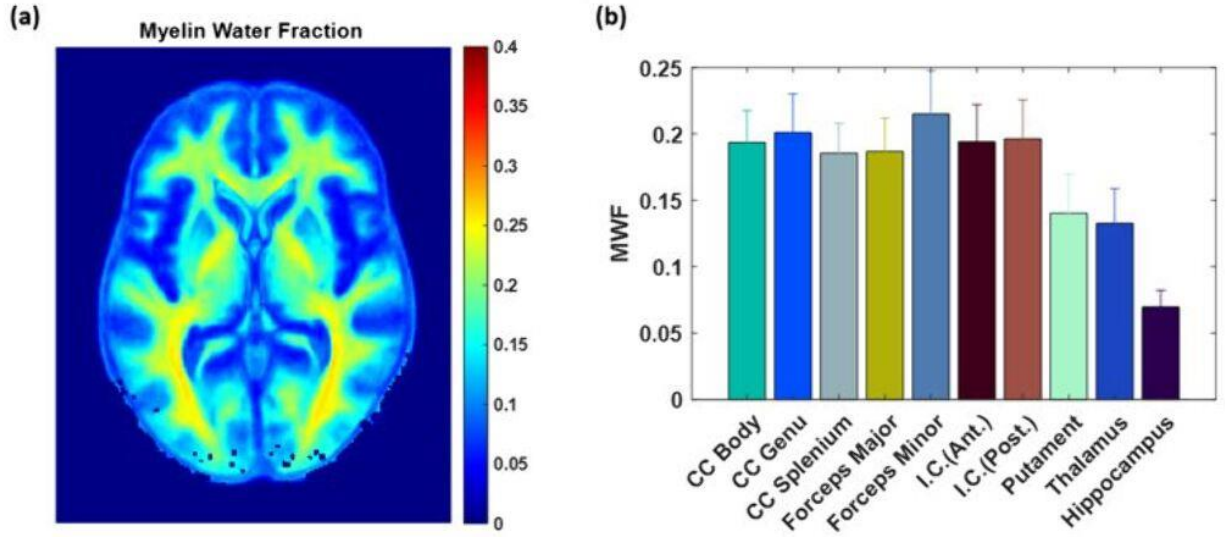

Figure1. (a) The averaged myelin water fraction (MWF) maps from our study participants (n=77, age=22-59, M/F=42/35) (b) The mean and standard deviation of MWF values at different brain regions. Note that subcortical gray matter region (i.e. putamen, thalamus and hippocampus) exhibit much lower levels of myelination compared to heavily myelinated white matter tracts (corpus callosum (CC), Internal Capsule (I.C.), Forceps major/minor).

Figure 2

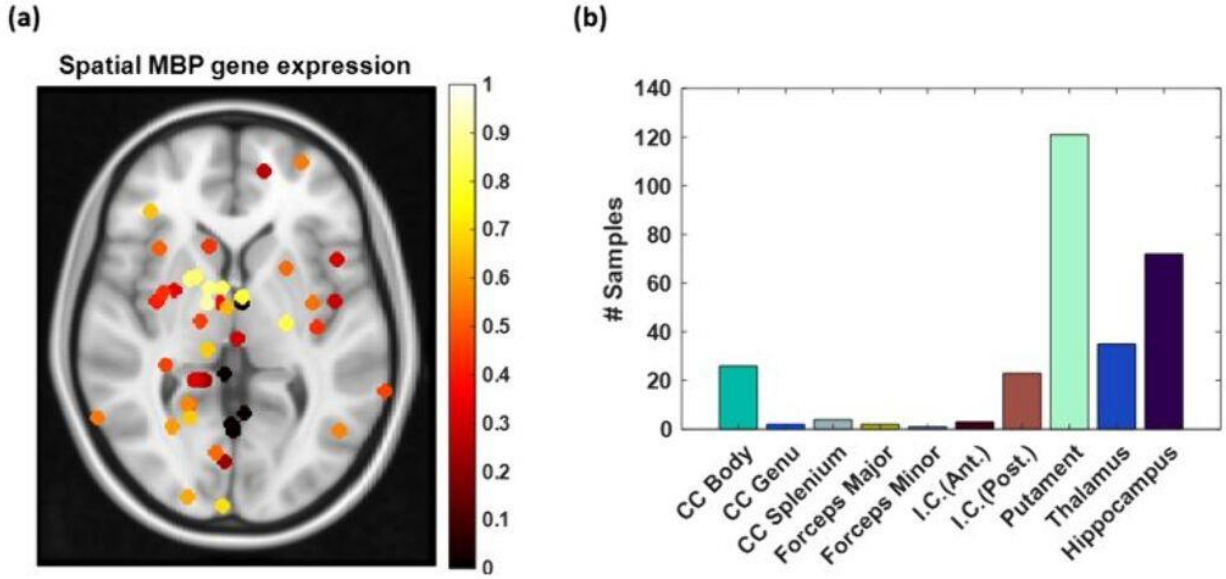

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Figure 3

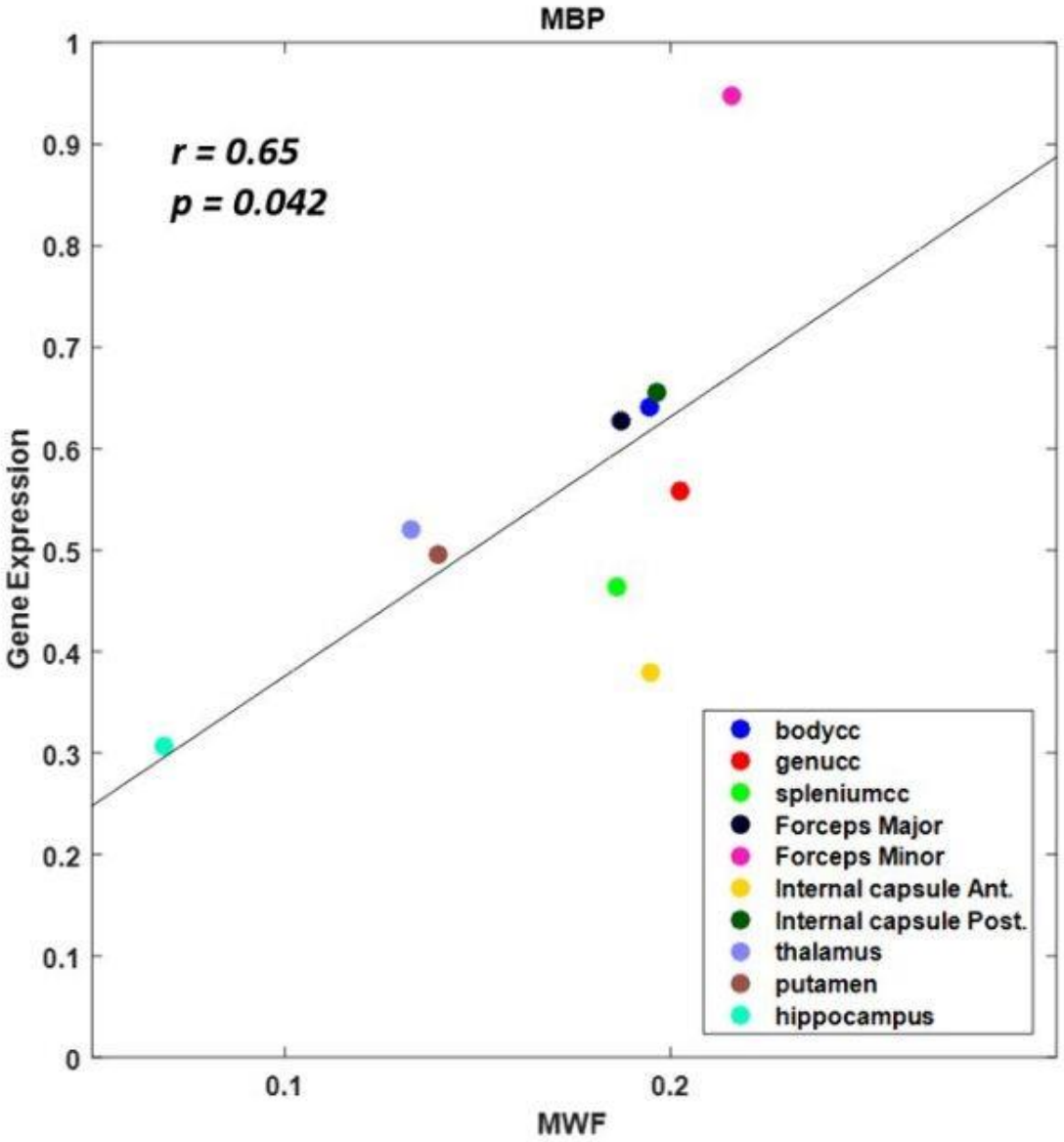

Figure 3. A correlation plot between the gene expression for myelin basic protein and measured myelin water fraction (MWF) values at different brain regions. We found a strong and significant positive correlation between these measures, suggesting high specificity of MWF.

Conclusions: Our results suggest that MWF measures derived using BMC-mcDESPOT correlates strongly with the genes associated with myelin basic protein, providing an innovative approach to validate the specificity of our neuroimaging marker.

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SLEEP QUALITY IS ASSOCIATED WITH CEREBRAL MYELIN IN FEMALES

Noam Fox, Zhaoyuan Gong, Jonghyun Bae, Nathan Zhang, John Laporte, Alex Guo, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

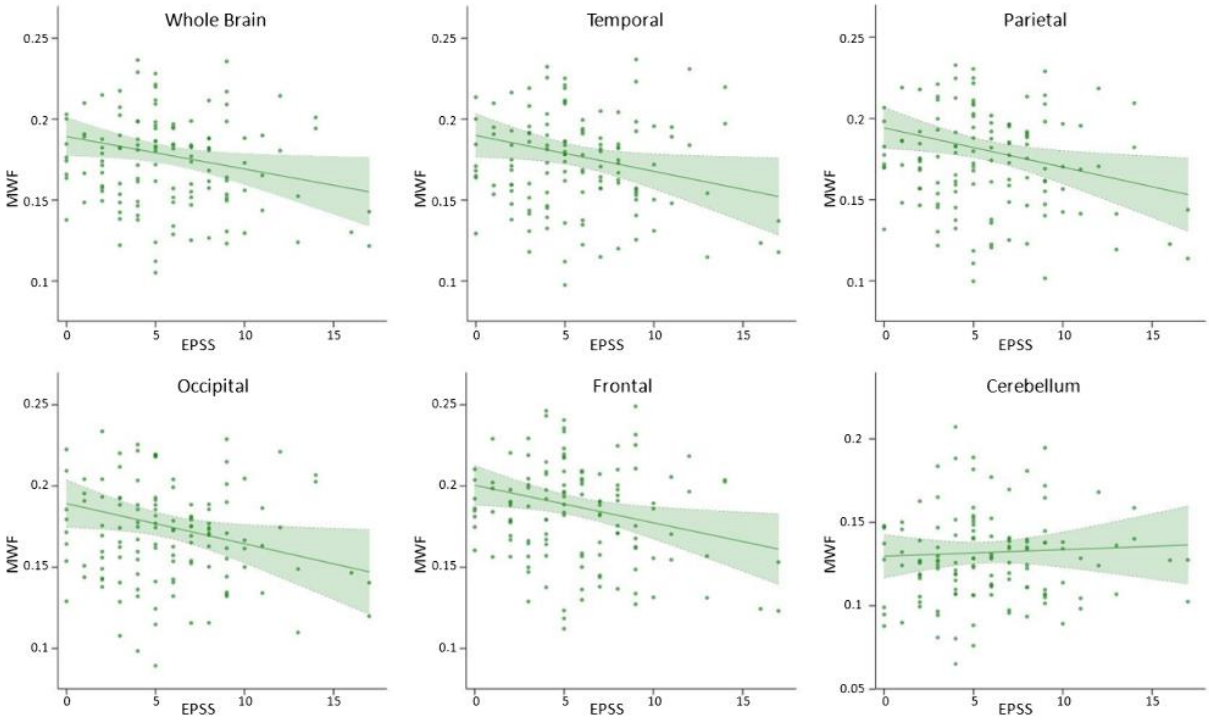
Aims: Poor sleep quality and chronic short sleep are linked to a myriad of emotional and cognitive issues, including impaired vigilance, impulsivity, and increased risk of neurological conditions such as Alzheimer's Disease (AD). Previous research has connected poor sleep and white matter (WM) microstructure deterioration, a hallmark of aging and neurodegenerative disorders. While studies have attempted to explore the relationship between sleep and WM myelin, they have relied on nonspecific measures of myelin. We investigated the relationship between sleep and myelin using myelin water fraction (MWF), a specific MRI marker of myelin content. Sex differences in this relationship were also explored.
Methods: 127 cognitively unimpaired participants from the BLSA and GESTALT cohorts underwent the BMC-mcDESPOT MRI protocol. We analyzed regional MWF values in relation to Epworth Sleepiness Scale (EPSS) scores using linear regression, accounting for age, age^2, and sex as relevant covariates. An interaction term between EPSS and sex was also included to explore sex differences. Continuous variables were z-scored.
Results: We found negative correlations between EPSS and MWF (Fig.1). This association was significant in all brain structures investigated except cerebellum (Table 1). Interestingly, this association was significant for females but not for males (Fig.2).

Table 1 Slope, θ, and significance, p, of the regression terms incorporated in the multiple linear regression given by: $MWF \sim \theta_0 + \theta_{age} \times age + \theta_{age^2} \times age^2 + \theta_{sex} \times sex + \theta_{EPSS} \times EPSS + \theta_{EPSS\ x\ sex} \times (EPSS \times sex)$.

β-coefficient (p-value)	Age	Age²	Sex	EPSS	EPSS x Sex
Whole Brain	-0.517 (p < 0.0001) *	-0.225 (0.0118) *	-0.326 (0.0198)	-0.261 (0.0305) *	0.327 (0.0266) *
Temporal	-0.444 (p < 0.0001) *	-0.228 (0.0163) *	-0.314 (0.0351)	-0.274 (0.0327) *	0.391 (0.0129) *
Parietal	-0.516 (p < 0.0001) *	-0.201 (0.0220) *	-0.443 (0.00147) *	-0.291 (0.0144) *	0.354 (0.0149) *
Occipital	-0.326 (0.000126) *	-0.219 (0.0317) *	-0.318 (0.0468)	-0.299 (0.0301) *	0.401 (0.0176) *
Frontal	-0.564 (p < 0.0001) *	-0.248 (0.00321) *	-0.280 (0.0328)	-0.275 (0.015) *	0.304 (0.0278) *
Cerebellum	-0.382 (p < 0.0001) *	-0.100 (0.310)	-0.259 (0.117)	0.0552 (0.697)	0.0748 (0.666)

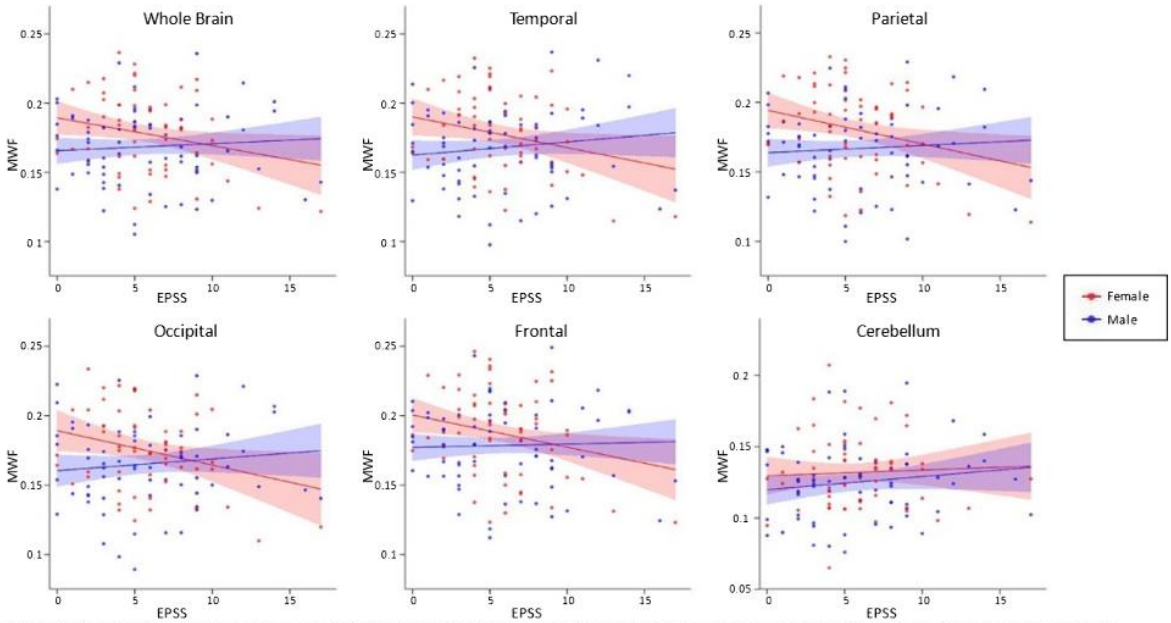
Asterisk (*) represents significance ($p < 0.05$) after FDR correction. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

Fig. 1: Regression results for the relationship between MWF and EPSS score adjusted for age, age², sex, and EPSS-sex interaction.



Results are shown for 6 brain ROIs. All ROIs, other than cerebellum, displayed significant negative correlations between MWF and EPSS score. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

Fig. 2: Regression results for the relationship between MWF EPSS score by sex adjusted for age and age².



Results are shown for 6 brain ROIs. All ROIs, other than cerebellum, displayed significant negative correlations between MWF and EPSS score x sex interaction. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

Table 1 Slope, β, and significance, p, of the regression terms incorporated in the multiple linear regression given by: $MWF \sim \beta_0 + \beta_{age} \times age + \beta_{age^2} \times age^2 + \beta_{sex} \times sex + \beta_{EPSS} \times EPSS + \beta_{EPSS\ x\ sex} \times (EPSS \times sex)$.

β-coefficient (p-value)	Age	Age²	Sex	EPSS	EPSS x Sex
Whole Brain	-0.517 (p < 0.0001) *	-0.225 (0.0118) *	-0.326 (0.0198)	-0.261 (0.0305) *	0.327 (0.0266) *
Temporal	-0.444 (p < 0.0001) *	-0.228 (0.0163) *	-0.314 (0.0351)	-0.274 (0.0327) *	0.391 (0.0129) *
Parietal	-0.516 (p < 0.0001) *	-0.201 (0.0220) *	-0.443 (0.00147) *	-0.291 (0.0144) *	0.354 (0.0149) *
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Frontal	-0.564 (p < 0.0001) *	-0.248 (0.00321) *	-0.280 (0.0328)	-0.275 (0.015) *	0.304 (0.0278) *
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Asterisk (*) represents significance ($p < 0.05$) after FDR correction. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

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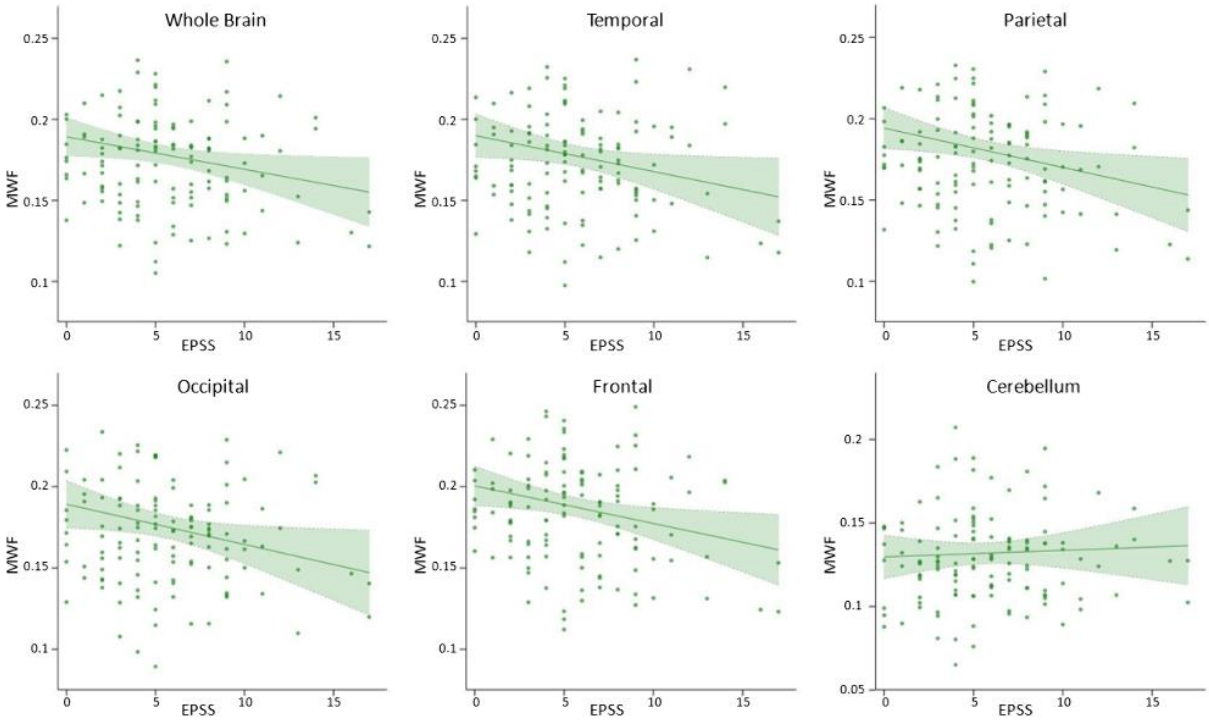
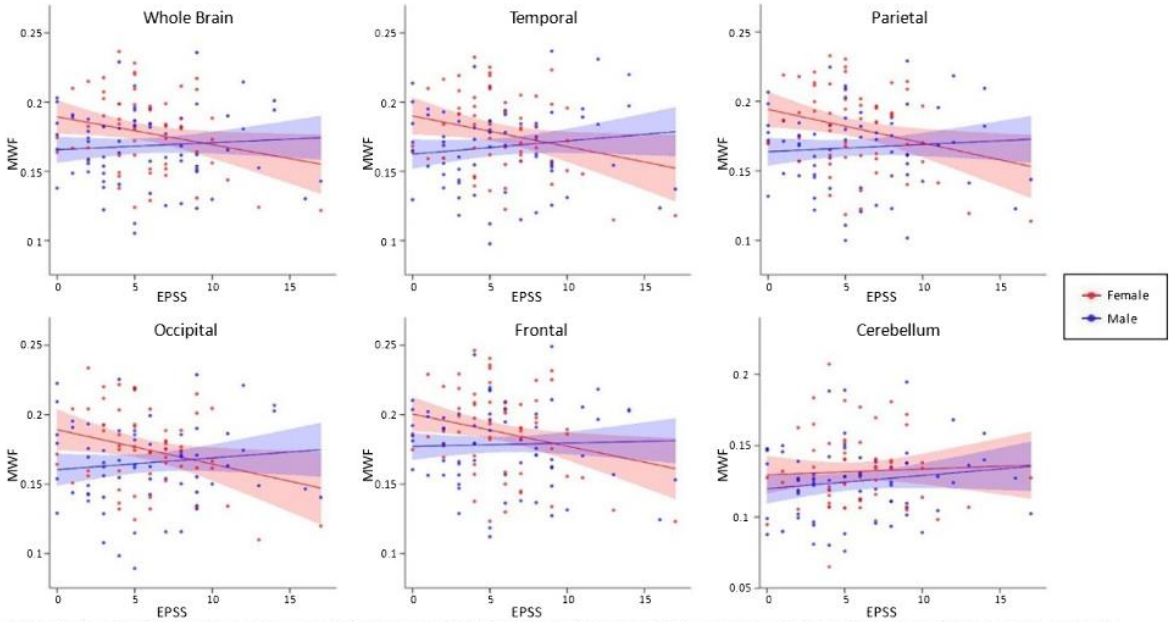


Results are shown for 6 brain ROIs. All ROIs, other than cerebellum, displayed significant negative correlations between MWF and EPSS score. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

Fig. 2: Regression results for the relationship between MWF EPSS score by sex adjusted for age and age².



Results are shown for 6 brain ROIs. All ROIs, other than cerebellum, displayed significant negative correlations between MWF and EPSS score x sex interaction. ROIs included: Whole Brain, *Temporal* temporal lobes, *Parietal* parietal lobes, *occipital* occipital lobes, *frontal* frontal lobes, and cerebellum.

Conclusions: Poor sleep quality was associated with reduced myelin content, with a more pronounced effect observed in females. This sex-dependent association warrants further investigation in larger cohorts as well as using more objective measures of sleep quality to elucidate the underlying mechanisms. This may provide valuable insights into the accelerated myelin decline at older ages, higher prevalence of sleep apnea observed in women, and sex-specific predispositions to AD.

Virtual OO - 150

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INSULIN RESISTANCE IS ASSOCIATED WITH LOWER CEREBRAL MYELINATION IN FEMALES

Nathan Zhang, Zhaoyuan Gong, Jonghyun Bae, Noam Fox, John Laporte, Alex Guo, Mustapha Bouhrara
National Institute on Aging, Baltimore, United States of America

Aims: Insulin resistance (IR), a key factor in metabolic disorders like type 2 diabetes, has been linked to alterations in cerebral white matter integrity. While studies suggest a negative correlation between IR and myelin levels, clinical investigations examining this association are scarce. To address this, we utilized Myelin Water Fraction (MWF), a specific MRI measure of myelin content, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) to examine their relationship in a well-characterized cohort of cognitively unimpaired participants.
Methods: 123 cognitively unimpaired adults (60 female, 63 male) underwent BMC-mcDESPOT MRI protocol for MWF mapping. Multiple linear regression analyses assessed HOMA-IR impact on MWF across 6 cerebral regions, adjusted for age, age^2, sex, and the sex × HOMA-IR interaction. Secondary analyses were performed for each sex independently. HOMA-IR was log-transformed to improve data normality, and continuous variables were z-scored.
Results: We found a negative correlation between IR and MWF in 3 brain regions (Fig. 1B, Table 1), with a significant sex × HOMA-IR interaction (Fig. 1C). Females showed significant negative correlations, while males exhibited nonsignificant positive correlations in most regions (Fig. 2, Table 2). However, the limited range of HOMA-IR values in males precluded any conclusions regarding MWF vs. HOMA-IR in males (Fig.1A).

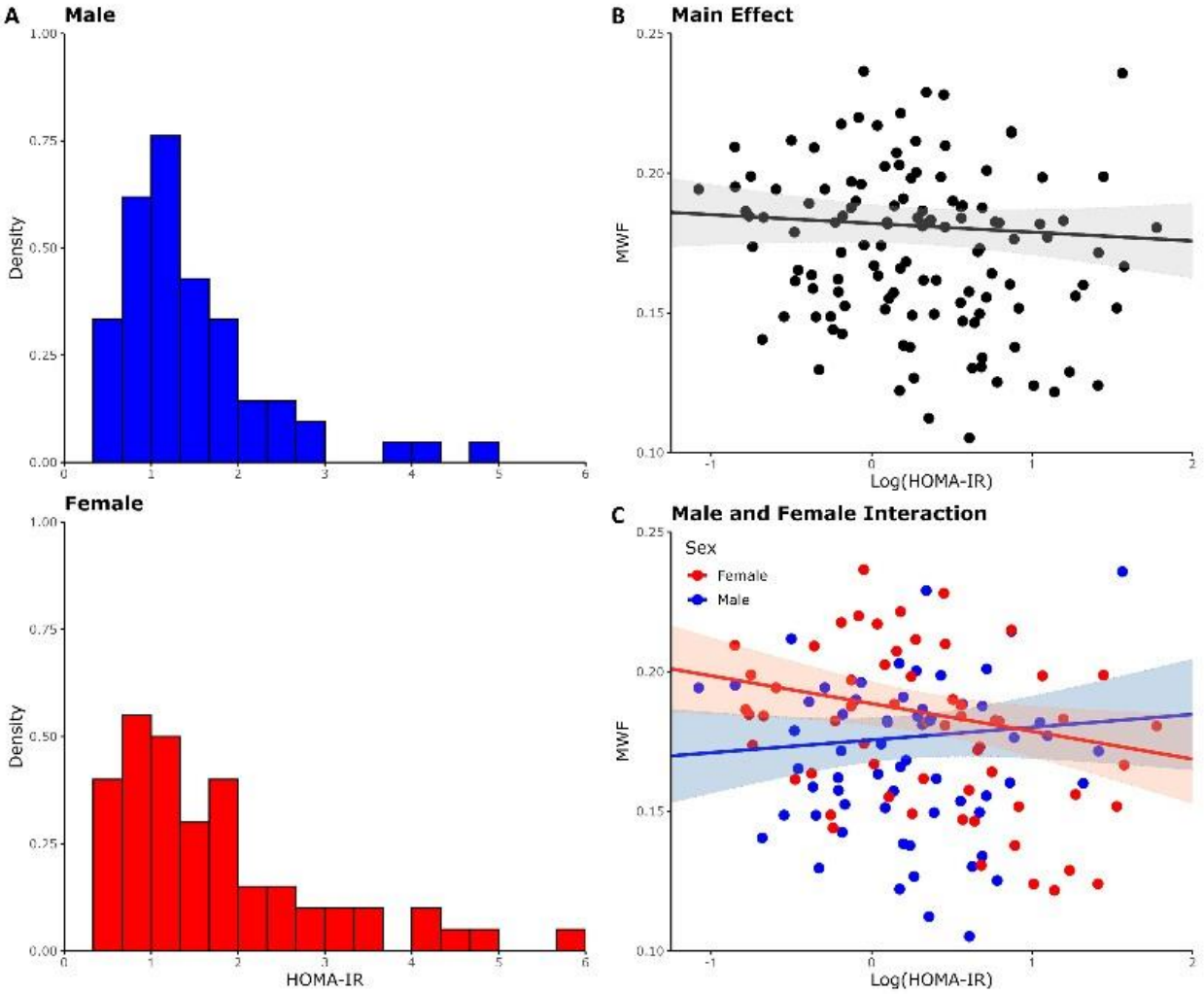

Fig. 1 . Associations between insulin resistance (IR) and MWF. A) Distribution of insulin resistance, stratified by sex. B) Regression analysis of whole-brain MWF vs. log(HOMA-IR), adjusted for age and age². Shaded regions indicate 95% confidence intervals. C) Regression analysis of whole-brain MWF vs. log(HOMA-IR), adjusted for age, age², sex, and log(HOMA-IR) sex.

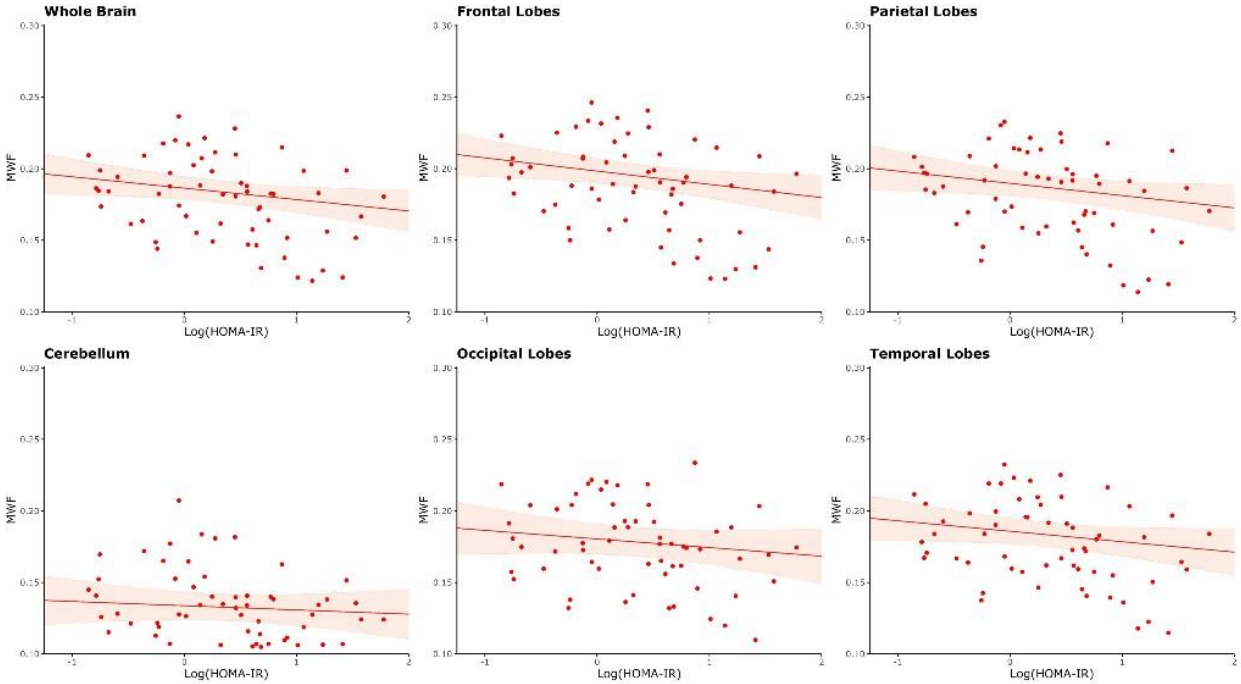

Fig. 2 Whole brain, four lobes, and cerebellum regression results between MWF and log(HOMA-IR) adjusted for age and age² in females. Shaded regions represent 95% confidence intervals.

Table 1. Slope, β, and significance, p, of terms incorporated in the multiple linear regression given by: $MWF \sim \beta_0 + \beta_{age} \times age + \beta_{age^2} \times age^2 + \beta_{sex} \times sex + \beta_{log(HOMA\text{-}IR)} \times log(HOMA\text{-}IR) + \beta_{(log(HOMA\text{-}IR) \times sex)} \times (log(HOMA\text{-}IR) \times sex)$. All slope values correspond to z-scored values of MWF, age, age², and log(HOMA-IR).

β- coefficient (p-value)	Age	Age²	Sex	Log(HOMA-IR)	Log(HOMA-IR) × Sex
Whole Brain	-0.4944 (p < 0.001)*	-0.2540 (p = 0.005)*	-0.3219 (p = 0.024)*	-0.2174 (p = 0.024)*	0.3172 (p = 0.033)*
Frontal Lobes	-0.5422 (p < 0.001)*	-0.2810 (p = 0.001)*	-0.2845 (p = 0.033)*	-0.2277 (p = 0.012)*	0.2512 (p = 0.071)
Parietal Lobes	-0.4918 (p < 0.001)*	-0.2288 (p = 0.010)*	-0.4316 (p = 0.002)*	-0.2109 (p = 0.025)*	0.2896 (p = 0.046)*
Occipital Lobes	-0.3121 (p < 0.001)*	-0.2506 (p = 0.017)*	-0.3043 (p = 0.065)	-0.1618 (p = 0.145)	0.2940 (p = 0.087)
Temporal Lobes	-0.4231 (p < 0.001)*	-0.2492 (p = 0.011)*	-0.3009 (p = 0.049)*	-0.1916 (p = 0.063)	0.3277 (p = 0.040)*
Cerebellum	-0.3581 (p < 0.001)*	-0.1067 (p = 0.320)	-0.2447 (p = 0.149)	-0.1121 (p = 0.326)	0.3054 (p = 0.085)

Asterisk (*) represents significance. ROIs included: Whole Brain, Temporal lobes, parietal lobes, occipital lobes, frontal lobes, and cerebellum

Table 2. Slope, β, and significance, p, of terms incorporated in the multiple linear regressions for male (left) and female(right) given by: $MWF \sim \beta_0 + \beta_{age} \times age + \beta_{age^2} \times age^2 + \beta_{log(HOMA\text{-}IR)} \times log(HOMA\text{-}IR)$. All slope values correspond to z-scored values of MWF, age, age², and log(HOMA-IR).

β- coefficient (p-value)	Male			Female		
	Age	Age²	log(HOMA-IR)	Age	Age²	log(HOMA-IR)
Whole Brain	-0.3285 (p = 0.004)*	-0.3268 (p = 0.013)*	0.0890 (p = 0.476)	-0.6915 (p < 0.001)*	-0.2024 (p = 0.093)	-0.1743 (p = 0.037)*
Frontal Lobes	-0.3874 (p < 0.001)*	-0.3328 (p = 0.007)*	0.0124 (p = 0.914)	-0.7292 (p < 0.001)*	-0.2578 (p = 0.028)*	-0.1858 (p = 0.022)*
Parietal Lobes	-0.3545 (p = 0.001)*	-0.2749 (p = 0.030)*	0.0688 (p = 0.567)	-0.6576 (p < 0.001)*	-0.2080 (p = 0.092)	-0.1739 (p = 0.043)*
Occipital Lobes	-0.1336 (p = 0.285)	-0.3955 (p = 0.008)*	0.1248 (p = 0.376)	-0.5110 (p < 0.001)*	-0.0918 (p = 0.530)	-0.1225 (p = 0.226)
Temporal Lobes	-0.2691 (p = 0.029)*	-0.3181 (p = 0.027)*	0.1262 (p = 0.357)	-0.6057 (p < 0.001)*	-0.1993 (p = 0.119)	-0.1518 (p = 0.086)
Cerebellum	-0.1862 (p = 0.142)	-0.2136 (p = 0.148)	0.1841 (p = 0.198)	-0.5561 (p < 0.001)*	-0.0044 (p = 0.978)	-0.0708 (p = 0.512)

Asterisk (*) represents significance. ROIs included: Whole Brain, Frontal Lobes, Parietal lobes, Occipital lobes, Frontal lobes, and Cerebellum

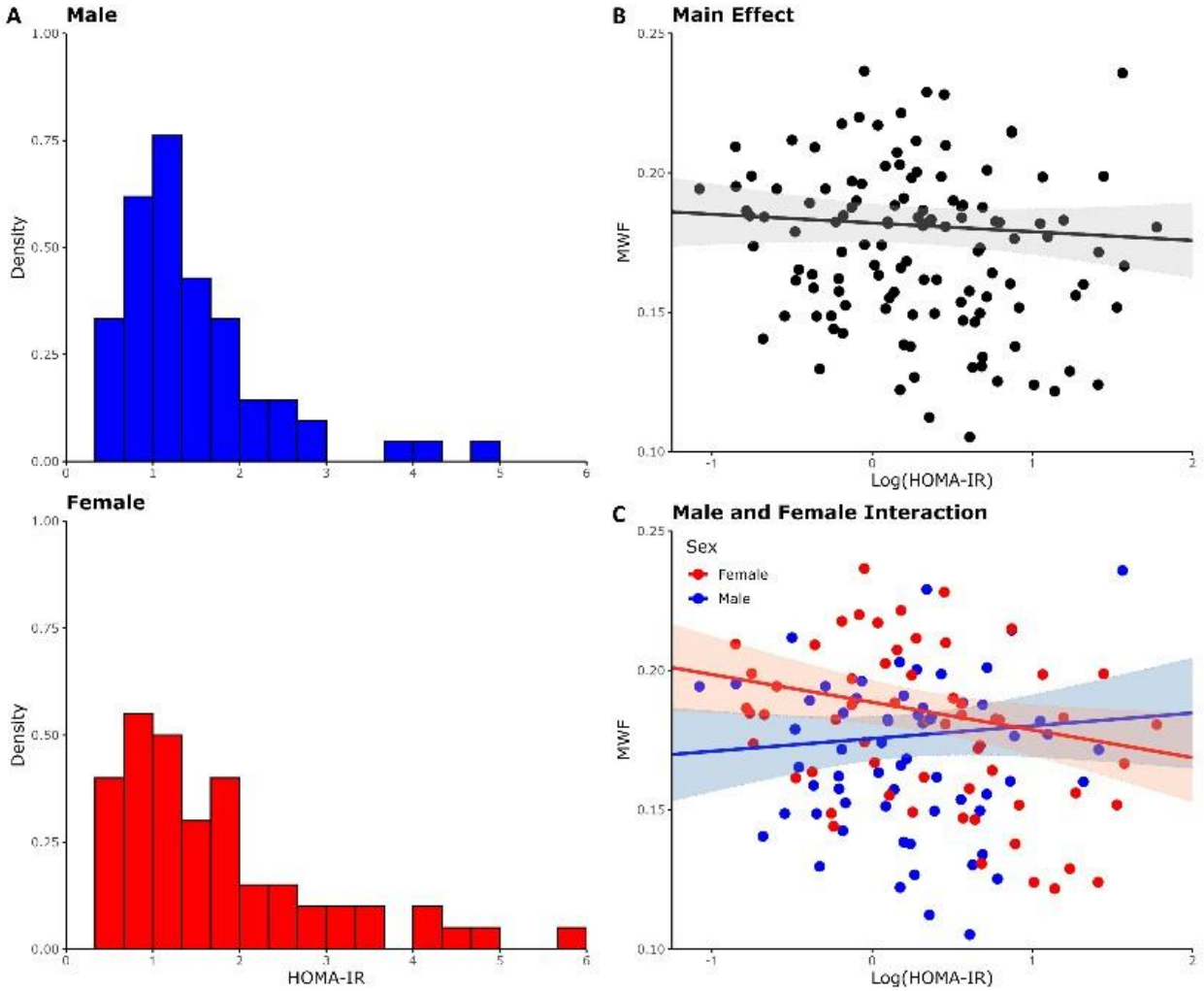

Fig. 1 . Associations between insulin resistance (IR) and MWF. A) Distribution of insulin resistance, stratified by sex. B) Regression analysis of whole-brain MWF vs. log(HOMA-IR), adjusted for age and age². Shaded regions indicate 95% confidence intervals. C) Regression analysis of whole-brain MWF vs. log(HOMA-IR), adjusted for age, age², sex, and log(HOMA-IR) sex.

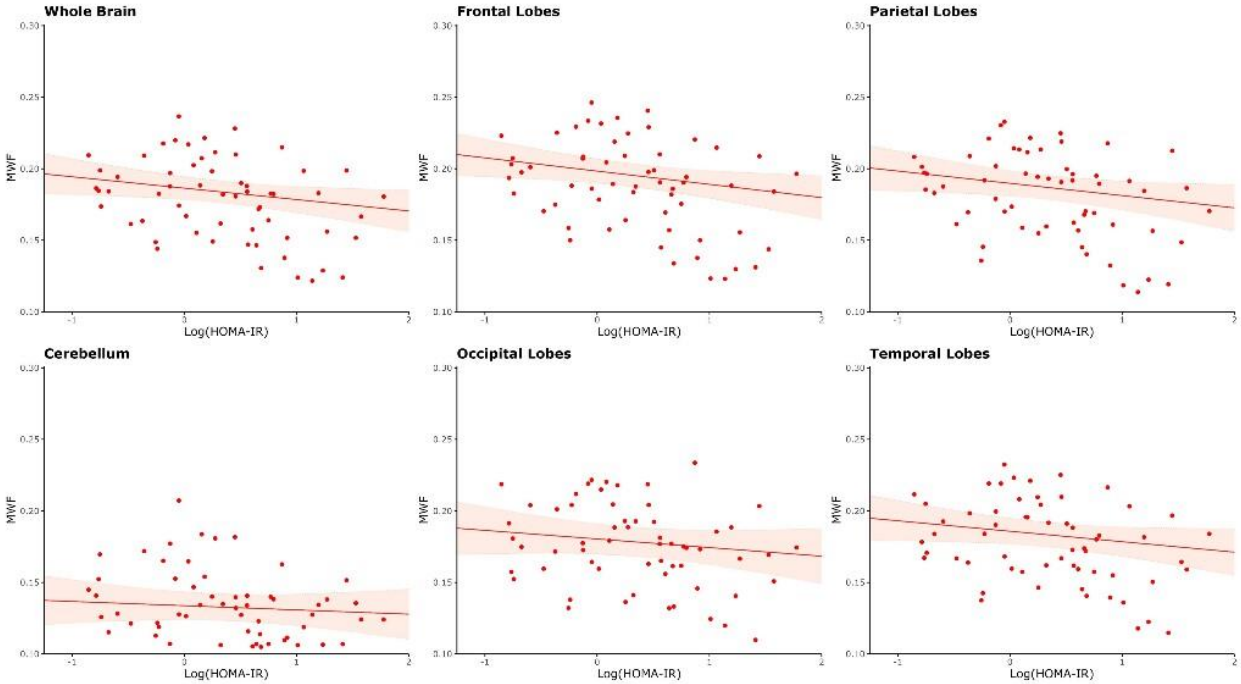

Fig. 2 Whole brain, four lobes, and cerebellum regression results between MWF and log(HOMA-IR) adjusted for age and age² in females. Shaded regions represent 95% confidence intervals.

Table 1. Slope, β, and significance, p, of terms incorporated in the multiple linear regression given by: $MWF \sim \beta_0 + \beta_{age} \times age + \beta_{age}{}^2 \times age^2 + \beta_{sex} \times sex + \beta_{log(HOMA\text{-}IR)} \times log(HOMA\text{-}IR) + \beta_{(log(HOMA\text{-}IR) \times sex)} \times (log(HOMA\text{-}IR) \times sex)$. All slope values correspond to z-scored values of MWF, age, age², and log(HOMA-IR).

β- coefficient (p-value)	Age	Age²	Sex	Log(HOMA-IR)	Log(HOMA-IR) × Sex
Whole Brain	-0.4944 (p < 0.001)*	-0.2540 (p = 0.005)*	-0.3219 (p = 0.024)*	-0.2174 (p = 0.024)*	0.3172 (p = 0.033)*
Frontal Lobes	-0.5422 (p < 0.001)*	-0.2810 (p = 0.001)*	-0.2845 (p = 0.033)*	-0.2277 (p = 0.012)*	0.2512 (p = 0.071)
Parietal Lobes	-0.4918 (p < 0.001)*	-0.2288 (p = 0.010)*	-0.4316 (p = 0.002)*	-0.2109 (p = 0.025)*	0.2896 (p = 0.046)*
Occipital Lobes	-0.3121 (p < 0.001)*	-0.2506 (p = 0.017)*	-0.3043 (p = 0.065)	-0.1618 (p = 0.145)	0.2940 (p = 0.087)
Temporal Lobes	-0.4231 (p < 0.001)*	-0.2492 (p = 0.011)*	-0.3009 (p = 0.049)*	-0.1916 (p = 0.063)	0.3277 (p = 0.040)*
Cerebellum	-0.3581 (p < 0.001)*	-0.1067 (p = 0.320)	-0.2447 (p = 0.149)	-0.1121 (p = 0.326)	0.3054 (p = 0.085)

Asterisk (*) represents significance. ROIs included: Whole Brain, Temporal lobes, parietal lobes, occipital lobes, frontal lobes, and cerebellum

Table 2. Slope, β, and significance, p, of terms incorporated in the multiple linear regressions for male (left) and female(right) given by: $MWF \sim \beta_0 + \beta_{age} \times age + \beta_{age^2} \times age^2 + \beta_{log(HOMA\text{-}IR)} \times log(HOMA\text{-}IR)$. All slope values correspond to z-scored values of MWF, age, age², and log(HOMA-IR).

β- coefficient (p-value)	Male			Female		
	Age	Age²	log(HOMA-IR)	Age	Age²	log(HOMA-IR)
Whole Brain	-0.3285 (p = 0.004)*	-0.3268 (p = 0.013)*	0.0890 (p = 0.476)	-0.6915 (p < 0.001)*	-0.2024 (p = 0.093)	-0.1743 (p = 0.037)*
Frontal Lobes	-0.3874 (p < 0.001)*	-0.3328 (p = 0.007)*	0.0124 (p = 0.914)	-0.7292 (p < 0.001)*	-0.2578 (p = 0.028)*	-0.1858 (p = 0.022)*
Parietal Lobes	-0.3545 (p = 0.001)*	-0.2749 (p = 0.030)*	0.0688 (p = 0.567)	-0.6576 (p < 0.001)*	-0.2080 (p = 0.092)	-0.1739 (p = 0.043)*
Occipital Lobes	-0.1336 (p = 0.285)	-0.3955 (p = 0.008)*	0.1248 (p = 0.376)	-0.5110 (p < 0.001)*	-0.0918 (p = 0.530)	-0.1225 (p = 0.226)
Temporal Lobes	-0.2691 (p = 0.029)*	-0.3181 (p = 0.027)*	0.1262 (p = 0.357)	-0.6057 (p < 0.001)*	-0.1993 (p = 0.119)	-0.1518 (p = 0.086)
Cerebellum	-0.1862 (p = 0.142)	-0.2136 (p = 0.148)	0.1841 (p = 0.198)	-0.5561 (p < 0.001)*	-0.0044 (p = 0.978)	-0.0708 (p = 0.512)

Asterisk (*) represents significance. ROIs included: Whole Brain, Frontal Lobes, Parietal lobes, Occipital lobes, Frontal lobes, and Cerebellum

Conclusions: Higher IR is associated with reduced myelin content in females. Insulin and insulin-like growth factor (IGF)-1 regulate oligodendrocytes, which produce and maintain myelin. Since insulin deficiency may impair brain cholesterol synthesis, a major myelin constituent, higher IR and consequent diminished insulin sensitivity could disrupt oligodendrocyte function and myelination. This effect is particularly pronounced in the frontal and parietal lobes, regions sensitive to neurodegeneration. Future research is needed to explore IR's impacts on these brain structures and neurodegenerative diseases.

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Virtual OO - 151

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PREVALENCE AND CORRELATES OF OBSTRUCTIVE SLEEP APNEA IN PARKINSON'S DISEASE: A LOGISTIC REGRESSION ANALYSIS

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Aims: This paper aims to investigate the prevalence of Obstructive Sleep Apnea (OSA) in patients with Parkinson's Disease (PD) and explore its correlations with various medical, demographic, and behavioral factors. Using logistic regression analysis, the study identifies significant predictors of OSA, such as higher BMI, male sex, and ethnicity (notably White and Pacific Islander patients). The findings highlight the importance of targeted screening and early intervention for OSA in PD patients to improve outcomes, and call for further research into the relationship between OSA and PD progression.
Methods: The methods of this paper involved analyzing data from 270 patients with confirmed Parkinson's Disease (PD), some of whom also had Obstructive Sleep Apnea (OSA). The researchers collected variables such as age, body mass index (BMI), sex, ethnicity, insurance status, sleep behaviors (e.g., insomnia, REM sleep behavior disorder), smoking history, hypertension, and PD medication use. Logistic regression analysis was employed to identify which of these factors were significantly associated with the presence of OSA in the PD population. The analysis focused on predictors with the smallest p-values to determine the strongest correlations with OSA.
Results: The results show that higher BMI, male sex, and White ethnicity are significant predictors of Obstructive Sleep Apnea (OSA) in Parkinson's Disease (PD) patients. Pacific Islanders showed a near-significant association, while other factors like insomnia and hypertension were not significant.
Conclusions: The paper concludes that Obstructive Sleep Apnea (OSA) is common in Parkinson's Disease (PD) patients, with higher BMI, male sex, and ethnicity (White and Pacific Islander) as key risk factors. Early screening and intervention for OSA in PD patients could improve treatment outcomes, and further research is needed to explore the link between OSA and PD progression.

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EVALUATION OF THE NEUROPHARMACOLOGICAL POTENTIALS OF PHOENIX DACTYLIFERA AND PARQUETINA NIGRESCENS

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Aims: To evaluate the ethnomedicinal use of crude methanol extracts of the seeds of *Phoenix dactylifera* (SPD) and leaves of *Parquetina nigrescens* (LPN) for their possible neurocognitive and neuropharmacological potentials
Methods: The extracts were evaluated for anti-inflammatory, phytochemical screening, antioxidant, and anticholinesterase activities using standard *in vitro* assays. They were also evaluated for their neuropharmacological potentials *in vivo*. Data obtained were expressed as mean ± standard error of mean (SEM) and analyzed using One-way Analysis of Variance followed by a post hoc test.
Results: Both SPD and LPN extracts possessed glycosides, tannins I & II, saponins, alkaloids, phenols, flavonoids, and anthraquinones. The SPD extract showed higher phenolic (807.77 ± 19.10) and flavonoid (103.99 ± 1.15) contents. Comparingly, SPD exhibited higher antioxidant activity in almost all the *in vitro* antioxidant assays: TAC (166.71±8.80), FRAP (336.12±0.52), CUPRAC (146.70±1.53), ABTS (1.03±0.16). However, both SPD and LPN significantly inhibited acetylcholinesterase with IC_{50} = 1.76 ± 0.08 mg/mL and 0.41 ± 0.03 mg/mL respectively. They consistently showed dose-dependent anti-inflammatory activities ($p < 0.05$). The LD_{50} of SPD and LPN were ≥ 5000 mg/kg. Both SPD and LPN extracts significantly stimulated the frequencies of rearing ($F_{6,31} = 7.068$, $p < 0.0001$) and grooming activities ($F_{6,31} = 55.9$, $p < 0.0001$) in mice but devoid of significant effect on their short-term memory. However, LPN showed a significant increase ($F_{7,41} = 8.610$, $p < 0.0001$) in the time spent in the open arm of the elevated plus maze (EPM).
Conclusions: The extracts of the seeds of *Phoenix dactylifera* (SPD) and leaves of *Parquetina nigrescens* (LPN) used ethnomedicinally in the management of dementia showed promising antioxidant, anti-cholinesterase, anti-inflammatory, and neuropharmacological potentials attributed to the presence of some polyphenols

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MOOD-RELATED NEUROPSYCHIATRIC SYMPTOMS AND THEIR ASSOCIATION WITH ALZHEIMER'S DISEASE PLASMA BIOMARKERS

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Aims: Mood-related neuropsychiatric symptoms (NPS) are common in AD and MCI but their neurobiological underpinning is unclear. Our aim was to explore the association between mood-related NPS (i.e. depression, anxiety, apathy) with blood NfL and p-tau181 longitudinally in people with MCI and AD.
Methods: This study used longitudinal data from 790 patients diagnosed with MCI and AD enrolled in ADNI with serial plasma NfL and p-tau181 levels. We analyzed the trajectory of NfL and p-tau181 in each NPS (as determined by the Neuropsychiatric Interview) using linear mixed-effects models with age and sex as covariates, with multiplicity adjusted p-values using the Benjamini-Hochberg procedure.
Results: There were 790 participants with AD and MCI (mean [SD] age 72.7 [7.6] years; 333 females, 42%). The most common NPS was depression (54%), followed by apathy (44%) and anxiety (43%). Apathy and anxiety were associated with higher levels of plasma NfL (Apathy-β = 0.18, 95% CI [0.10, 0.25], $p < 0.001$; Anxiety-β = 0.16; 95% CI [0.09, 0.23]; $p < 0.001$) and p-tau181 (Apathy-β = 0.15, 95% CI [0.06, 0.24], $p = 0.016$; Anxiety-β = 0.19, 95% CI [0.10, 0.29], $p = 0.001$) even after controlling for cognitive and functional decline. Moreover, apathy was associated with higher rate of NfL increase (β = 0.04, 95% CI [0.02 - 0.06], $p < 0.001$). Depression was initially associated with higher NfL and p-tau181 levels, but this did not remain significant in the sensitivity analyses.
Conclusions: This study demonstrates that apathy and anxiety are associated with greater neurodegeneration and tau pathology. Furthermore, apathy was associated with accelerated neurodegeneration. These findings suggest that NfL could serve as a biomarker for the early identification of apathy, a common and debilitating neuropsychiatric symptom in AD.

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CORRELATION OF T1W/T2W RATIOS WITH CLINICAL VARIABLES IN PD-MCI AND PD-NC

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[1]University of Alabama at Birmingham, Radiology, Birmingham, United States of America, [2]Cleveland Clinic Foundation, Las Vegas, United States of America

Aims: To examine the relationship between T1w/T2w ratio alterations in specific brain regions and clinical variables in patients with Parkinson's disease with mild cognitive impairment (PD-MCI) and Parkinson's disease with no mild cognitive impairment (PD-NC). The goal is to assess how structural brain changes correlate with disease severity, medication use, and cognitive decline.
Methods: This study involved 30 participants, 18 with PD-MCI and 12 with PD-NC. MRI-derived T1w/T2w ratios were analyzed across the whole brain using HCP Pipelines. Clinical variables, including disease duration (DDX), Levodopa Equivalent Daily Dose (LEDD), and the Unified Parkinson's Disease Rating Scale (ON State) (UPDRS ON), were collected and statistically correlated with the T1w/T2w ratios in these regions. Group comparisons and regression analyses were performed to evaluate differences between PD-MCI and PD-NC groups.
Results: The T1w/T2w ratio in regions such as the medial occipital and parieto-occipital areas showed distinct correlations with clinical variables. In the PD-MCI group, the T1w/T2w ratio negatively correlated with UPDRS ON scores ($r = -0.6591 \pm 0.0818$), while a positive correlation was observed in the PD-NC group ($r = 0.6803 \pm 0.0918$). Similarly, a positive correlation between the T1w/T2w ratio and LEDD was found in PD-MCI patients ($r = 0.6541 \pm 0.0700$), indicating that higher medication dosages corresponded with higher T1w/T2w ratios. Differences in disease duration were also evident, with PD-MCI showing distinct slopes when compared to PD-NC.
Conclusions: This study demonstrates significant correlations between T1w/T2w ratios and clinical variables, suggesting that these structural brain changes may reflect disease progression and treatment effects in Parkinson's disease.

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BEYOND MOVEMENT: THE ROLE OF ADIPORON IN MODULATING NEUROPSYCHIATRIC AND COGNITIVE IMPAIRMENTS IN PARKINSON'S DISEASE

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Aims: Parkinson's disease(PD) is a complex neurodegenerative disorder characterized by both motor and non-motor symptoms. While motor symptoms are the hallmark of PD,non-motor symptoms, including depression, anxiety, and cognitive impairment, significantly impact patients' quality of life and often precede motor manifestations. This study investigated the effects of intranasal AdipoRon(Ad),an adiponectin receptor agonist, on both neuropsychiatric and cognitive symptoms in a 6-hydroxydopamine(6-OHDA)-induced rat model of PD.
Methods: A hemiparkinsonian rat model was created by unilateral injection of 6-OHDA into the medial forebrain bundle.One week post-injection, rats were randomly assigned to treatment groups receiving either intranasal Ad(0.1, 1, or 10 µg), levodopa(10 mg/kg orally), or vehicle for21 consecutive days.For evaluation of anxiety-like behaviors, the open field test and elevated plus maze, and for depressive-like behaviors, sucrose splash test and forced swimming test were performed.Cognitive function,specifically recognition and spatial memory,was examined through the novel object recognition test and Barnes maze test,respectively
Results: Unlike conventional treatments such as levodopa,which primarily target motor symptoms,Ad(1 and 10 µg) demonstrated significant efficacy in ameliorating both neuropsychiatric and cognitive deficits.These behavioral improvements were accompanied by decreased expression of neuroinflammatory markers,including NLRP3,caspase 1, and IL-1β, and increased expression of Sirt-1 in the prefrontal cortex.Moreover, Ad significantly reduced oxidative stress markers,increased total antioxidant capacity, and elevated levels of antioxidant enzymes,including superoxide dismutase(SOD) and glutathione peroxidase(GPx) in the hippocampus.Furthermore,Ad increased the expression of brain-derived neurotrophic factor(BDNF) and postsynaptic density protein 95(PSD-95),suggesting enhanced synaptic plasticity.
Conclusions: These findings suggest that intranasal Ad ameliorates both neuropsychiatric and cognitive symptoms in PD through multiple mechanisms, including anti-inflammatory effects, activation of

AMPK/Sirt-1 signaling, reduction of oxidative stress, and promotion of synaptic plasticity.In conclusion,this study provides compelling evidence for the therapeutic potential of intranasal Ad in managing non-motor PD symptoms.

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INFORMAL CAREGIVERS OF PEOPLE WITH DEMENTIA IN ITALY: SOCIODEMOGRAPHIC CHARACTERISTICS AND UNMET NEEDS

Claudio Singh Solorzano[1], Orazio Zanetti[2], Giuliano Binetti[3], Roberta Rossi[4], Michela Pievani[1], Giovanni Tura[4], Cristina Festari[1]
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Aims: Informal caregivers (iCGs) of persons with dementia take on most of the responsibility for patient care, increasing their vulnerability to psychological and physical problems. However, little is known about the sociodemographic features of this population and their needs. This study aims to describe Italian iCG characteristics, their mental health status, and unmet needs.
Methods: This epidemiological study included 435 iCGs of outpatients of the memory clinic of Brescia. Participants fill out an anonymous questionnaire, including questions on sociodemographic characteristics, distress levels, and care needs. Distress included measures of anxiety and depressive symptoms through the Patient Health Questionnaire-4 (PHQ-4, clinical cut-off=3) and burden through the Zarit Burden Interview (ZBI, clinical cut-off=20). Care needs were collected with an ad-hoc scale consisting of a list of services helpful in managing patients at home (i.e., psychological support, practical administrative information, respite and educational programs).
Results: The majority of iCGs were women (74%), adult children (64%) aged between 50-59 years old, not cohabiting with the patient (88%) and in full or part-time employment (47%). They provided support to the patient for at least one year (88%) and for an average of 44.2±38.6 hours/week. Overall, iCGs reported mild to moderate burden levels (36.9±17.6), mild anxiety levels (2.9±1.9) and low depressive (2.0±1.8) symptoms. The top three primary needs expressed by iCGs are: i) individual psychological support (60%); ii) tax and/or legal benefits information (60%), and iii) knowledge about the progression of the disease and the strategies for managing symptoms and/or disruptive behaviours (55%).
Conclusions: In Italy, iCGs require primarily psychological support and educational interventions to support their own emotional and financial distress. Reforms to the clinical patient care service that reflect family caregivers' demands might be reasonable to explore.

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RELATIONSHIP BETWEEN CAREGIVING BURDEN AND ALTERATIONS IN CIRCADIAN RHYTHM AMONG SPOUSAL CAREGIVERS OF COGNITIVE IMPAIRMENT OLDER ADULTS

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Aims: Caring for individuals with dementia is an increasingly prevalent responsibility as the global population ages. Spousal caregivers (SCGs), who often assume the primary caregiving role, are particularly vulnerable to the physical and psychological tolls of caregiving. This demanding role can lead to significant stress and strain, potentially resulting in disruptions to both physical and mental health. Among the various health impacts, disturbances in circadian rhythms, which govern sleep-wake cycles and overall rest-activity rhythms (RARs), are of particular concern. Disruptions in these rhythms can exacerbate cognitive decline and increase cardiovascular risk. Despite the critical nature of these impacts, there is limited research focused on understanding how caregiving burden specifically influences circadian rhythms in SCGs. This study aims to fill this gap by investigating the relationship between caregiving burden and changes in sleep-wake cycles and RARs in SCGs, with a particular focus on those caring for spouses with dementia.
Methods: We recruited 104 SCGs from a geriatric psychiatry clinic. Participants underwent comprehensive clinical assessments, including the Zarit Caregiver Burden Interview (ZBI) and circadian rhythm evaluations using the Pittsburgh Sleep Quality Index (PSQI) and Fitbit devices. Multiple regression analyses were conducted to assess associations.
Results: Increased caregiving burden showed a trend-level association with earlier wake times ($\beta = -0.254$, $p = 0.091$) and a significant association with reduced RAR robustness as indicated by lower goodness-of-fit (GoF) values ($\beta = -0.306$, $p = 0.037$), especially among dementia caregivers. PSQI analysis revealed that higher caregiving burden correlated with worsened sleep disturbances ($\beta = 0.203$, $p = 0.046$).
Conclusions: Caregiving burden significantly affects circadian rhythms in SCGs, with potential implications for cognitive and cardiovascular health. Targeted interventions are needed to mitigate these effects and improve caregiver well-being.

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WHEN ALGORITHMS REPLACE BIOLOGISTS: A DISCRETE CHOICE EXPERIMENT FOR THE VALUATION OF EARLY DETECTION TOOLS IN NEURODEGENERATIVE DISEASES

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Aims: We study individual valuation for early diagnosis tests for neurodegenerative diseases when Artificial Intelligence Diagnosis is an option
Methods: We conducted a Discrete Choice Experiment on a representative sample of the French adult population (N=1017), where we presented participants with a hypothetical risk of developing in the future a neurodegenerative disease. We ask them to repeatedly choose between two possible early diagnosis tests that differ in terms of (1) type of test (biological tests vs AI tests analyzing electronic health records); (2) identity of whom communicates tests' results; (3) sensitivity; (4) specificity; and (5) price.
Results: Our results are twofold: respondents indeed reveal a psychological loss when AI testing is at stake (that is evaluated to 33.65 euros in average, IC = [20.11; 47.45]) and when results are communicated by a private company (M=99.48€, IC = [86.67; 113.75]).
Conclusions: People do not dislike algorithm *per se. They* are open towards the usage of AI in healthcare, but there is also a real patients' concern over information, privacy, and safety, including for neurodegenerative diseases. Given personal medical information is among the most private and legally protected forms of data, future scaling-up of commercial healthcare AI will first have to face serious privacy challenges

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EFFECTIVENESS OF I-VIRTUAL REALITY AND TELEMEDICINE BASED COGNITIVE REHABILITATION ON PROSPECTIVE MEMORY IN PARKINSON'S DISEASE WITH MILD COGNITIVE IMPAIRMENT: A PLACEBO-CONTROLLED TRIAL

Alberto Costa[1,2], Maria Stefania De Simone[1], Sara Taglieri[2], Giorgia Cona[3], Eleonora Fiorenzato[3], Valentina Massimi[2], Gaetano Tieri[4], Giovanni Carlesimo[2], Antonella Peppe[2], Carlo Caltagirone[2], Silvia Zabberoni[1]
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Aims: The ability to perform intended actions reflects the prospective memory skill (PM). PM is a multiprocess that includes both episodic memory and attentional-executive abilities. Several studies document PM difficulties in Parkinson's disease patients, particularly those wiith PD-MCI. This study was aimed at investigating the efficacy, of attention/executive functions training on PM abilities of PD-MCI patients through a immersive Virtual Reality and Telemedicine approach.
Methods: 30 PD-MCI underwent PM and executive measures and they were randomly assigned to two arms (training and placebo). Cognitive Training consisted in a real-like scenario that comprised planning, shifting and updating exercises with increasing difficulty progression. Participants were immersed in a virtual scenario wherein they performed daily actions. In the Placebo subjects were instructed to perform similar daily actions with less cognitive demands, in the same setting as the training. All exercises, remotely performed through a telemedicine approach, were implemented in iVR context in which users, wearing a standalone headset device, were surrounded by a 3D computer-generated representation and they were able to interact with the environment through a hand-controller. Outcome measures were administered before (T0), after 4 weeks of intensive training (T1) and two months later (T2). A randomized controlled trial was executed with Experimental Condition (cognitive training vs. placebo) as between factor and Time of Assessment (T0 vs. T1 and T2) as within factor.
Results: Mixed ANOVA's showed that trained subjects improved their performance on the PM task compared to the placebo group and this effect remained stable at T2.
Conclusions: Results suggest that iVR training improved certain skills crucial to PM functioning. **D**ata of this study highlight evidence on the efficacy of an innovative cognitive intervention integrating IVR and telemedicine in PD-MCI.

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ACCEPTABILITY OF ARTIFICIAL INTELLIGENCE BY GENERAL PRACTITIONERS: ANALYSIS OF AFFORDANCES AND PARADOXES IN THE SCREENING OF NEURODEGENERATIVE DISEASES

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Aims: This study analyses the acceptability of artificial intelligence (AI) to general practitioners, particularly in the early detection of neurodegenerative diseases.
Methods: An exploratory qualitative method was adopted, with nine semi-directive interviews conducted with doctors, interns and an AI designer. Analysis of the data produced a coding grid structured around an original theoretical framework in information systems (IS) that combines the concepts of affordances and paradoxes, concepts that are commonly used in Management Sciences to understand technology adoption.
Results: The results show that doctors have ambivalent perceptions of AI. Positive affordances include the reduction of errors, improved efficiency and support for complex diagnoses. AI is also seen as an opportunity to democratize medical knowledge, make practice more accessible, and improve productivity by allowing more patients to be treated in less time. However, the negative affordances raise several concerns, such as the biases that could affect the decision-making process, the loss of skills, increased dependence on technology, as well as the dehumanization of the doctor-patient relationship and the question of responsibility in the event of error. The study also identifies several paradoxes. For example, AI can both reduce and increase errors or improve skills while running the risk of degrading them because of technological dependence. These paradoxes are key to understanding the dynamics of AI acceptability.
Conclusions: The research shows the importance of involving healthcare professionals in the development of AI solutions, improving their technical training and developing new affordances that can overcome paradoxes. By integrating affordances and paradoxes, it proposes an original theoretical framework for studying the integration of AI in general medicine. Future studies should extend the sample to obtain new insights.

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ASSOCIATION BETWEEN FATIGUE AND SLEEP QUALITY IN PATIENTS WITH MULTIPLE SCLEROSIS (MS): A SYSTEMATIC REVIEW AND META-ANALYSIS

Asal Ebrahimian[1], Afshin Moradi[1], Amirreza Naseri[1], Mahnaz Talebi[2], Saeed Sadigh-Eteghad[2], Nima Nosratkhah[3]
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Aims: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by inflammatory demyelination leading to neurodegeneration. Patients with MS, suffer a variety of complications among which are fatigue and poor sleep quality. this systematic review aimed to determine the relationship between fatigue and poor sleep quality in MS patients.
Methods: A systematic search was conducted through PubMed (MEDLINE), Web of Science, Scopus, and Embase online databases and studies which reported the relationship between fatigue based on Modified Fatigue Impact Scale (MFIS) and sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) in MS patients were included. Risk of bias in each study was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools and through the sensitivity analysis, low quality studies were excluded. Random effect model by the third version of Comprehensive Meta-Analysis (CMA3), was used for meta-analysis.
Results: Out of 13 included studies and 1573 multiple sclerosis (MS) patients, 6 studies were included in the meta-analysis. Due to high heterogeneity (I2: 74.37%), the random effect model was used for correlation analysis. With an effect size of 0.47, 95% confidence interval 0.35 to 0.57, Z-value of 7.18 indicating a strong effect and P-value of 0.000 suggesting statistical significance, it was revealed that fatigue was significantly correlated with poor sleep quality in MS patients
Conclusions: Our study indicates that fatigue has a close relation with sleep quality in multiple sclerosis (MS) patients. In conclusion, this study demonstrates the importance of fatigue, sleep quality and their correlation which, demands more attention as it strongly affects quality of life of MS patients.

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PHYSICAL ACTIVITY AND AMINOACIDS: THEIR ROLE IN PROGRESSION TOWARD DEMENTIA. PRELIMINARY RESULTS FROM THE PHACADE STUDY

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AUSL Modena, Modena, Italy

Aims: In Mild Cognitive Impairment (MCI), individuals present overt cognitive impairment with little or no impact on Instrumental Activities of Daily Living (IADL). MCI could be the first cognitive expression of Alzheimer's disease (AD) and could be worsened by pathological processes such as sarcopenia and frailty. The aim of our project is to evaluate the effect of exercise training alone and combined exercise training and dietary intervention on the progression of MCI towards AD.
Methods: Single-center, prospective, open-label study comparing two cohorts of MCI patients during a 2-year follow-up period. The study began in May 2023. To participant in the control group (CG) were give a program of twice-a-week 60-minute sessions of adapted physical activity (AMA) conducted by a Kinesiologist. Participants in the intervention group (IG) were given both AMA and an essential amino acid supplement based on WHO guidelines. Participants were assigned to the intervention group if their baseline SPPB was between 9 and 10.
Results: Preliminary analyses include data from 20 participants (11 in the intervention group, 9 in the control group). At baseline, mean age of the sample is 78 years, mean MMSE is 26.2, mean IADL is 7. At 1-year follow-up, 2 patients (1 from the intervention group, 1 from the control group) were censored due to AD development. Mean difference in MMSE between follow-up and baseline was similar between groups (CG:1.2±2.3 vs IG:-0.7±2.3, p=0.215), mean SPPB variation was in favour of IG (CG:0.3±0.5 vs IG:2.9±0.9, p<.001). The adherence was above 66%.
Conclusions: The effect of AMA alone and AMA combined with dietary intervention on MCI seems to be effective in improving physical parameters even in most fragile participants. It seems that cognitive parameters are similar between the groups.

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THE EFFECT OF MULTI-COMPONENT EXERCISE INTERVENTION IN OLDER PEOPLE WITH PARKINSON'S DISEASE AND MILD COGNITIVE IMPAIRMENT: A RANDOMIZED CONTROLLED STUDY

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Aims: To examine the feasibility and effectiveness of a theory-based multi-component exercise intervention in older people with Parkinson's disease (PD) and mild cognitive impairment (MCI).
Methods: Participants were randomized into an intervention group (n=23) and an active control group (n=23), and received theory-based multi-component exercise intervention and Parkinson's health exercises, respectively. All participants performed 60-minute exercise training sessions, thrice a week, over a 12-week period.
Results: The retention rate at post-intervention was 95.7% (42/46) for the entire cohort. The attendance rates were 99.6% and 99.5% in the intervention and control groups, respectively. No adverse events occurred. The intervention group showed significantly greater improvements than the control group for global cognitive function, executive function, physical motor function, balance and gait, depression, and quality of life.
Conclusions: Theory-based multi-component exercise intervention demonstrates relatively high feasibility in promoting exercise adherence, and is an effective treatment option for older people with PD-MCI.

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EFFECTS OF A NEWLY DEVELOPED SOFT WEARABLE FOR SUPPRESSING HAND TREMOR IN PEOPLE WITH PARKINSON'S DISEASE – AN INITIAL PILOT

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Aims: Objective: To investigate the effects of a newly developed wearable device prototype for suppressing upper-limb tremor in people with Parkinson's disease based on Neuro-Fuzzy systems.
Methods: Method: We developed a wearable device prototype based on Neuro-Fuzzy systems to suppress hand tremors. The device stimulates target muscles, producing a damping force against individual tremors. A single group pre-post intervention pilot (n=10) was conducted in Hong Kong. Participants were recruited from the Hong Kong Parkinson's Disease Association. All participant continued their medications as usual. Hand tremors before and after wearing the tremor-suppressing device were assessed by an occupational therapist using Archimedes spiral drawings and TETRAS activities of daily living (ADL) subscale. Data collected during testing tasks performance with and without the tremor-suppressing device were analyzed.
Results: Results: Results of paired *t*-test revealed significant differences in pre-post outcome comparison as demonstrated by Archimedes spirals ($p = 0.011$), TETRAS ADL subscale rating including use of spoon ($p < 0.01$), pouring water from pot ($p = 0.011$), drinking from cup ($p < 0.01$), picking coins ($p < 0.01$), and use of key ($p < 0.01$).
Conclusions: Conclusions: A wearable device prototype for suppressing hand tremor in people with Parkinson's disease, based on Neuro-Fuzzy systems to stimulate the target muscles to produce a damping force against individual hand tremors when performing different daily tasks or actions, is effective. This initial feasibility testing has demonstrated its effectiveness and benefits for people with Parkinson's hand tremors. Further validation through larger-scale studies is warranted to establish its clinical utility. The potential underlying mechanisms will be a crucial focus for discussion.

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THE FIRST IN VIVO, CONTINUOUS, AND REAL-TIME INTERSTITIAL LEVODOPA MONITORING USING A BIOSENSOR IMPLANTED IN SPRAGUE DAWLEY RATS

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Aims: Parkinson's Disease patients rely on levodopa as the primary therapeutic for symptom mitigation, and disease management. While effective, there are key limitations, including the inability for clinicians or patients to receive real-time feedback levodopa concentrations. This study has the aim to demonstrate the first in vivo, subcutaneous implanted biosensor, which can measure interstitial fluid (ISF) levodopa concentrations real-time.
Methods: The levodopa biosensor was fabricated using a gold microwire with a diameter of 76 µm as the working and counter electrode while using Ag/AgCl wire as the reference electrode. A levodopa specific enzyme (Copper dehydrogenase; CoDH) was then immobilized to the working electrode. Fabricated levodopa biosensors were inserted into the upper back of Sprague Dawley rats using an 18-gauge needle, after which, levodopa was injected 6 cm proximal to the working electrode.
Results: CoDH, is an engineered enzyme which is specific to levodopa and is a direct electron transfer type enzyme. Levodopa is oxidized by an enzymatic reaction, which will be detected electrochemically without the interference of the presence of several potential ingredients. Ex-vivo investigation of levodopa biosensor revealed that the sensor can measure therapeutic concentrations of levodopa from 1 – 55 µM. The subcutaneously implanted levodopa biosensor reached a steady state response 2 minutes after interacting with the substrate. The sensor showed levodopa dose dependent response, with the range of 10 - 100 nmols, and demonstrated a stable signal over a single day of continuous application using both chronoamperometry, and potentiometry.
Conclusions: This is the first work that demonstrates real-time, in vivo monitoring of ISF levodopa using a subcutaneous implanted biosensor. We anticipate this work to be the foundation of future development, enabling continuous levodopa monitoring and feedback for patients and clinicians.

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EXPLORING THE EFFECTS OF CULTURALLY INFORMED DANCE MOVEMENT THERAPY USING INDIAN DANCE TECHNIQUES ON THE SYMPTOMS OF PARKINSON'S DISEASE

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Aims: The application of dance movement therapy and Western dance forms such as Tango and ballroom dancing for people with Parkinson's (PwPs) have received increased interest in recent years. This study focused on developing and evaluating a culture-specific community-based dance therapy program using elements from Indian dance forms for PwPs in India and examining the replication of this intervention in the longitudinal case study with a person with Young Onset Parkinson's Disease.
Methods: 34 people diagnosed with Parkinson's disease (Hoehn &Yahr stage- II to IV) were assigned to a 'dance therapy group' or a 'traditional exercise group' using convenient sampling. Participants attended weekly 90-minute group sessions over twelve weeks. Assessments for physical functioning, cognitive abilities, non-motor symptoms, anxiety, depression, mood, and quality of life; were conducted pre and post-intervention period using standardised tests. For the individual case study, the dance therapy intervention program was carried out once a week for 90 minutes, over 2 years. Standardized tests, therapist's observations and patient's feedback were analyzed for results.
Results: Participants in the dance therapy group improved significantly on positive affect measured by the PANAS and reduced depression score measured by the HADS scale, compared to those in the traditional exercise group, along with improvements on the language subtest of the ACE III test. Both groups showed similar changes after intervention on motor symptoms assessed by the MDS-UPDRS scale and on Quality of Life measured by the PDQ-39. Subjective feedback from PwPs supplemented the findings for the group study. The results from the case study included improvements in mobility, balance, flexibility, mind-body coordination, acceptance of the diagnosis, advocacy, improved mood and reduced depression.
Conclusions: Dance therapy using elements from Indian dance forms is promising as a supportive intervention for Parkinson's Disease.

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FLARE UP OF FUNCTIONAL MOVEMENT DISORDERS DURING COVID-19 VIRAL OUTBREAK

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Aims: To quantify the increase in frequency and identify contributing factors leading to heightened incidence of Functional Movement Disorders (FMD) during the pandemic compared to pre-pandemic times.
Methods: A cross-sectional study was conducted involving patients from a neurology outpatient department at a tertiary care center over a six-month period during the pandemic. The study compared the occurrence of FMD in this cohort against a baseline from the pre-pandemic period. Data collected included demographics, clinical features, duration of FMD, psychiatric comorbidities, and assessments of anxiety and depressive symptoms using the Hospital Anxiety and Depression Scale (HADS) and sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI).
Results: The findings indicated that 22 out of 382 patients (approximately 5.8%) seen during the pandemic had FMD, compared to 31 out of 1462 patients (2.1%) in the pre-pandemic period, reflecting a 2.71-fold increase. The most prevalent type of FMD identified was functional myoclonus (36.4%), followed by functional gait disorders (27.2%), functional tremors (18.2%), and functional dystonia (9.1%). A significant majority of these patients exhibited elevated anxiety and depression scores, with 90.9% scoring above 11 on the HADS and 86.3% indicating poor sleep quality (PSQI > 5). Statistical analyses showed a strong correlation between increased anxiety levels and poor sleep quality with the rise in FMD cases during the pandemic.
Conclusions: Incidence of FMD during the COVID-19 pandemic was significantly higher by 2.71 times, suggesting that individuals predisposed to these disorders may be particularly vulnerable to the psychological stressors associated with the pandemic. The co-occurrence of anxiety and depression was identified as a critical risk factor for the development of FMD.The study highlights the need for heightened awareness among healthcare providers regarding emergence of FMD during stressful times.

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CAN SARS-COV-2 PROTEINS ACCELERATE ABETA42-INDUCED NEURODEGENERATION IN VIVO?

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Aims: It has been found that SARS-CoV2 proteins or RNAs can persist in different tissues, including the brain, for several months after infection, but the pathological implications of this finding are largely unknown. Moreover, given that the brains from people infected with SARS-CoV-2 display structural changes in regions related to learning and memory, there is a growing concern that SARS-CoV-2-infected individuals could be at higher risk of developing Alzheimer's disease. We aim to investigate whether SARS-CoV-2 proteins may accelerate the onset, duration and severity of Abeta42 pathology in Drosophila.
Methods: The 30kb SARS-CoV-2 genome encodes 16 non-structural proteins, nine putative accessory factors, and four structural proteins. We manipulated all these proteins individually in transgenic flies to define their potential pathogenic role in vivo. Drosophila tools and conditional expression systems were used to test these transgenic lines in multiple tissues and to assess their contribution to Abeta42-dependent phenotypes in fly models of AD through pathological and behavioral analyses.
Results: After testing all SARS-CoV-2 proteins in flies, we found that one non-structural protein has an extraordinary ability to induce a very aggressive phenotype when expressed in the Drosophila eye as well as loss of axonal projections when expressed in memory-related neurons. Strikingly, we also found that this protein triggers Abeta42-induced neurodegeneration in the fly brain, accelerates the formation of thioflavin-positive Abeta42 structures, and contributes to early death in Abeta42-expressing flies.
Conclusions: Our studies suggest that SARS-CoV-2 proteins display different degrees of neurotoxicity in vivo and that the expression of at least one non-structural protein accelerates the onset and severity of Abeta42 pathology, which may have important pathological implications in the field. We are currently validating this in mouse models of AD.

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WIDESPREAD SAA DETECTION OF A-SYNUCLEIN SEEDS IN THE GASTROINTESTINAL TRACT OF SYNUCLEINOPATHY CASES WITH NO INITIAL EVIDENCE OF "BODY-FIRST" HYPOTHESIS.

Christina Orru[1], Sarah Vascellari[2], Geidy Serrano[3], Andrew Hughson[1], Bradley Groveman[1], Sabiha Parveen[1], Parvez Alam[1], Jessica Walker[3], Anthony Intorcia[3], Ileana Lorenzini[3], Charles Adler[4], Byron Caughey[1], Thomas Beach[3]
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Aims: The site of initial prodromal deposition of pathological alpha-synuclein (α-Syn^D) is still a matter of debate. Early gastrointestinal (GI) tract symptoms, such as constipation, have been linked to the development of Parkinson's disease (PD) later in life. We investigated the deposition of α-Syn^D in the GI tract of PD, Dementia with Lewy Body (DLB) and neurologically asymptomatic elderly individuals using the rapid real-time quaking-induced conversion (RT-QuICR) seed amplification assay (SAA).
Methods: We performed neuropathological evaluations on 200 individuals and collected 10 sequential GI tract sections post-mortem (submandibular salivary gland, upper and lower esophagus, stomach, duodenum, jejunum, ileum, transverse colon, sigmoidal colon, and rectum). Homogenized tissues were screened in a blinded manner for α-Syn^D seeding activity using RT-QuICR.
Results: Unblinding of a subset of representative cases indicated that identification of α-Syn^D-positive and negative cases matched their neuropathological diagnoses. Results for α-Syn^D seeding activity were positive for 16/16 PD patients and 8/17 Incidental Lewy Body Disease (ILBD) cases. We currently see a similar rate of assay positivity throughout all GI tract subdivisions. Unified brain stages for PD cases included 13 with Neocortical stage (USSLB IV) and 3 with Brainstem and Limbic stage (USSLB III). Of positive ILBD cases, 6 were Brainstem Predominant stage and 2 were Brainstem and Limbic stage. Furthermore, immunohistochemically-assessed total brain LB pathology is so far significantly greater for GI tract-positive cases. Importantly, no cases without immunohistochemical brain evidence of LB pathology were positive for α-Syn^D seeding activity in the GI tract.
Conclusions: Our findings show widespread deposition of α-Syn^D in the GI tract of PD, DLB and some ILBD individuals but no evidence to date supportive of the "body-first" hypothesis. We expect to present further findings at the conference.

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THE STRUCTURE AND SURFACES OF ALPHA-SYNUCLEIN STRAINS DERIVED FROM DISTINCT SYNUCLEINOPATHIES DEFINE THEIR INTERACTOMES, FUNCTIONAL ACTIVITIES, AND TURNOVER

Tetiana Serdiuk[1], Virginie Redeker[2], Alexis Fenyi[2], Sandesh Neupane[3], Thomas Braun[4], Roland Riek[5], Adriano Aguzzi[3], Natalie De Souza[1], Ronald Melki[6], Paola Picotti[1]
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Aims: The aggregation of the protein alpha-synuclein (aSyn) is a common feature of multiple neurodegenerative diseases, including Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple Systems Atrophy (MSA). Here, we aim to characterize the structure-function relationship of aSyn disease specific strains at a proteome-wide level with a novel structural proteomics method.
Methods: We employ the Limited proteolysis coupled with mass spectrometry (LiP-MS) technique to detect structural changes and altered protein-protein interactions across thousands of proteins, with a resolution of ~10-20 amino acids. This allows LiP-MS to provide a new layer of structural insights that remain undetectable by other omics approaches.
Results: *In vitro* and *in situ* within neurons and directly in native patient brain homogenates, we show that pathogenic aSyn from distinct synucleinopathies (PD, DLB and MSA) are structurally different. Further, we found that fibrillar structural differences are associated with different structural responses of neuronal proteomes and strain-specific degradation pathways.
Conclusions: We revealed that fibrillar structure differences translate directly into fibrils interactomes and neuronal responses. Furthermore, our selected hits, involved in aSyn turnover, were validated with CRISPR-based tools.

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SOLUBLE ALPHA-SYNUCLEIN AND TAU POST-TRANSLATIONAL MODIFICATIONS: A NOVEL REGULATION MECHANISM FOR PATHOLOGICAL PROTEIN TRANSMISSION IN AD AND PD WITH THERAPEUTIC POTENTIAL

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Aims: Cell-to-cell transmission and amplification of pathological α-synuclein and tau are critical for the progression of Alzheimer's disease (AD) and Parkinson's disease (PD). However, the molecular mechanisms that regulate the spreading of pathological proteins remains largely unknown. Previous studies of pathological protein spreading have focused on the pathological seeds. However, successful amplification of pathological α-synuclein and tau involves two components: the formation of pathological α-synuclein and tau (i.e., the seeds) and the transformation of normal, soluble α-synuclein and tau (i.e., the substrate). What has been generally ignored is the potential effects of soluble α-synuclein and tau, as a substrate, on pathological α-synuclein and tau spreading. The Aim of our study is to analyze how soluble α-synuclein and tau post-translational modifications (PTMs) regulate the amplification of pathological α-synuclein and tau in AD/PD.
Methods: Using cell models, we evaluated how soluble α-synuclein and tau PTMs regulate the amplification of pathological α-synuclein and tau in AD/PD. Furthermore, we systematically identified soluble α-synuclein and tau PTMs in AD/PD by LC-MS/MS. Finally, using small compounds and enzymes we tested the therapeutic potential of soluble α-synuclein and tau PTMs for AD/PD.
Results: We identified many novel PTMs on soluble α-synuclein and tau in AD/PD by LC-MS/MS. Moreover, we showed that phosphorylation and acetylation on soluble α-syn and tau dramatically affects the amplification of pathological α-synuclein and tau, in a conformation-specific manner. Finally, by manipulating soluble α-synuclein and tau PTMs with small compounds or enzymes, we successfully reduced the amplification of pathological α-synuclein and tau purified from AD/PD.
Conclusions: Our study represents the first to analysis of how soluble α-synuclein and tau PTMs affect the amplification of pathological α-synuclein and tau in AD/PD, which provides novel drug targets for new therapies.

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AGE-RELATED LIPID ACCUMULATION DRIVES CELLULAR SENESCENCE IN DOPAMINERGIC NEURONS

Markus Riessland, Taylor Russo
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Aims: Neurodegenerative diseases, including Parkinson's disease (PD), are generally associated with aging, but the exact role of cellular senescence in neurodegeneration remains unclear. Given the age-related lipid accumulation observed in dopaminergic (DA) neurons of the substantia nigra, we aimed to explore how genetic risk factors for PD, such as *GBA, SNCA* and *SATB1*, alongside lipid accumulation, influence cellular senescence in DA neurons.
Methods: We utilized highly enriched cultures of stem cell-derived DA neurons, alongside cell lines and mouse models, to explore the interplay between the PD risk genes *GBA, SNCA* and *SATB1*. To elucidate their molecular connections, we employed multiple sequencing techniques, functional studies incorporating imaging, biochemical assays, and energy metabolism analyses.
Results: We found a regulatory interaction between three risk factors for PD: GBA, SNCA and SATB1, which is mediated through regulation of the miRNA gene *MIR22HG*, another PD risk gene. miRNA miR-22-3p downregulates GBA leading to lipid and α-SYN accumulation. Given that PD is age-related, it is notable that both *GBA* and *SATB1* expression declines with age, while miR-22-3p expression increases. Additionally, elevated miR-22-3p levels were observed in REM sleep behavior disorder, a strong predictor of PD, as well as in Lewy body disease. The resulting accumulation of lipids (glucocerebrosides) is sufficient to induce cellular senescence in DA neurons leading to inflammaging.
Conclusions: Our findings suggest that age-related lipid accumulation-induced senescence in dopamine neurons contributes to the pathology of PD. Previous studies have noted significant inflammation in the midbrain of PD patients even before the onset of symptoms and DA neuron degeneration. We propose that senescence of DA neurons, driven by lipid accumulation, may trigger this inflammation, leading to an "inflammaging" process that ultimately results in the loss of DA neurons.

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A NOVEL THERAPEUTIC FOR THE TREATMENT OF PARKINSON'S DISEASE TARGETING THE TPA-NMDAR INTERACTION

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[1]University of Michigan, Internal Medicine, Ann Arbor, United States of America, [2]Normandy University Unicaen, Inserm, U1237, Phind "physiopathology And Imaging Of Neurological Disorders", Neuropresage Team, Caen, France, [3]Lys Therapeutics, Lyon, France

Aims: The therapeutic potential of glunomab, a monoclonal antibody designed to inhibit the interaction between the endogenous protease tissue plasminogen activator (tPA) and the N-methyl-D-aspartate receptor (NMDAR), has been demonstrated in multiple animal models of neurological diseases. Specifically in Parkinson's Disease (PD), we identified tPA+ GABAergic striatal neurons that innervate substantia nigra (SN) dopaminergic neurons and observed increased tPA protein levels in the SN in a human α-synuclein (hα-syn) mouse model of PD. Additionally, we demonstrated that both tPA deficiency or repeated intravenous administrations of glunomab protected dopaminergic neurons from hα-syn-induced degeneration. We further evaluated the therapeutic effect of glunomab treatment initiated at various stages of disease onset, evaluating whether glunomab remains effective when treatment starts later in PD progression, simulating clinical situations.
Methods: WT, $tPA^{-/-}$ and mice overexpressing proteolytically inactive tPA were unilaterally injected with AAV-empty or AAV-hα-syn in the SN. Glunomab was administered weekly intravenously at different starting points. Mice were evaluated 4 weeks later for lateralized neglect using the corridor test; dopaminergic neurodegeneration, and immune cell activation and invasion of the SN were investigated by immunohistochemistry.
Results: Glunomab administration protected dopaminergic neurons from α-syn-induced degeneration even when treatment was initiated after disease onset. This neuroprotection was accompanied by reduced immune cell infiltration, along with a reduction in lateralized sensory-motor deficit in the corridor test.
Conclusions: Our data highlight that tPA promotes neuroinflammation and dopaminergic neurodegeneration induced by overexpression of hα-syn, and that glunomab prevents neurodegeneration and inhibits tPA-induced neuroinflammation, translating into improved sensory-motor function in a hα-syn mouse model of PD. A humanized version of glunomab, LYS241, is currently undergoing IND/CTA-enabling studies in preparation for future clinical trials in PD patients.

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EFFECT OF A-SYNUCLEIN INDUCED TUNNELING NANOTUBES ON ASTROGLIAL FATE: AGGREGATE CLEARANCE AND STEMNESS

Rachana Kashyap A N, Abinaya Raghavan, Anirudh Sreenivas Bk, Ahana Das, Ravi Manjithaya, Sivaraman Padavattan, Sangeeta Nath
Manipal Academy of Higher Education, Manipal Institute Of Regenerative Medicine, Bangalore, India

Aims: Aim: Neurons and glial cells are important for brain homeostasis. α-Synuclein (α-SYN), a crucial protein in the development of Parkinson's disease (PD) pathology, is known to facilitate glial crosstalk via tunneling nanotubes (TNTs) between neuroglial cells. We investigate how TNTs aid in rescuing astroglial cells by facilitating the clearance of α-SYN protofibrils-induced toxic burdens. Subsequently, the cells acquire characteristics of cancer stem-like progenitor cells (CSCs).
Methods: Methods: Exogenous α-SYN protofibrils in both murine astrocytes and human astroglia induce enhanced organelle toxicities, reactive oxygen species (ROS) generation, and transient TNT biogenesis. TNTs were characterized by membrane dye DiD and actin staining dye phalloidin using 3D-confocal images. The TMRE dye was used to measure mitochondrial membrane potential (Ψm), as well as fission-fusion dynamics and TNT-mediated transfer. RNA-sequencing data and spheroid assay validated the increase of signalling pathways regulating pluripotency of stem cells in relation to mitochondrial Ψm.
Results: Results: We found that a low mitochondrial Ψm resulting from α-SYN protofibrils treatments plays a crucial role in regulating cellular stemness. Increased ROS in these cells causes translocation of phosphorylated focal adhesion kinase (pFAK) to the nucleus, where it co-localizes with Nanog, a key transcription factor of CSCs. α-SYN protofibrils promote the biogenesis of TNTs via modulation of ROCK inhibitory signaling pathways. Both α-SYN protofibrils and ROCK inhibitor treatment cause higher CSC marker expression.
Conclusions: Conclusion: Our study delineates how TNT biogenesis and transient nuclear translocation of pFAK lead to the upregulation of transcription factors related to stem-like pluripotency in astroglia, aiding the survival of α-SYN treated toxic cells. This study thus opens up potential therapeutic strategies that involve targeting the biogenesis of TNTs to overcome conventional treatment-resistant CSC populations.

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SCREENING APPROVED DRUGS TO RESTORE MITOCHONDRIAL FUNCTION IN PARKINSON'S DISEASE

Svein Isungset Støve[1,2,3], Kunwar Jung Kc[2,3], Charalampos Tzoulis[1,2,4], Aurora Martinez[2,3]
[1]Haukeland University Hospital, Nevroklinikken, Bergen, Norway, [2]KG Jebsen Center for Parkinson's disease, Bergen, Norway, [3]University of Bergen, Department Of Biomedicine, Bergen, Norway, [4]University of Bergen, Department Of Clinical Medicine, Bergen, Norway

Aims: Parkinsons disease (PD) imposes a significant personal and socioeconomic burden, characterized by progressive disabilities and premature death. Recently, our lab identified a PD subtype characterized by neuronal mitochondrial complex I deficiency, leading to mitochondrial dysfunction, providing a clear molecular target for future drug discovery. In this project, we thus aim to develop disease modifying therapies (DMTs) for PD targeting mitochondrial function.
Methods: We have established a cellular drug discovery platform using In-cell western to identify compounds that influence mitochondrial function and specifically mitochondrial complex I. All hit compounds will be validated and characterized, and the most promising among them will be tested in preclinical models. Successful compounds will be nominated for clinical trials conducted by our national and international network.
Results: We have screened a library of already approved drugs and identified several hit compounds that increase mitochondrial complex I protein levels. Our most promising hit (Hit1) is currently being characterized in cell models with very positive preliminary data that among other include increased CI protein expression and enhanced mitochondrial function. All hits from the screening will be thoroughly validated and characterized, and the most promising hits will be tested in a PD-mouse model (Thy1-aSyn).
Conclusions: By cellular screening of already approved drugs, this innovative project has identified several hit compounds that positively influence mitochondrial function. One particularly promising compound (Hit1) is nearing readiness for testing in mouse models. By advancing our understanding of PD and developing innovative treatments, this project has the potential to significantly improve the quality of life for patients and pave the way for future breakthroughs in neurodegenerative disease research.

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MOLECULAR SIGNATURES OF ALTERED ENERGY METABOLISM AND CIRCADIAN RHYTHM PERTURBATIONS IN A MODEL OF EXTRA-NIGRAL SYNUCLEINOPATHY

Lin Lin[1], Nanna Møller Jensen[2], Sara Ferreira[1], Alberto Delaidelli[3], Marina Romero-Ramos[4], Poul Henning Jensen[2], Ian Mackenzie[5], Jens Nyengaard[6], Asad Jan[1]
[1]Aarhus University, Aarhus, Denmark, [2]Aarhus University, Dandrite, Dept. Of Biomedicine, Aarhus C, Denmark, [3]University of British Columbia, Vancouver BC, Canada, [4]Aarhus University, Dept. Of Biomedicine, Aarhus C, Denmark, [5]University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada, [6]Aarhus University, Clinical Medicine, Aarhus, Denmark

Aims: A pathological role of alpha-Synuclein (aSyn) aggregation in the central nervous system (CNS) is a recognized feature in Parkinson disease (PD) and related neurodegenerative conditions termed synucleinopathies. In order to characterize the cellular response in CNS to incipient and advanced aSyn pathology, we applied spatial transcriptomics on brain sections derived from a transgenic mouse model (M83$^{+/+}$ line, *Prnp-SNCA*A53T*) in which aSyn aggregation was induced in a prion-like fashion through hindlimb intramuscular delivery of pre-formed fibrillar (PFF) murine aSyn.
Methods: Spatial Transcriptomics, Histopathology (Mouse and Parkinson disease post-mortem brains)
Results: Our spatially-resolved data point to unique perturbations in brain energy metabolism during the progression of aSyn pathology, such that there is a prodromal phase of mitochondrial hypermetabolism in disease-affected regions, which is followed by a profound decline in glycloysis, oxidative phosphorylation and fatty acid metabolism leading to the symptomatic phase. This latter stage was also associated with drastic reduction in mRNA translation machinery, neuroinflammation and aberrant expression of molecular drivers controlling circadian rhythms. Moreover, we also discovered that cellular aSyn pathology triggers distinct transcriptional response in the components of white matter and choroid plexus, which otherwise remain underrepresented features in studies of PD and related disorders.
Conclusions: Collectively, we anticipate that these transcriptomics datasets offer novel opportunities in knowledge translation for mechanism-based drug discovery, and hold promise for exploring novel hypotheses concerning the neuronal stress response to pathological aSyn aggregation.

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LOCALISED COPPER DECREASES IN ALZHEIMER'S, PARKINSON'S DISEASE DEMENTIA, AND DEMENTIA WITH LEWY BODIES

Melissa Scholefield[1], Stephanie Church[1], Jingshu Xu[2], Richard Unwin[1], Garth Cooper[2]
[1]University of Manchester, Division Of Cardiovascular Sciences, Manchester, United Kingdom, [2]University of Auckland, School Of Biological Sciences, Auckland, New Zealand

Aims: Metallomic analyses of the Alzheimer's disease (AD) and Parkinson's disease dementia (PDD) brain have revealed several metallic alterations across multiple regions of the brain-most markedly, widespread copper decreases. As an enzyme and antioxidant co-factor, decreased levels of copper may lead to several downstream effects, including mitochondrial dysfunction and increased oxidative stress. This study aimed to investigate whether metallic dysregulation is also present in the DLB brain.
Methods: Eight essential metals (Na, Mg, K, Ca, Mn, Cu, Fe, and Zn) and the metalloid Se were quantified using inductively coupled plasma mass spectrometry (ICP-MS) in 20 DLB cases vs 19 matched controls, covering eleven different brain regions. Case-control differences were determined by Mann–Whitney U tests and the results were compared with those previously obtained for AD and PDD.
Results: The DLB brain showed no significant alterations in Mg, K, or Zn and only very localised decreases in Mn, Ca, and Se. Increased Fe was found in the motor cortex and cingulate gyrus, while increased Na was observed in the medulla, cingulate gyrus, middle temporal gyrus, and cerebellum. As in AD and PDD, Cu decreases were the most widespread change, affecting the cingulate gyrus, middle temporal gyrus, substantia nigra, primary visual cortex, and putamen. However, PCA was able to distinguish DLB cases from AD cases using data from the cingulate gyrus, middle temporal gyrus, and primary visual cortex, and DLB from PDD using the primary visual cortex alone.
Conclusions: Copper depletion appears to be a common alteration across AD, PDD, and DLB, suggesting a potential shared mechanism via copper's downstream effects on antioxidation and mitochondrial function. However, other metallic alterations may be useful in distinguishing different types of dementias at earlier stages.

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MACHINE LEARNING PREDICTION OF CLINICALLY RELEVANT MDS-UPDRS III MILESTONES USING BASELINE FEATURES

Matthew Miyasaka, Mohsin Ahmed, Andreja Avbersek, Danni Tu, Quang Nguyen, Rong Liu, Olivier Harari, Oren Levy, Farshid Sepehrband
Regeneron Pharmaceuticals, Inc., Tarrytown, United States of America

Aims: Parkinson's disease progression exhibits significant variability, complicating the prediction of future outcomes. Previous studies have developed models to predict the overall MDS-UPDRS score worsening. However, a limitation of the MDS-UPDRS is the lack of milestone ratings that indicate a clinically meaningful worsening, to identify patients suitable for trials of disease-modifying therapies. This study posits MDS-UPDRS III item milestones to explore models to predict clinically meaningful progression.
Methods: For this exercise, a score ≥3 (indicating at least 'moderate' impairment) on an individual item was posited as a clinically significant milestone. For each Part III item, patients from the Parkinson's Progressive Markers Initiative were categorized as progressors or non-progressors based on whether the milestone was achieved within 4 years. If more than 100 patients reached the milestone, random forest models were trained using baseline demographic, clinical, and imaging features to classify progressors versus non-progressors, with an 80:20 training:test data split. Feature importance was derived using the out-of-bag error change based on mean-square-error.
Results: Three Part III items met the criteria for model development (standing from seated, gait impairment, and stooped posture; **Fig.1**); all achieved specificity >60%, sensitivity ~80%, and area under curve >0.7 (**Fig.2**). In the model, age and specific MDS-UPDRS III subscores (other than the milestone-defining item) were predictive of these 4-year milestone-defined progressions. The MDS-UPDRS II total score was also predictive for all three milestones (**Fig.3**).

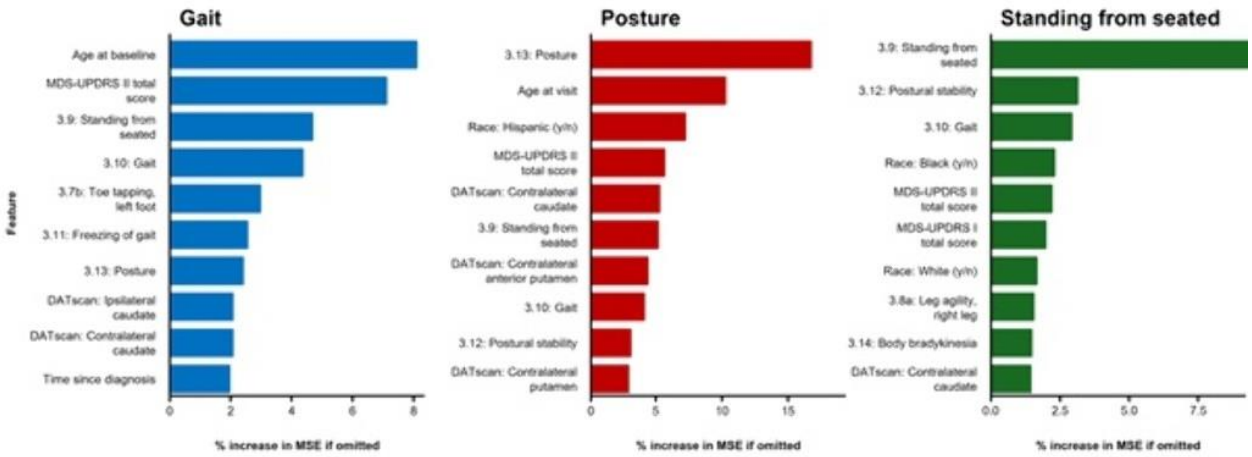
Figure 1. Motor symptom progression milestones for each MDS-UPDRS III subscore of interest

Subscore	Progressors (n)	Nonprogressors (n)	Milestone
3.9: Standing from seated	114	1125	Needs to push off arms of chair, but now tends to fall back; or may have to try more than once using arms of chair, but can get up without help
3.10: Gait	153	1073	Gait impairment now requires an assistance device for safe walking (walking stick, walker) but not a person
3.13: Posture	116	1123	Stooped posture, scoliosis or leaning to one side that can no longer be corrected volitionally to a normal posture by the patient

Figure 2. Random forest model performance for each clinically relevant motor symptom

Symptom	Model	AUC	Sensitivity	Specificity
Gait	All predictors	0.70	0.55	0.85
	Top 10 features	0.72	0.63	0.82
Posture	All predictors	0.68	0.54	0.81
	Top 10 features	0.70	0.61	0.78
Standing from seated	All predictors	0.85	0.67	0.89
	Top 10 features	0.77	0.69	0.87

Figure 3. Top 10 baseline features for each motor symptom, ranked by descending importance



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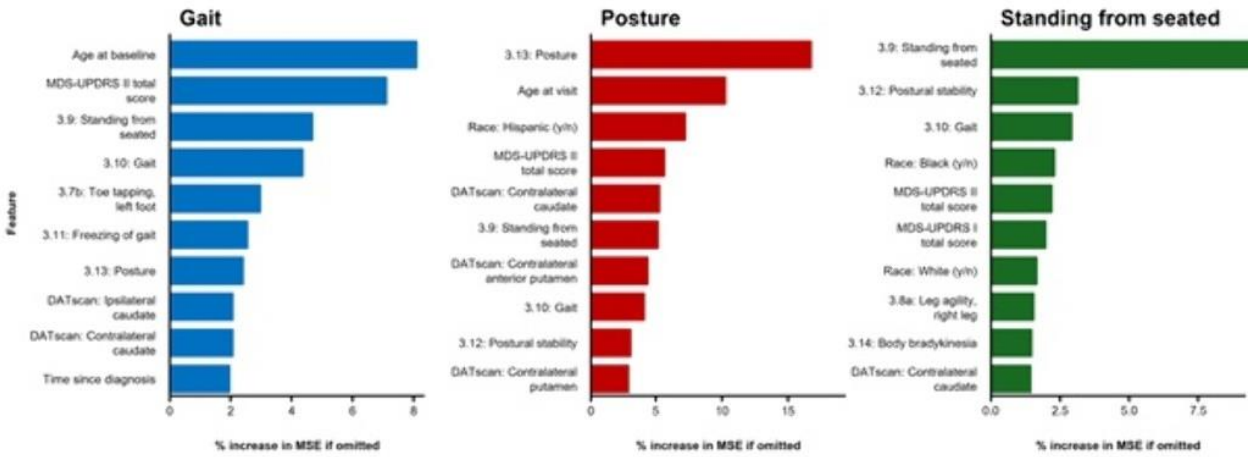

Conclusions: Random forest models demonstrated the ability to assess the prognostic utility of putative MDS-UPDRS III progression milestones. Prognostic variables included age and specific MDS-UPDRS items. Further refinement of this methodology may enhance the accuracy of future progression predictions in Parkinson's disease, accompanied by a consensus approach to identifying clinically meaningful progression milestones.

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AGEING IN PARKINSON'S DISEASE: CLINICAL AND BIOMARKERS PROFILING OF YOUNGER AND OLDER PATIENTS

Giulia Di Lazzaro[1], Federico Paolini Paoletti[2], Giovanni Bellomo[2], Tommaso Schirinzi[3], Piergiorgio Grillo[4], Guido Maria Giuffrè[1], Martina Petracca[1], Anna Picca[5], Nicola Biagio Mercuri[6], Anna Rita Bentivoglio[1], Lucilla Parnetti[2], Paolo Calabresi[1]
[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, [2]University of Perugia, Department Of Medicine And Surgery, Section Of Neurology, Perugia, Italy, [3]Policlinico Universitario Tor Vergata, Rome, Italy, [4]IRCCS Mondino Foundation, Pavia, Italy, [5]LUM University, Casamassima, Italy, [6]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy, Roma, Italy

Aims: PD is increasingly diagnosed in younger patients, even if it was classically defined as a disease of the elderly [1]. Clinical evidence indicates that PD patients have different progression rates and disease characteristics[2, 3] the older being more cognitively affected and experiencing less motor fluctuations. Given the well-known clinical differences and natural history of Parkinson's disease (PD) according ot patients age, this study aims at exploring the different pathophysiological mechanisms underlying PD in patients of different age, independently from disease duration, through CSF biomarkers.
Methods: Patients with clinically established diagnosis of PD were enrolled at three different sites in Italy. They underwent clinical evaluation through MDS-UPDRS, NMSS and MoCA scales. CSF inflammatory (YKL-40, TREM-2) and neurodegeneration/synaptopathy (A-beta42 and 40, tau, p-tau, sAPP-a and -b, NfL, Ng) biomarkers were analysed.
Results: 95 patients were recruited, 42 younger than 65 years-old, and 53 older. Age strongly correlated with NfL, YKL-40 and Alzheimer's related pathology biomarkers, in a stronger manner with tau species. Younger and older patients showed different biomarkers profile. In particular, younger patients showed significantly lower levels of inflammatory molecules (YKL-40) and of degeneration biomarkers (neurogranin, tau species, neurofilaments), independently from disease duration. Clinically, younger patients had better scores at UPDRS parts I, II, III and IV and MoCA.
Conclusions: Our data support the hypothesis that PD has different features in younger and older patients, with a differentunderlying pathology. This could reflect a more preponderant loss of integrity of neuronal circuits independently from the nigro-striatal degeneration, as the higher prevalence of amyloid pathology and higher burden of neurodegeneration could be related to worse cognitive performances in older patients and lower levodopa-induced dyskinesia, for which an aberrant plasticity is the major recognized pathophysiological mechanism.

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MECHANISMS UNDERLYING THE INFLUENCE OF BIOLOGICAL SEX ON PARKINSON'S DISEASE.

Sabina Marciano[1], Claudia Rodriguez-Lopez[1], William Tower[1], Garrett Sommer[2], Rong Chen[3], Ted Dawson[3], Michael Kaplitt[1], Teresa Milner[2,4], Roberta Marongiu[1]
[1]Weill Cornell Medical College, Neurological Surgery, New York, United States of America, [2]Weill Cornell Medical College, Feil Family Brain And Mind Institute, New York, United States of America, [3]John Hopkins University, Baltimore, United States of America, [4]Rockefeller University, New York, United States of America

Aims: Sex dimorphism in Parkinson's disease (PD) incidence and symptoms has been reported. Compelling evidence suggest that ovarian hormones and menopause age influence women's susceptibility to PD. Yet, the biological mechanisms influencing the sex-specific selective neuronal vulnerability in PD are largely unknown.
Methods: To study the role of ovarian hormones on PD, prior works mainly used toxin models of the disease and ovariectomy as surgical menopause model. In our research, we employed two alpha-synuclein mouse models of PD, which better mimic the disease progressive nature and pathology, and the novel accelerated ovarian failure (AOF) model in females, which fully recapitulates the human menopause compared to the ovariectomy. This work delves into the longitudinal study of motor/non-motor phenotypes, alpha-synuclein pathology, and neuronal vulnerability in males, and intact and AOF females.
Results: Our data show a sexually dimorphic phenotype in the development of motor and non-motor symptoms in our alpha-synuclein mice, and an accelerated onset of motor symptoms in peri-menopausal females with PD compared to age-matched intact females and corresponding control group. Histological analysis of brain tissue showed sexually dimorphic levels of phosphorylated pSer129 alpha-synuclein (pSyn) species and neurodegeneration across multiple brain regions over time, including the basal ganglia, suggesting that different brain circuits may be preferentially affected in a sex-specific manner. Characterization of the underlying sex-specific molecular mechanisms is currently ongoing.
Conclusions: Our data strongly support a role for menopause on PD onset and progression. Furthermore, this work shows that the use of the AOF model has the potential to unravel the sex- and menopause-specific molecular mechanisms of PD pathogenesis. This will provide crucial insights for developing sex-specific therapeutic approaches for distinct vulnerabilities for individuals with and at risk of PD.

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JANUS KINASE INHIBITOR CONFERS NEUROPROTECTION VIA MODULATING THE AMYLOIDOGENIC, NF-KB, AND NRF2 PATHWAYS AGAINST SCOPOLAMINE-INDUCED ALZHEIMER'S DISEASE IN RATS

Khushboo Faldu, Jigna Shah
Institute of Pharmacy, Nirma University, Pharmacology, Ahmedabad, India

Aims: Alzheimer's disease (AD) is a neurodegenerative disease characterised by impaired learning, memory, and cognitive function. Janus kinase inhibitor (JKI) has been reported to suppress pro-inflammatory cytokine production and activate the PI3K-Akt-GSK-3β pathway, providing neuroprotection through its anti-inflammatory properties. The current research aimed to evaluate the neuroprotective and senomorphic potential of JKI in a rat model of Alzheimer's disease induced by scopolamine by modulating the amyloidogenic, NF-κB, and Nrf2 pathways.
Methods: The rats received 2 mg/kg of scopolamine through an intraperitoneal injection every day for 14 days, which was followed by administration of JKI at doses of 0.45, 0.9, and 1.8 mg/kg and 5 mg/kg of donepezil orally as per group allocation, for the following 28 days while still receiving daily scopolamine injections. The behaviour of the rats was evaluated using Modified Y-Maze and Novel object recognition tasks. Biochemical examinations included AD pathology indicators (Amyloid beta peptide 1-40, Amyloid beta peptide 1-42, acetylcholinesterase, BACE1, total tau, and p-tau), inflammation markers (NF-κB, TNF-α, IL-6, and interferon γ), antioxidants (Nrf2 and HO-1), as well as evaluations of synaptophysin and GFAP immunohistochemistry and hippocampal histopathology.
Results: Our results showed that JKI significantly improved scopolamine-induced behavioural alterations. The levels of acetylcholinesterase, BACE1, amyloid beta 1-40, amyloid beta 1-42, total tau, p-tau, NF-κB, IFN-γ, IL-6, and TNF-α levels were significantly diminished. Whereas the levels of HO-1 and Nrf2 showed a marked rise. Further, it also halted the degeneration of neurons, increased synaptophysin reactivity, and decreased GFAP reactivity.
Conclusions: The study suggests that JKI may exhibit senomorphic potential via modification of the transcription factor- NF-κB and senescence-associated secretory phenotype and thus, confers neuroprotection via modulation of NF-κB and Nrf2 signalling axis in Alzheimer's disease.

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CINNAMALDEHYDE ALLEVIATES ALPHA-SYNUCLEIN TOXICITY VIA MODULATION OF GLP-1/PI3K/AKT CASCADE IN ROTENONE-INDUCED MOUSE MODEL OF PARKINSON'S DISEASE

Jigna Shah, Kirti Mathur, Ritu Soni
Institute of Pharmacy, Nirma University, Pharmacology, Ahmedabad, India

Aims: The second most common neurodegenerative disease, Parkinson's disease (PD), is marked by a gradual and significant loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc). A naturally occurring flavonoid called cinnamaldehyde may upregulate secretion of GLP1 and thereby stimulation of GLP1/PI3K/AKT cascade. This may lead to phosphorylation and inhibition of GSK-3β. GSK-3β is responsible for hyperphosphorylation of alpha-synuclein leading to its aggregation. Thus, stimulation of this cascade would potentially impede aggregation of alpha-synuclein and consequently the progression of Parkinson's pathology. The goal of the study was to investigate the neuroprotective potential of cinnamaldehyde in the C57/BL6 mouse model of Parkinson's disease that was produced by rotenone.
Methods: Ten mice each were assigned to one of four groups: NC (normal control), DC (disease produced by rotenone, 30 mg/kg p.o.), T (cinnamaldehyde alone treatment group, 50 mg/kg p.o.), and RT+ T (rotenone plus cinnamaldehyde treatment group). The study was conducted for 28 days. The Y-maze, pole test, wire hang, and beam walk were performed to test various behavioural parameters. Animals were sacrificed at the end of fourth week, and brain samples were collected. In addition to histological investigation and Nissl staining, neuroprotective parameters (alpha-synuclein, PI3K, AKT, BDNF, GSK-3β, GLP1, NF-κB) were analysed.
Results: The findings demonstrated that cinnamaldehyde reduced rotenone-induced behavioural abnormalities. It decreased NF-κB, GSK-3β, MDA, and α-synuclein levels, and upregulated BDNF, PI3K, AKT, GLP-1, Nrf2, CREB, and reduced glutathione. According to the histological investigations, cinnamaldehyde restored the structural abnormalities induced by rotenone.
Conclusions: Cinnamaldehyde diminished motor abnormalities, and upregulated PI3K, AKT, Nrf2 and BDNF levels. It also decreased alpha-synuclein levels. Moreover, it restored neuronal density and integrity. The results are indicative of the neuroprotective potential of cinnamaldehyde in Parkinson's disease.

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DEVELOPMENT OF MORPHOMER-ANTIBODY DRUG CONJUGATES - A NEW CLASS OF DRUGS FOR NEURODEGENERATIVE DISEASES

Madiha Derouazi, Nampally Sreenivasachary, Elpida Tsika, Oskar Adolfsson, Camille Martin, Romain Ollier, Sebastien Menant, Sylvain Pautet, Lorène Aeschbach, Johannes Brune, Nadine Ait-Bouziad, Alexis Fenyi, Aline Fuchs, David Ribas, Marie Kosco-Vilbois, Andrea Pfeifer
AC Immune, Research, Lausanne, Switzerland

Aims: Aggregation of misfolded proteins are key contributors to the progression of neurodegenerative diseases (NDD). We explore the potential of antibody-drug conjugates (ADC) to increase efficacy and brain exposure of therapeutic monoclonal antibodies (mAbs) using small molecules of our proprietary Morphomer® platform, which are brain penetrant and target aggregation-prone proteins. We expect that similar to oncology, this approach would represent a major advancement in the NDD field.
Methods: Several morADCs were engineered by conjugating mAbs and morphomers using different linkers. The morADC blood-brain-barrier (BBB) permeability was assessed *in vitro* and their effects on aggregation were evaluated by Thioflavin-T and electron microscopy. Neuron seeding assays were used to study their effects on internalization and accumulation of aggregates. Brain exposure of selected molecules was tested in mice compared to parental mAbs. Proof-of-concept efficacy of morADC is being assessed in transgenic mice inoculated with alpha-synuclein fibrils (tg-PFF mice).
Results: Over 30 morADCs were produced to target pathological proteins, e.g., Abeta, Tau and alpha-synuclein. Drug-to-antibody ratios of 2.5-4.5 were achieved exhibiting excellent purity and plasma stability. The morADC molecules demonstrated significantly higher potency *in vitro* than parental molecules in various seeding assays. MorADCs showed 3-6-fold enhanced BBB penetration *in vitro* as compared to parental mAb and 2.5-fold increase of morADC exposure in mouse parenchyma. Ongoing work in tg-PFF mice will assess *in vivo* effects of morADCs targeting pathological alpha-synuclein at inhibiting disease propagation.
Conclusions: Bioconjugating functionally active mAbs and small molecules provides therapeutic morADCs as a new treatment modality with synergistic potential to target NDD pathologies. Ongoing studies focus on further characterization of the striking synergistic effect observed as well as proof-of-concept studies in relevant pathological models. This novel morADC platform represents a promising breakthrough approach in NDDs.

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DISCOVERY AND OPTIMIZATION OF THERAPEUTIC SMALL MOLECULES TARGETING ALPHA-SYNUCLEIN AGGREGATION

Elpida Tsika, Nadine Ait-Bouziad, Nicolas Dreyfus, Coralie Vallet, Karishma Bhawnani, Sylvain Pautet, Lorène Aeschbach, Johannes Brune, Thomas Jaquier, Aline Fuchs, David Ribas, Nicolas Sanchez, Nicolas Fournier, Heiko Kroth, Francesca Capotosti, Marie Kosco-Vilbois, Andrea Pfeifer, Madiha Derouazi
AC Immune, Lausanne, Switzerland

Aims: Parkinson's disease (PD) and other neurodegenerative diseases (NDD) are characterized by the accumulation of alpha-synuclein (a-syn) aggregates that correlate with clinical manifestations. We aim to discover cell-permeable, orally bioavailable and brain penetrant small molecules that inhibit aggregation and intracellular accumulation of pathological a-syn as a treatment for PD and NDDs.
Methods: Small molecules were designed based on our unique, proprietary Morphomer® platform and characterized in assays evaluating their inhibitory effects on a-syn aggregation. These included cell-based assays to study small molecules' potency in preventing a-syn aggregate accumulation within neurons and binding studies to measure affinity to brain-derived aggregates. Pharmacokinetics, brain exposure and tolerability were evaluated in mice after single and repeated dosing while efficacy was demonstrated *in vivo* in a spreading model of a-syn using transgenic mice inoculated with human a-syn preformed fibrils (tg hPFF mice).
Results: Through iterative medicinal chemistry and screening cycles identified the optimized compound, ACI-21018, an orally bioavailable, CNS penetrant and potent aggregation inhibitor that reduces the formation of intracellular aggregates in neurons with nanomolar IC_{50} and demonstrates target engagement on brain-derived a-syn aggregates with nanomolar dissociation constants. Importantly, treatment of tg hPFF mice with ACI-21018 led to a reduction of seeding-competent a-syn aggregates, together with significant neuroprotective effects.
Conclusions: Concerted Medicinal Chemistry optimization and robust *in vitro* assays led to the discovery of ACI-21018, a highly brain penetrant compound that reduces levels of propagating pathological a-syn species mitigating neurodegeneration in a mouse model of PD. ACI-21018 holds promise in providing therapeutic benefit for PD and other alpha-synucleinopathies.

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NOVEL APPROACH TO OPTIMIZATION OF ALPHA-SYNUCLEIN VACCINE COMPOSITION FOR MAXIMAL TARGETING OF TOXIC ALPHA-SYNUCLEIN SPECIES

Johanne Kaplan[1], Scott Napper[2], Ebrima Gibbs[3], Erin Scruten[2], Juliane Coutts[3], Joel Watts[4], Marco Prado[5], Neil Cashman[1]
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Aims: Vaccination against pathogenic species of alpha-synuclein (ASyn) has the potential to protect against synucleinopathies. Vaccine constructs containing computationally-derived conformational B cell epitopes in the EKTKEQ region of misfolded pathogenic ASyn were generated. The objective was to design an optimal vaccine composition to elicit antibodies that selectively target toxic species of ASyn and avoid cross-reactivity with physiologic and non-toxic forms of ASyn.
Methods: Mice were vaccinated with four different conformational B cell epitopes conjugated to KLH and formulated with QS-21 adjuvant. Serum IgG titers against the peptide epitopes were measured by ELISA. The binding profile of the antibodies was assessed against monomers and pathogenic ASyn in soluble brain homogenates from dementia with Lewy bodies (DLB) patients by SPR, and reactivity with Lewy bodies/neurites by immunohistochemistry.
Results: All 4 epitopes elicited robust antibody responses when administered either individually or together as part of a quadrivalent vaccine. The serum antibodies reacted with pathogenic ASyn in DLB soluble brain homogenate but not with physiologic monomers or non-toxic insoluble fibril deposits in brain sections. Comparison of binding responses to DLB brain homogenate and dissociation rates of equal amounts of IgG from immune serum of monovalent vaccines vs mixtures of 2, 3 or 4 sera was used to rank all 15 possible vaccine configurations. Maximal, equivalent reactivity was observed with a combination of immune IgG from 2 select epitopes or a mixture of all 4.
Conclusions: Vaccination with conformational B cell epitopes produced antibodies with the desired selectivity for pathogenic ASyn. The potential advantage of this approach, as opposed to inducing pan-ASyn reactivity, lies in preserving normal ASyn function and minimizing the diversion of active antibody by the more abundant non-toxic forms of the protein in blood and CNS.

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DENDRITIC CELL BASED IMMUNOTHERAPY TARGETED ON AGGREGATED ALPHA SYNUCLEIN FOR PARKINSON'S DISEASE

Haiqiang Yang[1], Ning Shen[1], Xiaoyang Lin[2], Chuanhai Cao[3]
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Aims: The accumulation and aggregation of α-synuclein (α-Syn) play central role in the pathogenesis of Parkinson's disease (PD). The immunotherapeutic approaches that focus on this molecule have shown promising results. In this study, we explored the effectiveness of a novel dendritic cell (DC)-based vaccine targeting on pathological α-Syn in a mouse model expressing α-Syn.
Methods: The mouse model was established by injecting C57BL/6 wild type mice with AAV-a-Syn. AAV-α-Syn administrated through Stereotaxic Surgery to the mouse brain striatum. The DC vaccine was created by using mouse bone marrow and sensitized with aggregated recombinant a-Syn. The vaccine was administered by tail vein injection for 4 times in biweekly schedule.
Results: Significant motor deficits were observed in the AAV-α-Syn injection group through the rotarod test. Following the administration, considerable behavior enhancements were noted in the vaccinated group. The titer of anti-a-Syn antibody was consistently present in the blood of mice from the third injection onward. Furthermore, the antibody was detectable in different mouse brain regions.
Conclusions: Research has shown that vaccine and immunotherapy strategies are effective in animal models of neurodegenerative diseases like PD and AD. Immunotherapy stands out as an appealing option for AD treatment. Our results further reinforce the notion that active immunotherapy aimed at aggregated α-Syn could serve as a possible therapeutic approach for slowing the progression of symptoms of PD.

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CHANGING THE COURSE OF DISEASE PROGRESSION WITH PARKIN THERAPEUTICS: THE MASTER REGULATOR OF MITOCHONDRIA, AUTOPHAGY AND INFLAMMATION

Jennifer Johnston, Marshall Goodwin, Amy Poirier, Elizabeth Higgins, Ron Mandel
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Aims: Mutations in the Parkin gene are the most common genetic cause of Young Onset PD. Parkin enzyme is established as a master regulator in PD: Mitochondrial repair, autophagy and ubiquitin, and studies demonstrate neuroprotective activity after delivery of the enzyme. Our team is advancing Parkin Gene Therapy to the clinic based on rodent and NHP studies demonstrating efficacy, dose range and tolerability.
Methods: Parkin KO rats were used for dose-range finding for efficacy to modulate pUb (Parkin substrate) using extracts from isolated Substantia nigra, +/- adminstration of NB001 (AAV-Parkin) at multiple test doses. Drug exposure analysis using qPCR to demonstrate total drug levels in nigra, and Human Parkin Elisa assay used to determine the amount of human parkin protein produce in the nigra after intraprenchymal dosing. HUman Parkin levels compared to endogenous Parkin levels were used to determine effective doses compared to endogenous amounts of Parkin protein. In NHP, similar intranigral deliveryof NB001 was used to establish tolerability ranges, and drug exposure per dose, and expressed as a fold over endogenous NHP parkin levels.
Results: Parkin KO rats were treated intranigrally with three doses of NB001 for 9 weeks, after which time animals were scrificed and examined for increases in MOA based biomarkers for changes from baseline. All doses tested demonstrated efficacy to alter MOA-based biomarkers. In NHP, intranigral delivery of increasing doses of NB001 demonstrated excellent tolerability, with initial data demonstrating activity to alter MOA-based biomarkers in NHP.
Conclusions: NB001 (AAV-Parkin) delivered intraparenchymally to the Substantia nigra, is safe, well-tolerated and efficacious at multiple doses, defining a dose range for human testing based on rodent and NHP studies. Preliminary data from Parkin-PD patient tissue supports dose range efficacy and MOA-based biomarker relevance for human Parkin-PD patient testing.

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ANTISENSE OLIGONUCLEOTIDES THERAPY REDUCES ALPHA-SYNUCLEIN PATHOLOGY IN PRIMARY ENTERIC CULTURES FROM HUMAN A53T ALPHA-SYNUCLEIN TRANSGENIC MICE

Fabiana Miraglia[1], Jessica Grigoletto[1], Eleonora Crocco[1], Alexia Tiberi[1], Rebecca Senter[2], Federico Cremisi[1], Stewart Campbell[2], Emanuela Colla[1,3]
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Aims: This study aimed to assess the efficacy of three distinct antisense oligonucleotides (ASOs) in mitigating alpha-synuclein (aSyn) pathology in primary enteric cultures isolated from the colon of adult Prp human A53T aSyn transgenic mice, an established model of Parkinson's Disease.
Methods: Three ASOs targeting different regions of the aSyn gene were administered together with aSyn Pre-Formed Fibrils (PFFs) alone or in combination with CsgA, a component of *E.coli* bacterial amyloid protein, to induce aSyn aggregation in primary enteric cultures. The progression of aSyn pathology was evaluated by immunofluorescence.
Results: The combination of aSyn PFFs and CsgA triggered the formation of phosphorylated aSyn (phospho-aSyn) inclusions in primary enteric neurons, structurally resembling the toxic fibrillary species typically observed in the CNS. These pathological inclusions had severe impact on neuronal excitability and caused a significant decrease in GFAP expression, a glial cell marker, with concomitant reorganization of the glial network in regions distal to phospho-aSyn inclusions. Notably, two of the three ASOs tested were particularly effective in reducing endogenous aSyn expression. Co-administration of these ASOs with PFFs and CsgA significantly decreased phospho-aSyn fibrillary species in enteric neurons, lowering the number of larger aggregates with a resulting accumulation of smaller inclusions. Such effect demonstrated that selected ASOs efficiently interfered with the formation of new toxic species of aSyn in primary enteric cultures.
Conclusions: These findings demonstrate that ASOs-based therapy could be a promising strategy to target aSyn pathology in the gastrointestinal system.

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PROBIOTIC BACILLUS SUBTILIS NATTO REGULATES THE AGING-RELATED INSULIN-IGFR1-FOXO AND THE OXIDATIVE STRESS-RELATED P38MAPK-NRF2 SIGNALING ROUTES TO PROTECT AGAINST PARKINSON'S DISEASE IN CAENORHABDITIS ELEGANS

Roberto Grau, Marcos Francisco
Kyojin S.A., R&d, Rosario, Argentina

Aims: The approaches for PD should involve a cocktail of different agents or therapies, each targeting different risk factors. Here we use the probiotic bacterium Bacillus subtilis natto DG101, to test its several beneficial effects against PD in the animal model Caenorhabditis elegans.
Methods: We use the probiotic B. subtilis natto DG101 strains and isogenic derivatives deficient in biofilm formation and quorum sensing. The C. *elegans* strains wereobtained from CGC. We studied 6-Hydroxydopamine dopaminergic injuries, Lifespan analysis, Locomotion and motricity, dopamine-dependent basal slowing response, Dopaminergic neurodegeneration, dopamine-dependent ethanol avoidance response, analysis of human α-synuclein aggregation.
Results: *Caenorhabditis elegans* colonized by *Bacillus subtilis* is resistant to oxidative injury of dopaminergic neurons caused by treatment with the neurotoxin 6-hydroxydopamine (6-OHDA). *B. subtilis*-colonized *C. elegans* display dopamine-dependent behaviors indistinguishable from those of 6-OHDA-untreated worms colonized by gut commensal *E. coli* OP50. Life expectancy is longer and dopaminergic neurons are more strongly protected in *B. subtilis*-colonized *C. elegans dat-1p::CAT-2* worms, which exhibit early dopaminergic decay, than in biofilm-deficient or quorum sensing-deficient *B. subtilis*-colonized *dat-1p::CAT-2* worms. Increases in healthy life expectancy and behavioral fitness are also observed in *B. subtilis*-colonized worms overexpressing human alpha-synuclein and Parkin synthesis-deficient worms. The *B. subtilis*-controlled insulin/IGF-1 signaling (ILS), whose downregulation prevents aging-related PD, is not involved in protecting against oxidative damage-related PD. We demonstrate that *B. subtilis* activates PMK-1 (p38 MAPK)/SKN-1 (Nrf2) signaling, which exerts antioxidant effects to protect *C. elegans* from oxidative injury-induced PD. This work opens the possibility of a novel strategy against PD involving probiotic *B. subtilis* to simultaneously attacks two crucial and independent risks factors for PD: aging and oxidative stress.
Conclusions: Our results open the possibility of a therapeutic scenario for the human probiotic *Bacillus subtilis* natto DG101 to delay and prevent PD.

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BRAIN ALTERATIONS IN GLOBAL AND LOCAL EFFICIENCY IN PRODROMAL SYNUCLEINOPATHY

Christina Tremblay[1], Alexandre Pastor-Bernier[1], François Rheault[2], Véronique Daneault[1], Violette Ayral[1], Marie Filiatrault[1], Liane Desaulniers[1], Andrew Vo[3], Jean-François Gagnon[1,4,5], Ronald Postuma[1,6], Johannes Klein[7], Michele Hu[7], Stéphane Lehéricy[8], Isabelle Arnulf[8], Marie Vidailhet[8], Jean-Christophe Corvol[8], The Iceberg Study Group[8], Petr Dusek[9], Stanislav Marecek[9], Zsoka Varga[9], Shady Rahayel[1,10]
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Aims: Isolated REM sleep behavior disorder (iRBD) is a parasomnia characterized by abnormal movements during REM sleep. This prodromal synucleinopathy provides a critical window to study neural disruptions preceding Parkinson's disease (PD) and dementia with Lewy bodies. While brain network efficiency is disrupted in PD, its alteration in iRBD remains unclear. Here we investigated the efficiency of the brain's structural architecture of iRBD patients using a large international MRI dataset of polysomnography-confirmed patients.
Methods: Diffusion-weighted MRI data were processed using Tractoflow-ABS and Connectoflow to generate structural connectivity (SC) matrices of 448 cortical and 14 subcortical regions (Cammoun atlas) for the 198 participants with iRBD and 174 controls. After quality control, global and local efficiency were computed from these matrices using the Brain Connectivity Toolbox and harmonized between centers using ComBat. W-scores were calculated to control for age and sex effects based on controls' values. Differences in efficiency between iRBD and control groups were tested using t-tests (FDR correction). Correlations between efficiency and clustering coefficient, connection strength, and degree (i.e., number of connections in each region) were also examined using Pearson's correlations against spatial null models.
Results: A significant decrease in global efficiency was observed in iRBD (W-score = -0.31, p-value < 0.001). Local efficiency was reduced in 18 cortical and 3 subcortical regions and increased in 9 cortical regions (Figure 1A). Local efficiency correlated positively with clustering coefficient and negatively with connection strength and degree ($p\text{-value}_{spin\text{-}FDR} = 0.001$) (Figure 1B and 1C).

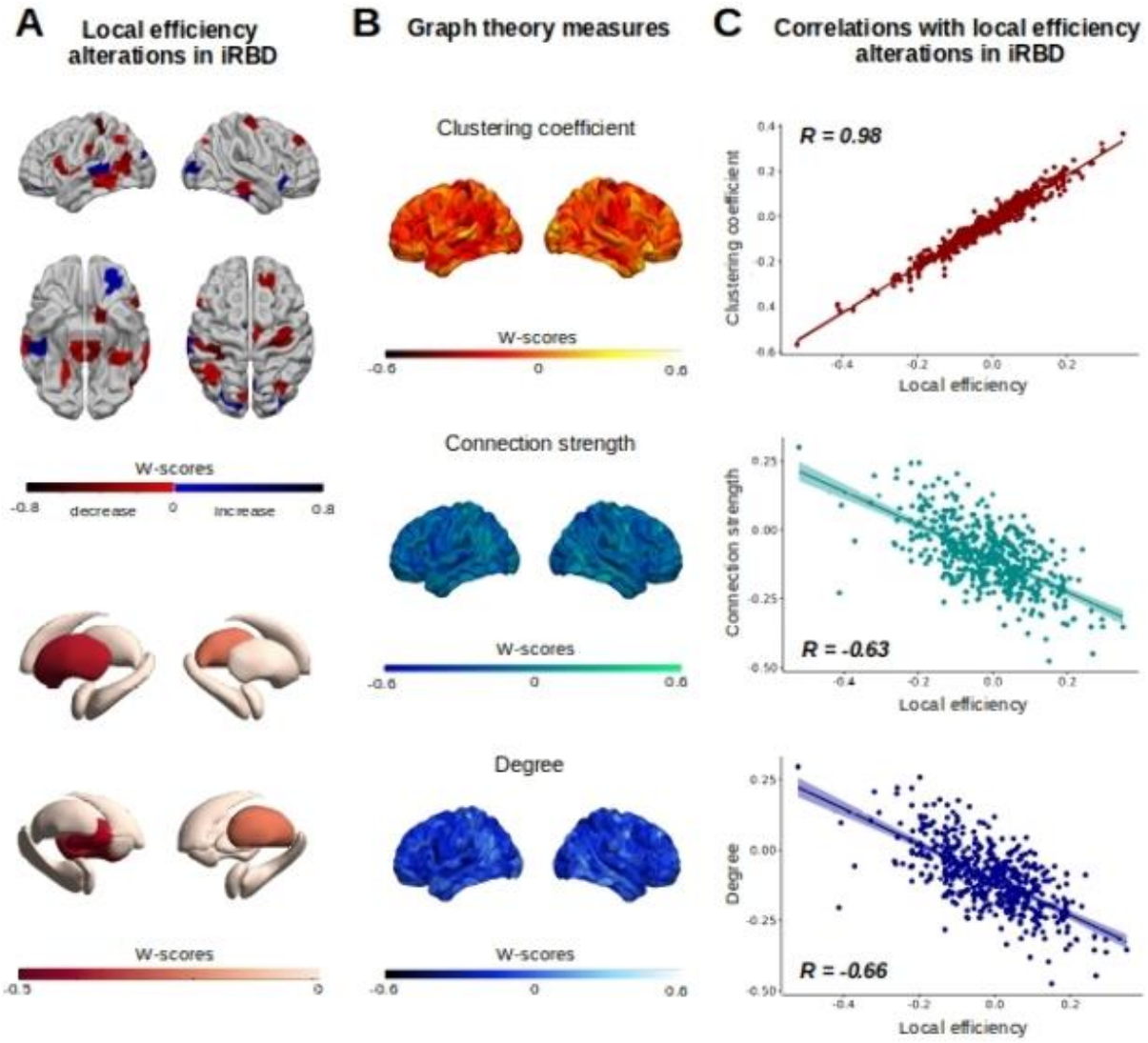

Figure 1.(**A**) Cortical and subcortical regions showing significant decreases (red) and increases (blue) in local efficiency in the group with idiopathic REM sleep behavior disorder (iRBD) compared to controls (HC) ($p\text{-value}_{FDR}<.05$). (**B**) Cortical brain maps illustrating regional differences in iRBD compared to HC (W-scores) in three graph theory measures: clustering coefficient, connection strength and degree (i.e., number of connections). (**C**) Significant spatial correlations between local efficiency alterations in iRBD (W-scores) and the three graph theory measures. All correlations (Pearson's r) were compared against null coefficient distributions using a model that preserves spatial autocorrelation between regions (1000 spins), with FDR correction ($p\text{-value}_{spin\text{-}FDR}<.05$).

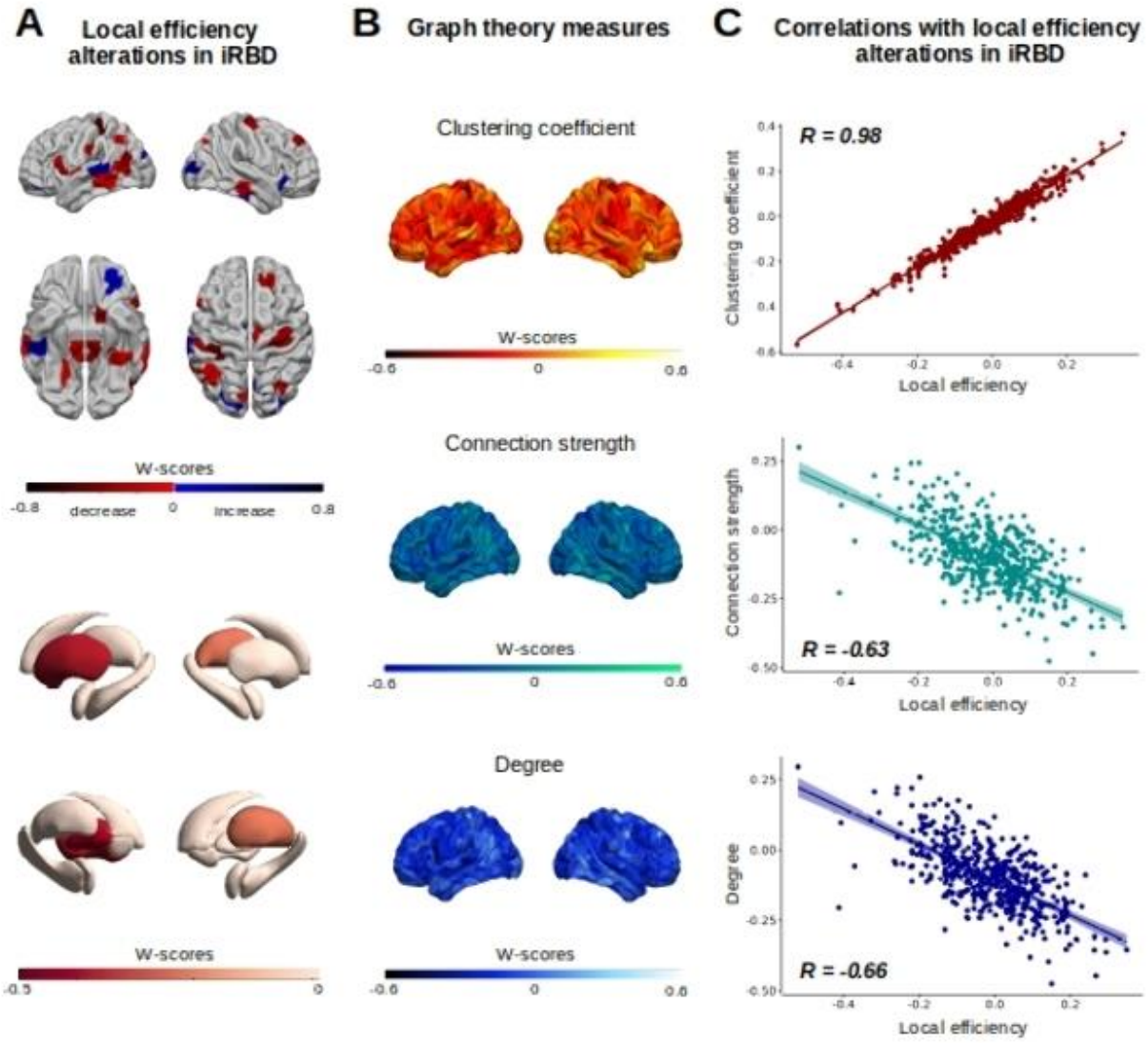

Figure 1.(**A**) Cortical and subcortical regions showing significant decreases (red) and increases (blue) in local efficiency in the group with idiopathic REM sleep behavior disorder (iRBD) compared to controls (HC) ($p\text{-value}_{FDR}<.05$). (**B**) Cortical brain maps illustrating regional differences in iRBD compared to HC (W-scores) in three graph theory measures: clustering coefficient, connection strength and degree (i.e., number of connections). (**C**) Significant spatial correlations between local efficiency alterations in iRBD (W-scores) and the three graph theory measures. All correlations (Pearson's r) were compared against null coefficient distributions using a model that preserves spatial autocorrelation between regions (1000 spins), with FDR correction ($p\text{-value}_{spin\text{-}FDR}<.05$).

Conclusions: iRBD is associated with global and local efficiency changes, reminiscent of what is seen in PD and dementia. These findings suggest early network disorganization and offer insights into the mechanisms underlying neurodegeneration.

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MAPPING RESTING-STATE FUNCTIONAL CONNECTIVITY BETWEEN SUBCORTICAL NUCLEI: EMERGING INSIGHTS INTO PARKINSON'S DISEASE DIAGNOSIS

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Aims: Previous resting-state functional MRI (rs-fMRI) analysis of the basal ganglia in Parkinson's disease (PD) relied on T1-weighted imaging (T1WI). Delicate subcortical structures can't be accurately identified on T1WI. In this study, we aimed to introduce and validate a method that incorporates quantitative susceptibility mapping (QSM) into the rs-fMRI analytical pipeline to achieve precise subcortical nuclei segmentation and improve the diagnosis of Parkinson's disease.
Methods: A total of 321 participants (148 patients with PD and 173 normal controls) were enrolled. We performed cross-modal registration at the individual level for rs-fMRI to QSM and T1WI, respectively. The resting state functional connectivity (RSFC) among the caudate, putamen, globus pallidus, red nucleus, and substantia nigra were calculated.The consistency and accuracy of RSFC measurements in two approaches were assessed by intraclass correlation coefficient (ICC) and mutual information. Bootstrap analysis was performed to validate the stability of the RSFC differences between PD and normal controls. RSFC-based Machine learning models were constructed for PD classification.
Results: The consistency of RSFC measured by the two registration methods was poor, ICC ≤ 0.50 was observed in 75.6% of RSFC. While the QSM-guided approach showed better mutual information values ($p < 0.001$), suggesting higher registration accuracy. The disruptions of RSFC identified with the QSM-guided approach was more stable and reliable, as confirmed by bootstrap analysis. In the classification models, the QSM-guided method persistently outperformed in the test set, achieving higher area under the receiver operating characteristic curve (AUC) values (range, 0.74-0.79), compared to the TIWI-guided method (AUC range, 0.56-0.61) ($p = 0.001$, DeLong's test).
Conclusions: The QSM-guided approach effectively enhanced the accuracy of subcortical segmentation and the stability of RSFC measurement, thus improving the diagnostic performance in Parkinson's disease at the individual level.

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IMPACT OF ALZHEIMER'S DISEASE CO-PATHOLOGY ON FDG-PET PATTERNS IN PARKINSON'S DISEASE WITH COGNITIVE IMPAIRMENT

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[1]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain, [2]Unidad de Trastornos del Movimiento, Servicio de Neurología, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain, [3]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Instituto de Salud Carlos III, Madrid, Spain, [4]Wallenberg Centre for Molecular and Translational Medicine, 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]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [7]Unidad de Radiodiagnóstico, Hospital Universitario Virgen del Rocío, Seville, Spain, [8]Unidad de Medicina Nuclear, Hospital Universitario Virgen del Rocío, Seville, Spain, [9]Departamento de Medicina, Facultad de Medicina, Univesidad de Sevilla, Seville, Spain

Aims: To explore how Alzheimer's disease (AD) co-pathology affects the pattern of cortical neurodegeneration and clinical phenotype in patients with Parkinson's disease (PD) and cognitive impairment (CI). We used plasma ptau217 to study the effect of AD co-pathology on cognitive profile and cortical hypometabolism on FDG-PET in a well-characterized cohort of PD-CI patients.
Methods: Eighty-eight PD patients were classified into PD-CI (N=50; 24 PD-MCI, 26 PDD) and PD with normal cognition (PD-CN; N=38) using neuropsychological testing with the PD-Cognitive Rating Scale. All underwent blood sampling and FDG-PET scanning. Plasma ptau217 levels were measured using the ALZpath ptau217 Simoa immunoassay, with a threshold of 0.4 pg/mL for ptau217 positivity. APOE4 alleles were genotyped and coded as a binary variable. FDG-PET data was processed using SPM12 and brain-wide hypometabolism patterns (vs PD-CN) were assessed across 52 atlas-defined brain regions.

Results: Fourteen PD-CI (28%) patients were classified as ptau217(+).PD-CI-ptau217(+) patients showed a higher prevalence of APOE4 carriers (50% vs 16%, p=0.04) and more impaired memory scores (p=0.03) compared to PD-CI-ptau217(+). When compared to PD-CN (excluding 5 PD-CN-ptau217(+)), both PD-CI-ptau217(-) and PD-CI-ptau217(+) showed significant hypometabolism in posterior-occipital, temporal, and

frontal areas ($p<0.05$, FDR-corrected), but hypometabolism in PD-CI-ptau217(+) was considerably more extensive, particularly in temporo-parietal areas typically associated with AD (Fig1).

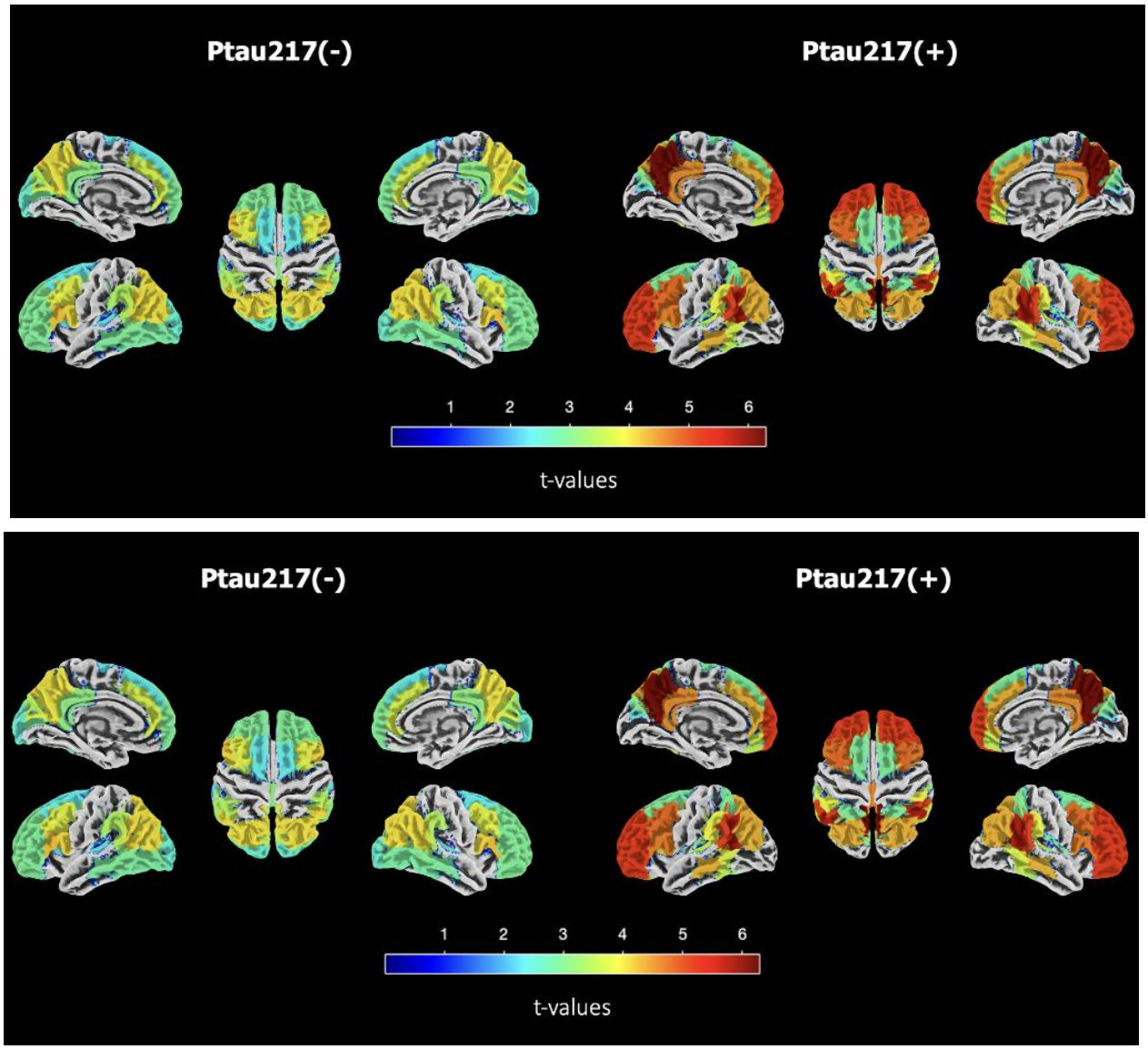

Fig1: Hypometabolism patterns of PD-CI-Ptau217(-) and PD-CI-Ptau217(+) subgroups in comparison to PD-CN. Maps reflect region-wise t-values and were displayed with a significance threshold of $p < 0.05$, FDR-corrected. Warmer colors indicate more pronounced hypometabolism.

Conclusions: AD co-pathology results in a more memory-predominant cognitive profile and AD-like neurodegeneration phenotype in PD-CI. Novel plasma biomarkers may significantly facilitate clinical detection of AD co-pathology, which may have important implications for personalized diagnosis, prognosis, and treatment of PD patients.

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DISCORDANCE BETWEEN STRIATAL DOPAMINERGIC IMAGING AND MOTOR PERFORMANCES IN REM SLEEP BEHAVIOR DISORDER

Cinzia Zatti[1], Toji Miyagawa[2], Amélie Pelletier[3], Bradley Boeve[2], Erik St. Louis[2], Julie Fields[4], Val Lowe[5], Kejal Kantarci[5], Ronald Postuma[3,6,7]
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Aims: Idiopathic REM sleep behavior disorder (iRBD) is a marker of early neurodegenerative synucleinopathy. Nigrostriatal dopaminergic dysfunction is often considered the primary pathological mechanism behind motor symptoms; however, other mechanisms have been proposed. The study aim was to identify whether there were iRBD patients with a discordance between motor testing and abnormal nigrostriatal uptake, and to characterise those patients.
Methods: This multicenter study included 95 subjects with polysomnography-confirmed iRBD who underwent [123I]-Ioflupane SPECT (DaT-SPECT) and quantitative motor testing within the same year. Participants were divided into 4 groups (motor abnormal/DAT normal, motor normal/DAT abnormal, both normal and both abnormal) and were investigated for differences in clinical characteristics. All participants were followed prospectively for a median of 2.58 years.
Results: 34/95 (36%) had discordance between DaT-SPECT and quantitative motor testing, with an equal proportion motor abnormal/DAT normal and motor normal/DAT abnormal participants (n=17 in each group). Motor abnormal/DAT normal participants had worse MoCA scores (25.12 vs 26.42), a higher frequency of MCI (59% vs 26% p=0.008), and more autonomic symptoms (SCOPA-AUT=18.62 vs 11.92) compared to the other groups. 3/17 (18%) of the motor abnormal/DAT normal group phenoconverted (PD=2, DLB=1), at a median interval of 1.8 years.
Conclusions: This study revealed that motor alterations and abnormal nigrostriatal uptake are commonly discordant in iRBD, and that motor abnormalities are common even in those with normal DaT-SPECT. The presence of substantial cognitive and autonomic dysfunction in the motor abnormal/DAT normal group suggests a different, likely more diffuse, progression pattern.

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MAGNETIC RESONANCE IMAGING DATA PHENOTYPES FOR THE PARKINSON'S PROGRESSION MARKERS INITIATIVE

Brian Avants[1], Leon Fonville[2], Alexandra Reardon[3], Olivia Hampton[3], Andrew Stenger[3], Xue Wang[3], Barbara Marebwa[4], Lana Chahine[5], Kathleen Poston[6], Ken Marek[7], Lino Becerra[3]
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Aims: The Parkinson's Progression Markers Initiative (PPMI) ppmi-info.org delivers a comprehensive multi-modality longitudinal study of Parkinson's Disease (PD). These provide quantitative indices of deep brain and cortical structure (structural MRI i.e. sMRI), microstructural integrity of brain tissue (diffusion-weighted imaging i.e. dMRI) and resting brain function (resting state functional MRI i.e. rsfMRI). This study systematically organizes these complex data -- current as of April 2024 -- into a structured format, provides a PD-focused evaluation of the methodologies and evidence for technical robustness.
Methods: We report data from sMRI, dMRI and rsfMRI represented as imaging data phenotypes (IDPs) in tabular form for accessible statistical analysis. The ANTsPyMM formalism was employed to consistently analyze these data and organize them into parallel high-resolution and tabular formats. An additional step of imaging-based dimensionality reduction was used to link select sMRI, dMRI and rsfMRI features into predictor sets that can be used in multiple modality prediction settings. We implement these analyses with linear mixed effects models (LMMs) in the R programming language.
Results: LMMs demonstrate significant differences between controls and sporadic Parkinson's Disease (PD) groups (synuclein seed amplification assay +/-) in both the cross- sectional and longitudinal context. The linked features also reveal joint relationships between IDPs and clinical progression that are both robust and multivariate (i.e. involve multiple modalities).
Conclusions: We present standardized and reproducible MRI IDPs for PPMI. We present support for the validity of the IDPs and illustrate an application to contrasting asyn SAA+ (baseline n=608) and asyn SAA- (baseline n=49) PD groups from controls (baseline n=242). These publicly available MRI IDP data will enable others to implement reproducible PPMI-based analyses of PD not only within the sporadic symptomatic cohort but also within other prodromal and genetic groups.

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DEEP LEARNING FOR MULTIPLE SYSTEM ATROPHY CLASSIFICATION: A DATA-DRIVEN STUDY USING MULTIMODAL MULTICENTRIC MRI

Giulia Maria Mattia[1], Lydia Chougar[2,3,4], Wassilios G. Meissner[5,6,7], Alexandra Foubert-Samier[5,6,8], Anne Pavy-Le Traon[1,9,10,11], Olivier Rascol[1,9,10,11], Margherita Fabbri[1,9,10,11], David Grabli[12,13], Bertrand Degos[14,15], Stéphane Lehéricy[2,3], Patrice Péran[1]
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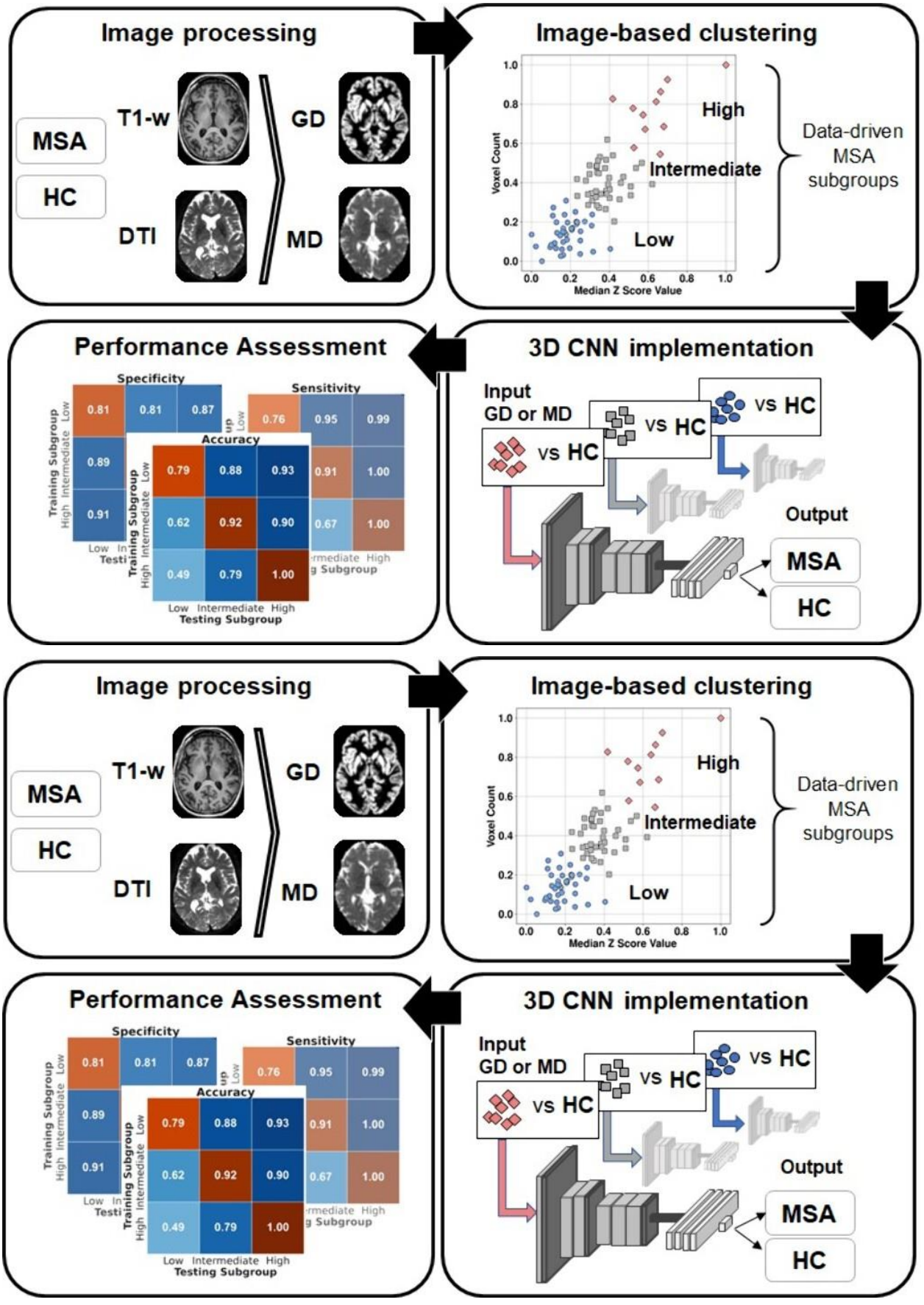
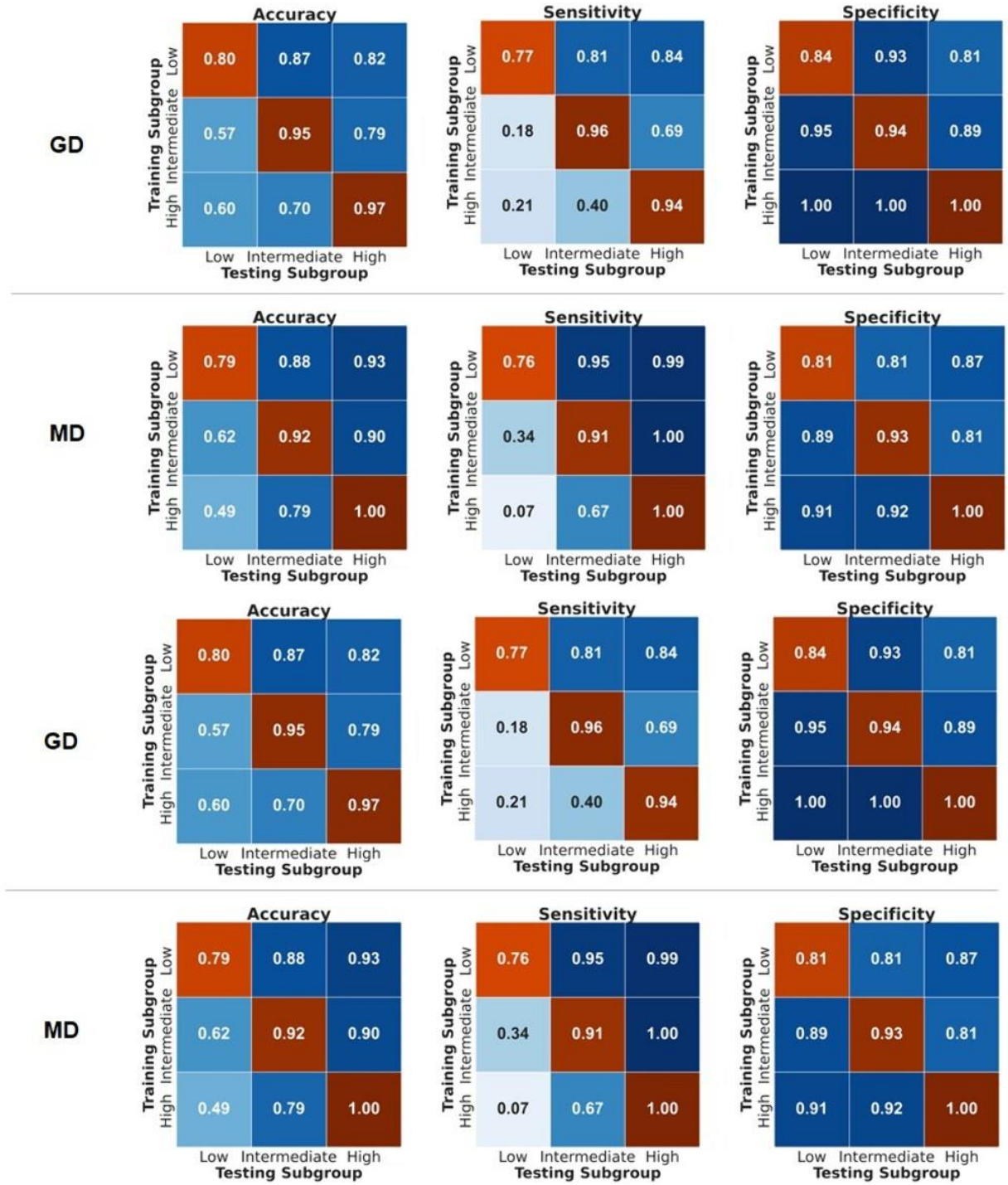
Aims: To automatically classify data-driven subgroups of multiple system atrophy (MSA) patients from healthy controls (HC) using a 3D convolutional neural network (CNN) and multimodal multicentric MRI.
Methods: MRI data from 126 HC and 92 MSA patients were gathered from three French MSA reference centers. We computed gray density (GD) probability maps from T1-weighted (T1-w) and mean diffusivity (MD) maps from diffusion tensor imaging (DTI). We proposed distinguishing MSA patients from HC using a 3D CNN, fed with specific training content. First, MSA patients were divided into subgroups with an unsupervised algorithm using imaging-based features from the Z score of patients compared to HC, considering GD and MD. We established three MSA subgroups, representing the deviation of MSA patients from HC in three grades (low, intermediate, and high). Second, each MSA subgroup along with HC was used to train the CNN while testing on the others serving as hold-out sets. Figure 1 provides an overview of our approach.



Results: Patients belonging to the low-grade subgroups were the youngest and presented lower disease

duration. This result seemed coherent with the fewer and less considerable variations of low-grade MSA patients found in the imaging data. CNN performances tended to improve when training with the lower grade subgroups and testing on higher grades, whereas the opposite did not occur (Figure 2). This behavior was found for both MRI maps.



Conclusions: Our findings suggest a better CNN generalization ability using MSA patients with milder alterations for training rather than more severe ones. Therefore, given appropriate disease trajectories, an earlier stage may reveal more suitable to differentiate a later one. Future works include combining multiple MRI modalities as input and extending our study to differentiate other Parkinsonian syndromes.

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HYPERACTIVATION OF THE NORADRENERGIC SYSTEM AS POTENTIAL PROTECTIVE FACTOR AGAINST THE DEVELOPMENT OF ANXIETY IN PD: A FUNCTIONAL CONNECTIVITY ANALYSIS

Manuela Moretto[1,2], Lucia Batzu[1,3,4], Silvia Rota[1,3,4], Mattia Veronese[1,2], Olabisi Awogbemila[4], Alexandra Rizos[3,4], Anette Schrag[5], Steven Williams[1], K Ray Chaudhuri[3,4]
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Aims: Anxiety is a strong predictor of quality of life in people with Parkinson's disease (PD), but little is known about its physiopathology. This study aims to identify the underlying biological changes associated with anxiety in PD through the investigation of neurotransmitter-based brain functional connectivity (FC) differences among PD patients with anxiety (PDa), without anxiety (PDna), and healthy controls (HC).
Methods: Thirteen people with PDa, 31 people with PDna and 17 HC were included from the AND-PD study. Using previously established procedures and pipelines, resting state functional MRI data were collected from all participants and a receptor-enriched analysis of FC by targets (REACT) analysis was conducted. Voxel-wise maps of FC related to the transporters of dopamine (DAT), noradrenaline (NET) and serotonin (SERT) were compared between groups. Age, sex, total intracranial volume and framewise displacement were included as covariates in the statistical models.
Results: The NET-enriched maps showed increased FC in the PDna group compared to HC ($p_{corr}<0.05$), within three separated clusters involving the left cerebellum, the insular cortex and the brainstem. In DAT-enriched functional networks, the PDa group had greater FC than HC ($p_{corr}<0.05$) in the right parietal, occipital, insular cortex, as well as in the right putamen. No significant differences were observed in SERT-enriched functional networks among groups.
Conclusions: The noradrenergic system is a powerful modulator of serotonergic brainstem pathways involved in anxiety and depression, as well as a target of serotonin–noradrenaline reuptake inhibitors used to treat these symptoms. The noradrenergic hyperactivation we observed in several brain areas, including the brainstem, may serve as protective factor against the development of anxiety in PD. Additionally, further studies are needed to explore potential levodopa-induced alteration in DAT-enriched FC.

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CLINICAL CHARACTERISTICS OF SPORADIC PARKINSON'S DISEASE WITH NEGATIVE CEREBROSPINAL FLUID ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY

Sarah Brooker[1], Jacopo Pasquini[2], David-Erick Lafontant[3], Seung Ho Choi[3], Ken Marek[4], Tanya Simuni[1], Paulina Gonzalez Latapi[1], Nicola Pavese[2], Kathleen Poston[5]
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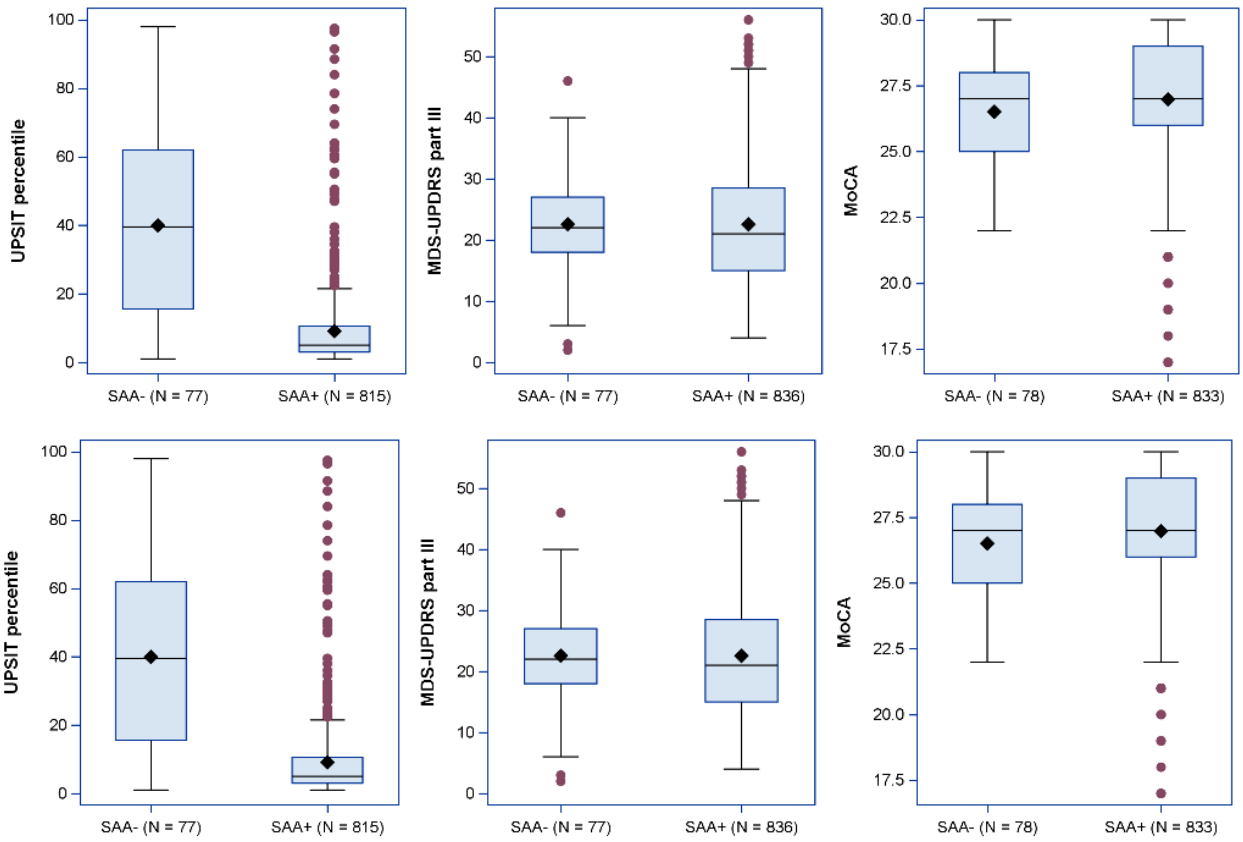
Aims: Define baseline clinical characteristics of individuals with sporadic Parkinson's disease (sPD) enrolled in the Parkinson's Progression Markers Initiative (PPMI) who have a negative cerebrospinal fluid seed amplification assay (a-syn SAA) and evaluate how these characteristics compare to SAA positive sPD participants.
Methods: We analyzed data from the PPMI sPD cohort, identifying participants who had a negative CSF a-syn SAA (n = 78) or positive CSF a-syn SAA (n = 838) result during their baseline assessment. A comprehensive array of baseline clinical characteristics was assessed including motor and non-motor disease scales.
Results: sPD SAA negative participants were median age 66.5 years (IQR 61.0-71.6) and 64% male, while sPD SAA positive participants were median age 63.9 years (IQR 57.2-69.9) and 65% male. The median percentile score on the University of Pennsylvania Smell Identification Test (UPSIT) was 39.5 (IQR 15.5-62.0) for SAA negative sPD compared to 5.0 (IQR 3.0-10.5) for SAA positive sPD participants. The percentage of participants with an UPSIT score less than or equal to the 15th percentile was 25% for SAA negative versus 86% for SAA positive participants. All other clinical metrics were comparable between the SAA negative and positive cohorts including MDS-UPDRS Part III median score of 22.0 (IQR 18.0-27.0) versus 21.0 (IQR 15.0-28.5) respectively, and median score on the Montreal Cognitive Assessment (MoCA) of 27.0 in both groups.



Conclusions: sPD participants in the PPMI cohort with negative alpha-synuclein SAA at baseline evaluation have similar baseline clinical characteristics as those with positive alpha-synuclein SAA with the exception of a substantially lower rate of hyposmia amongst the SAA negative participants. Therefore, clinical parameters alone are insufficient to differentiate the small subset of people diagnosed with PD, who lack alpha-synuclein pathology in the CSF.

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PHOSPHORYLATED ALPHA SYNUCLEIN IN ERYTHROCYTES AS DIAGNOSTIC MARKERS FOR PARKINSON'S DISEASE.

Anne Roberts[1], Malcolm Horne[2], Shaima Nazaar[1], Ryan Coyle[1], Lenora Higginbotham[1], Blaine Roberts[1]
[1]Emory School of Medicine, Neurology And Biochemistry, Atlanta, United States of America, [2]Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Aims: Phosphorylated alpha-synuclein at position S129 is widely used as a pathological marker in post-mortem brain and in skin biopsies. Here we aimed to determine if phosphorylated alpha-synuclein at position S129 and five additional phosphorylated sites on alpha-synuclein measured in red blood cells could serve as a biomarker for the diagnosis of idiopathic Parkinson's disease (iPD).
Methods: We developed a quantitative liquid chromatography mass spectrometry (LC-MS) assay that targets phosphorylation at S129 and five other phosphorylation sites on alpha-synuclein. We discovered the additional phosphorylated sites on alpha synuclein in red blood cells using discovery phosphoproteomic. Synthetic peptide standards labeled with 13C and 15N to each site were made and we developed a robust and highly sensitive, quantitative LC-MS assay on a triple quad platform. This included a novel streamlined phosphopeptide-enrichment strategy.
Results: We measured total and phosphorylated alpha synuclein in red blood cells from Control, iPD and AD samples (n>100 per group) obtained from the Victorian Parkinson's Disease Registry and the Emory Lewy body cohort within the Emory Goizueta Alzheimer's Disease Research Center. We established normal levels of total and phosphorylated alpha synuclein in red blood cells. We observed a significant increase in total alpha synuclein levels and a surprising change in phosphorylated alpha-synuclein.
Conclusions: Our findings show that the diversity of phosphorylated alpha-synuclein in red blood cells was far greater than we expected. This included the pathological phosphorylated S129 proteoform. The total abundance of alpha-synuclein is increased in iPD RBCs and this is specific to iPD as no change was observed in the AD samples. Overall, the changes observed have the potential to serve as the basis of a blood based diagnostic test.

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COMPARISON OF SMELL TESTING AND POLYSOMNOGRAPHY FOR DETECTION OF ALPHA-SYNUCLEIN PATHOLOGY IN INDIVIDUALS WITH DREAM ENACTMENT BEHAVIOR

Ethan Brown[1], Andrew Siderowf[2], Lana Chahine[3], Micah Marshall[4], Ryan Kurth[4], Chelsea Caspell-Garcia[4], Michael Brumm[4], Craig Stanley[5], Claudio Soto[6], Luis Concha[7], Todd Sherer[8], Tanya Simuni[9], Ken Marek[5], Caroline Tanner[1]
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Aims: To compare the ability of olfactory testing and polysomnogram testing to identify alpha-synuclein pathology in individuals with dream enactment behavior and without clinical signs of parkinsonism or cognitive decline
Methods: Participants were enrolled in the Parkinson's Progression Markers Initiative (PPMI) with either had REM sleep behavior disorder (RBD) or reported dream enactment behavior (DEB). Participants had to be at least 60 years old and have no diagnosis of Parkinson's disease. Participants with a diagnosis of RBD had polysomnogram (PSG) confirmation. Participants recruited online had DEB and hyposmia defined as below the 10th percentile for age and gender. Participants subsequently had cerebral spinal (CSF) alpha-synuclein seed amplification assay (SAA). Analyses compared the probability of a positive SAA result in participants with DEB and a positive PSG to participants with DEB and hyposmia who did not undergo PSG. In addition, we compared SAA result in PSG-confirmed RBD cases with and without hyposmia.
Results: 240 participants had PSG confirmed RBD (RBD-PSG) and 136 participants had dream enactment behavior (DEB) with hyposmia. Groups were comparable in age (67.6 (SD 6.3) vs. 68.6 (SD 5.6)). The RBD-PSG group was less likely to be female (21% vs. 46%). The proportion of cases with positive CSF SAA results was significantly higher among DEB/hyposmia cases than RBD-PSG (114/136 (84%) vs. 171/240 (71%); p=0.006). Among participants with RBD-PSG, those with hyposmia were significantly more likely to have positive SAA results than normosmic cases (128/139 (92%) vs. 43/101 (43%); p<0.001).
Conclusions: Olfactory testing is a powerful adjunct to PSG and may be an efficient alterntive to PSG to identify individuals with DEB with synuclein pathology. In turn, these high-risk individuals could be candidates for clinical trials aimed at slowing or preventing progressive synucleinopathy.

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A NETWORK PERSPECTIVE ON COGNITION IN INDIVIDUALS WITH PARKINSON'S DISEASE: EXPLORATORY GRAPH ANALYSIS OF COGNITIVE TEST DATA IN THE LANDSCAPE STUDY

Daniel Scharfenberg[1], Elke Kalbe[1], Landscape Consortium[2], Anja Ophey[1]
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Aims: Neuropsychological diagnostics rely on cognitive domains to evaluate cognitive performance. However, assignments of cognitive tests to domains are rather theoretically than empirically based. Hence, we aimed to assess the dimensionality structure of cognitive functioning in individuals with Parkinson's disease (PD) from a network perspective and to replicate these findings in cognitively healthy individuals (CHI).
Methods: We performed Exploratory Graph Analysis (EGA) to assess the dimensionality structure of cognitive test scores in *N*=698 individuals with PD (M_{age}=67.62, SD_{age}=7.88, 67.48% male) from the DEMPARK/LANDSCAPE study. Results were compared to a theoretically assumed domain structure qualitatively and by confirmatory factor analysis. We used Unique Variable Analysis (UVA) to reduce redundancy in the model and re-performed EGA afterwards. Data of *N*=60,398 CHI derived from 55 studies served as an exploratory replication base for analyses.
Results: EGA identified five dimensions that differed from the theoretically assumed cognitive domain structure in individuals with PD but showed better model fit. However, UVA revealed that test scores derived from the same test paradigms showed substantial redundancy, even across theoretically assumed cognitive domains. After removing redundant tests, EGA identified a unidimensional structure of cognitive test scores. Findings were replicated in data of CHI.
Conclusions: Findings imply the need for re-evaluating the composition of cognitive test batteries to reduce redundancy and improve validity of cognitive impairment subtype diagnoses. Further, results suggest that cognition in PD and beyond may be better described as a complex network of interrelated cognitive functions rather than a factorial structure of latent cognitive domains.

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RELATIONS OF GAIT PARAMETERS AND DOPAMINE TRANSPORTER BINDING IN EARLY AND PRODROMAL PARKINSON'S DISEASE

Cinzia Zatti[1], Andrea Pilotto[1], Andrea Rizzardi[1], Alice Galli[1], Clint Hansen[2], Tiziana Comunale[1], Robbin Romijnders[2], Silvia Caminiti[3], Walter Maetzler[2], Alessandro Padovani[1]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Neurology Unit, Brescia, Italy, [2]Christian-Albrechts-University of Kiel, Department Of Neurology, Kiel, Germany, [3]IRCCS Fondazione Mondino, Section Of Neurosciences, Pavia, Italy

Aims: Gait impairments are among the most disabling symptoms of Parkinson's disease (PD) and subtle gait changes have been described even in idiopathic REM sleep behavior disorder (iRBD), condition widely recognized as an incipient stage of synucleinopathy. Previous studies have shown that dopaminergic medications improve certain aspects of walking, whereas others may be dopa-resistant. Aim of this study was to investigate the relationship between different gait parameters and striatal dopaminergic imaging in a group of well-characterized prodromal and early PD patients.
Methods: Sixty patients were enrolled, mainly 44 de novo PD and 16 iRBD. They underwent a comprehensive gait assessment and gait parameters were measured via wearable sensors in normal, fast and dual-task conditions. All patients underwent 123I-FP-CIT-SPECT imaging to quantify dopaminergic depletion. The relationship between motor parameters and dopamine binding was analyzed using the region-of-interest (ROI) analysis for the striatal regions and voxel-based analysis.
Results: PD had shorter step length in fast pace, in cognitive and in motor dual tasks in comparison to iRBD. Both ROI-based and voxel-wise analyses revealed a positive correlation between step length in dual task conditions and left putamen and pallidum in PD, whereas in iRBD step length of cognitive dual task only was positively correlated with bilateral striatal regions.
Conclusions: Our results suggest that step length is associated with striatal dopamine depletion in both early and prodromal stages, particularly in dual task conditions, representing a potential marker of disease progression and of dopamine responsiveness. In addition, the independence of step time from the striatal

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DIMINISHING PALLIDUM VOLUME IS ASSOCIATED WITH HYPERSYNCHRONOUS PALLIDAL BETA POWER IN PARKINSON'S DISEASE

Samantha Cohen[1], Jeong Woo Choi[2], Nader Pouratian[2], Dominique Duncan[3]
[1]University of Southern California, Biomedical Engineering, Los Angeles, United States of America, [2]UT Southwestern, Neurological Surgery, Dallas, United States of America, [3]University of Southern California, Neuroimaging And Informatics Institute, Los Angeles, United States of America

Aims: Exaggerated beta range (13-35 Hz) oscillations with great patient variability are an electrophysiological hallmark of Parkinson's disease (PD). Little work has focused on the role of anatomic changes in pathological neural activity and symptom severity in globus pallidus, an important and common DBS target. This work investigates the relationship between globus pallidus volume and beta oscillations in GPi and GPe.
Methods: Relationships between low and high beta power and pallidal volume were assessed using nonparametric correlations. A LMEM was built to inform on the importance of scaled beta power, age, and years since diagnosis on bradykinesia-rigidity UPDRS III severity scores. Scaled pallidal volume was considered as an interaction term of beta power.
Results: We divided patients into subgroups based on the center frequency of their largest peak of LFP power. In the low beta subgroup, low beta GPi power significantly increased as volume decreased. In GPe, peak power had a negative relationship with volume in the low beta subgroup. In both GPi and GPi LMEMs, power was a significant but negative predictor of severity. In GPi, years since diagnosis and the modulation of power by volume were significant positive contributors. A predictive model found at low values of power in both GPi and GPe, there was a negative relationship between severity and power, and low interaction between volume and power. At higher power, there was a positive relationship between severity and power, and a strong interaction between power and volume.
Conclusions: Our results indicate that pallidal beta hypersynchrony in PD is in part related to diminishing pallidal volume in a subset of patients. We found a nonlinear modulation of the relationship between beta power and severity through the interaction of volume on power.

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ELECTRORETINOGRAPHY AS A FUNCTIONAL MARKER OF NEURODEGENERATION IN PARKINSON'S DISEASE

Jelena Stamenović[1], Biljana Živadinović[1], Vanja Đurić[2]
[1]University of Niš, Medical faculty, Department Of Neurology, Niš, Serbia, [2]Polyclinic "Neuromedic", Niš, Serbia

Aims: Aim: Determination of retinal function disorders in the initial stages of Parkinson's disease using "pattern" electroretinogram (PERG).
Methods: Using "pattern" electroretinography, 35 patients with idiopathic Parkinson's disease in stages I and II of the disease according to the classification of Hoehn and Yahr were examined. The control group consisted of 15 healthy subjects of the control group, of the appropriate age. The equipment for registering PERG contained: a monitor for "pattern" structured stimulation in the form of a checkerboard with black and white squares, electrodes for registration, a signal amplification system and a computer for stimulus averaging with a readout system.
Results: In the early stages of PD, a linear increase in the latency of the PERG N50 wave was registered in comparison to healthy subjects of the control group. The diagnostic application of PERG enables the confirmation of retinal dysfunction in PD.
Conclusions: Conclusion: The neurophysiological method PERG can register early changes in the function of retinal structures in PD, which can be significant from both a diagnostic and a therapeutic point of view.

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ASSOCIATIONS BETWEEN POLYGENIC RISK SCORES, CHOROID PLEXUS VOLUME, AND CLINICAL PROGRESSION IN EARLY-STAGE SPORADIC PARKINSON'S DISEASE: A LONGITUDINAL STUDY

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The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Aims: Parkinson's disease (PD) is a complex neurodegenerative disorder. Polygenic risk scores (PRS) are emerging tools for stratifying sporadic PD. The choroid plexus (CP), responsible for clearing harmful brain metabolites, is linked to aging processes. This study aims to explore the impact of PRS on CP volume changes and clinical symptom progression in a longitudinal PD cohort.
Methods: This study included 361 drug-naïve, early-stage sporadic PD patients with normal cognition. The PRS was calculated from the GWAS meta-analysis. Cognitive decline was defined as the time of first converted to mild cognitive impairment (MCI). Rapid motor progression was an increase of 30 points in UPDRS-III scores. CP segmentation was performed using a 3D U-Net deep learning model. A linear mixed-effects model and Cox proportional hazards models were used, with covariates including sex, age, education level, PRS principal components, and total intracranial volume.
Results: Higher PRS was associated with faster cognitive and motor decline. Each 1 SD increase in PRS, the HR for motor progression was 4.05 (95% CI: 2.19-7.49). Higher PRS group had a greater risk of conversion to PD-MCI (HR = 2.05, 95% CI: 1.20-3.49). PRS significantly interacts with follow-up time to affect CP volumes, with high PRS groups showing a more rapid increase in both left and right CP volumes. (left CP, β= -36.69, SE = 8.97, $p < 0.001$; left CP, β = -30.13, SE = 9.58, $p < 0.01$). Larger left CP volumes were significantly associated with increased motor impairment ($p = 0.017$) and cognitive decline ($p = 0.020$).
Conclusions: Polygenic risk scores are predictive of both motor and cognitive decline in early-stage PD patients and are associated with longitudinal increases in choroid plexus volume.

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Virtual OO - 208

Virtual E-Posters and Oral On-Demand
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NANOROD-ASSOCIATED PLASMONIC CIRCULAR DICHROISM DETECTS HANDEDNESS AND COMPOSITION OF ALPHA-SYNUCLEIN FIBRILS FROM PARKINSON'S DISEASE MODELS AND POST-MORTEM BRAIN

Arianna Bellucci[1], Francesca Longhena[1], Rihab Boujebene[1], Viviana Brembati[1], Michele Sandre[2], Luigi Bubacco[2], Sergio Abbate[1], Giovanna Longhi[1]
[1]University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy, [2]University of Padova, Department Of Biology, Padova, Italy

Aims: Human full-length (fl) alpha-synuclein (aSyn) fibrils, key neuropathological hallmarks of Parkinson's disease (PD), were recently found to generate intense optical activity in correspondence of the surface plasmon resonance of interacting gold nanorods. We thus aimed at investigating whether nanorod-based plasmonic circular dichroism (PCD) can provide information on the features of aSyn fibrils.
Methods: We analysed fibril-enriched protein extracts from mouse and human brain samples as well as from SK-N-SH cell lines with or without human fl and C-terminally truncated (Ctt) aSyn overexpression and exposed to aSyn monomers, recombinant fl or Ctt aSyn fibrils. In vitro-generated human recombinant fl and Ctt aSyn fibrils and fibrils purified from SK-N-SH cells with fl or Ctt aSyn overexpression were also analysed by transmission electron microscopy (TEM) to gain insight into the nanorod-fibril complexes.
Results: We found that bisignate nanorod-based PCD spectra of Ctt aSyn fibrils always exhibited a wavelength blue shift when compared to fl aSyn. TEM supported that this could be ascribed to the different disposition of nanorods on fl and Ctt aSyn fibrils. Interestingly, the fibril-enriched PD brain extract produced broadening of the longitudinal surface plasmonic band with a bisignate PCD couplet centred in correspondence of the absorption band maximum. PCD couplets of in vivo- and in vitro-generated fibrils displayed sign reversal indicative of opposite handedness. Moreover, incubation of in vitro-generated human recombinant fl aSyn fibrils in mouse brain extracts from aSyn null mice resulted in PCD couplet inversion, supporting that biological environment shapes aSyn fibril handedness.
Conclusions: Our findings support that nanorod-based PCD can provide useful information on the composition and features of aSyn fibrils from biological material.

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Virtual OO - 209

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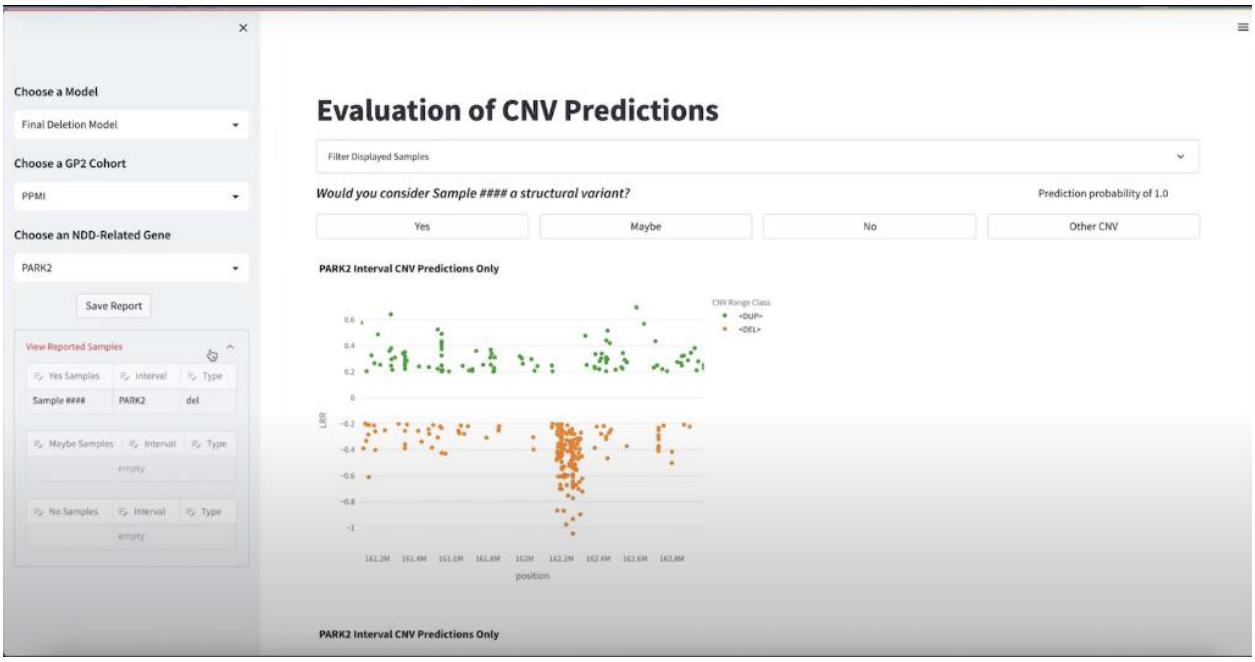
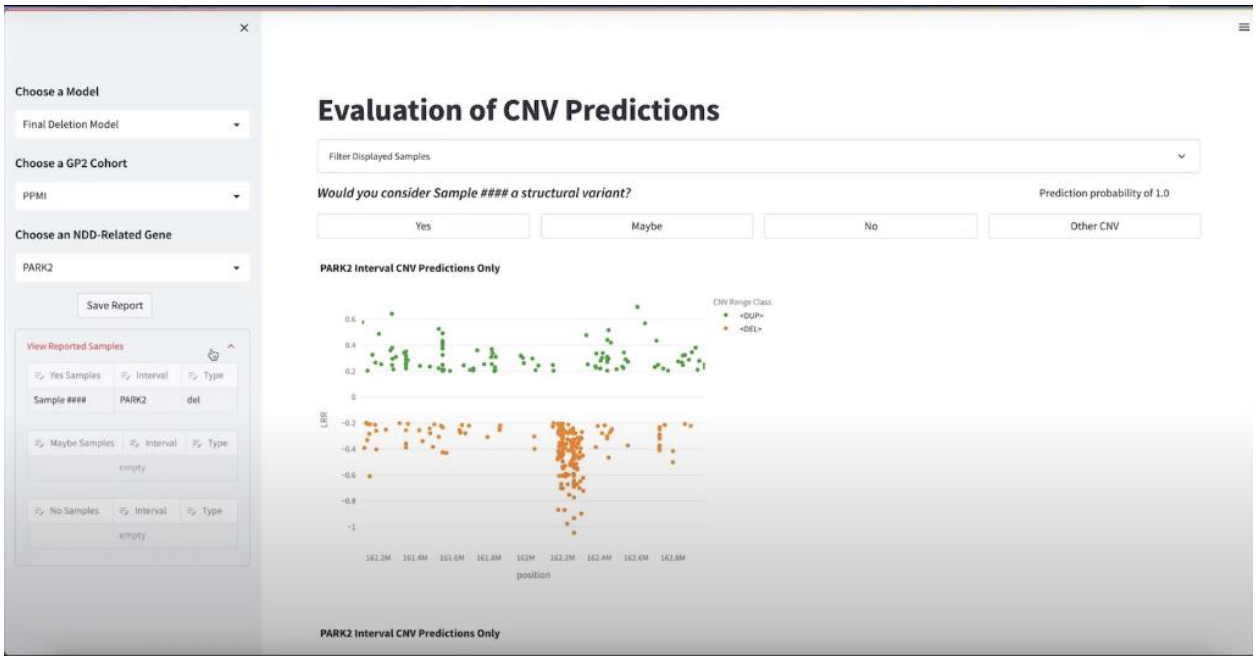
CNV-FINDER: STREAMLINING COPY NUMBER VARIATION DISCOVERY

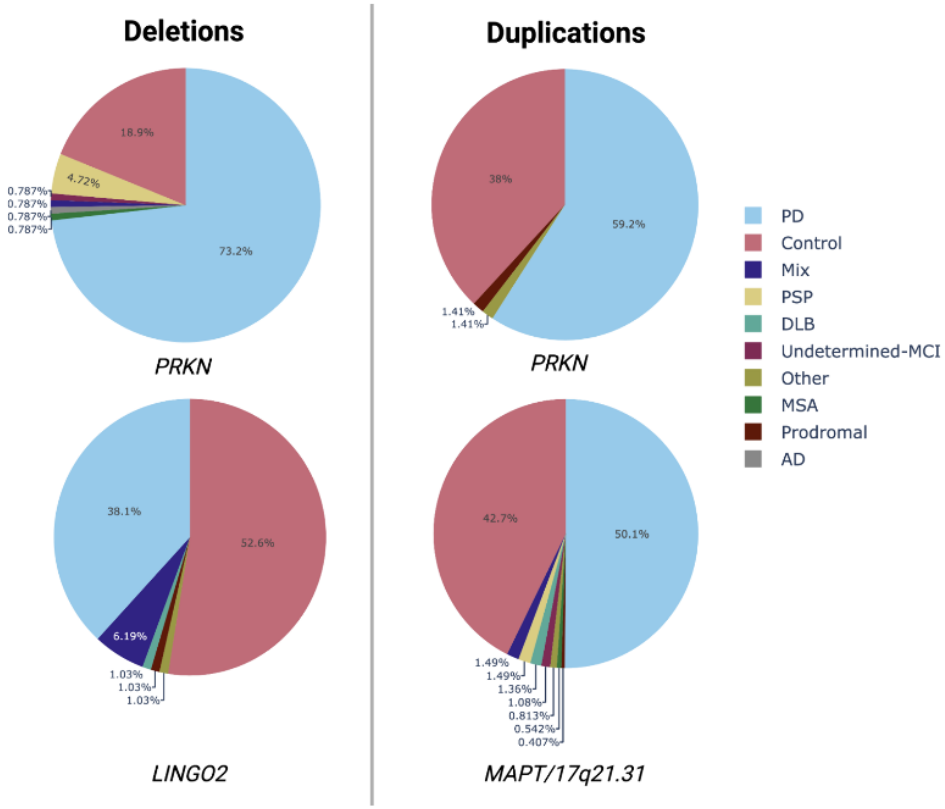
Nicole Kuznetsov[1], Kensuke Daida[1], Mary Makarious[1], Kimberley Billinglsey[1], Michael Nalls[2], Dan Vitale[1], Andrew Singleton[1], Sara Bandres-Ciga[1], Samantha Hong[1], Mathew Koretsky[1], Miriam Ostrozovicova[3], Cornelis Blauwendraat[1], Hampton Leonard[1], Kristin Levine[1]
[1]National Institute of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [2]NIH, Nia, Ninds, Bethesda, United States of America, [3]UCL Queen Square Institute of Neurology, Department Of Neuromuscular Diseases, London, United Kingdom

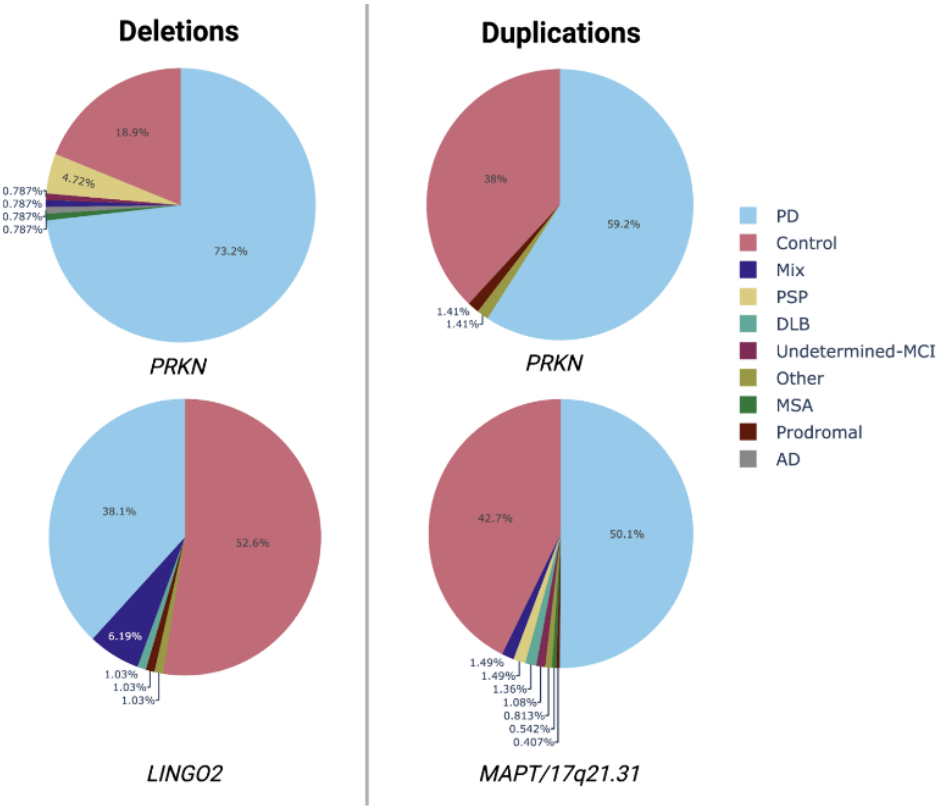
Aims: Copy Number Variations (CNVs) play key roles in complex diseases and vary across populations. We present CNV-Finder, a pipeline leveraging deep learning on cost-effective array data to expedite large-scale CNV identification in specific genomic regions. We target three genes: *PRKN*, *LINGO2*, and *MAPT*. Training on Global Parkinson's Genetics Program (GP2) expert-annotated samples and validating across diverse cohorts, CNV-Finder accurately detects deletions and duplications. The pipeline also incorporates semi-automated human validation to enhance performance and reduce false positives.
Methods: CNV-Finder uses a Long Short-Term Memory (LSTM) neural network to capture long-term dependencies in sequential data, predicting likelihoods between 0 and 1 for any gene, regardless of size. The results are visualized in an interactive web application, allowing researchers to review and confirm samples for re-submission (Figure 1). Initially, 184 samples annotated by 13 GP2 researchers were used for training, which expanded to 939 samples through validation in the app.





Results: In comparison to a manually-curated list of *PRKN* CNVs from 4,332 GP2 samples, CNV-Finder achieved an AUC of 0.99 for deletions and 0.92 for duplications. Across 12,580 GP2 samples, 223 deletions were found in *PRKN* and *LINGO2*, while 809 duplications were identified in *PRKN* and 17q21.31/*MAPT* (Figure 2).


Deletions
18.9%
4.72%
0.787%
0.787%
0.787%
0.787%
73.2%
PRKN
38.1%
52.6%
6.19%
1.03%
1.03%
1.03%
LINGO2
Duplications
38%
59.2%
1.41%
1.41%
PRKN
42.7%
50.1%
1.49%
1.49%
1.36%
1.08%
0.813%
0.542%
0.407%
MAPT/17q21.31
PD
Control
Mix
PSP
DLB
Undetermined-MCI
Other
MSA
Prodromal
AD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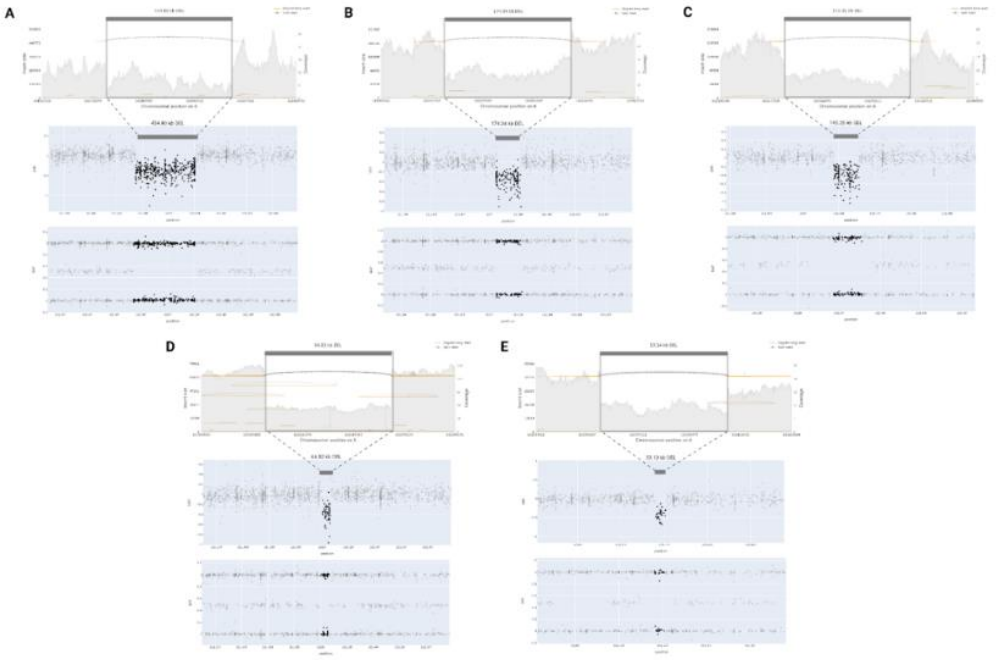
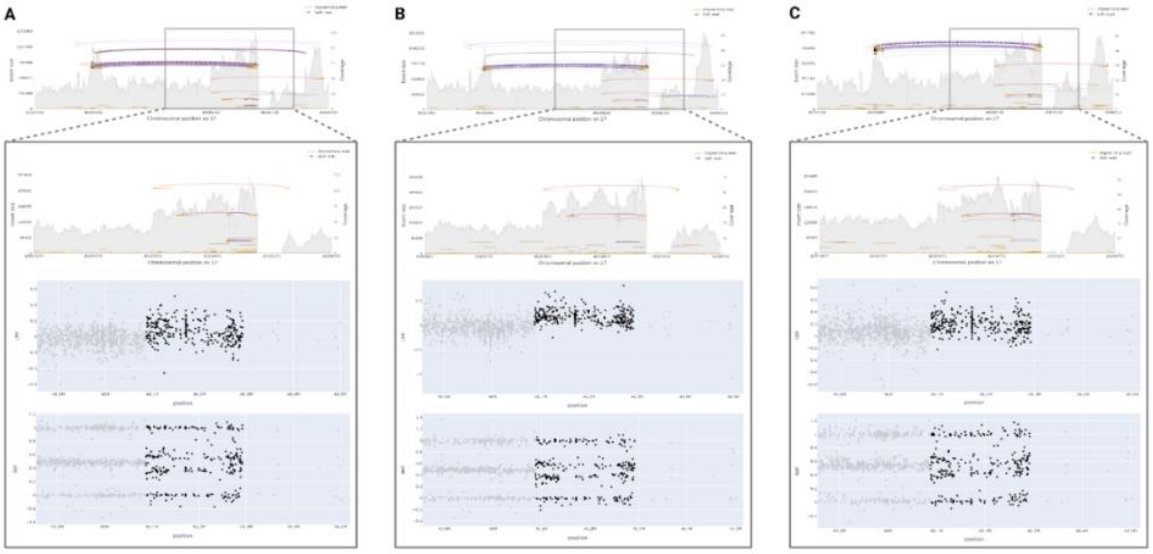
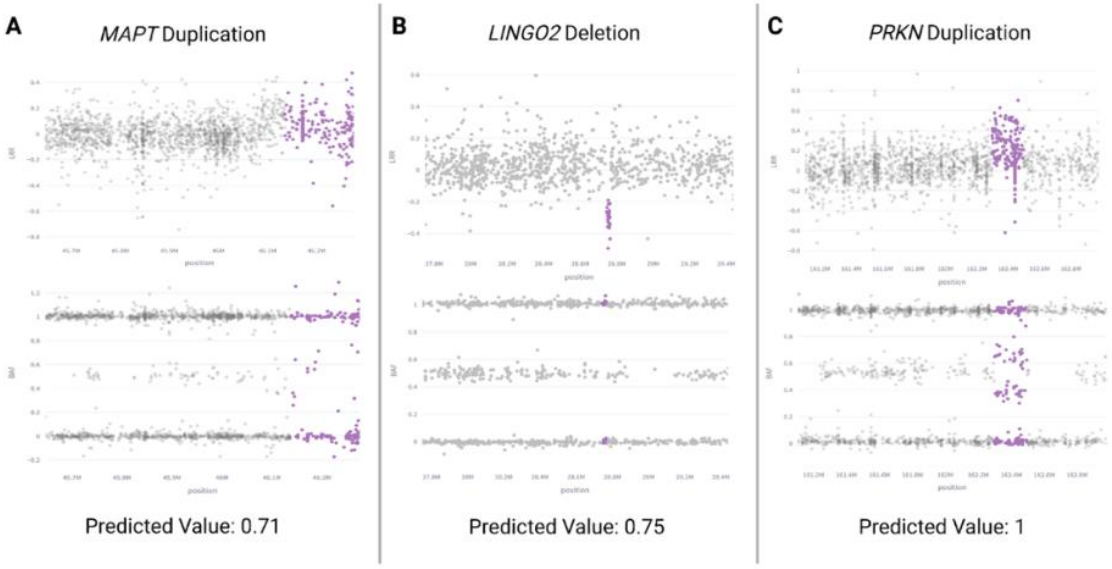
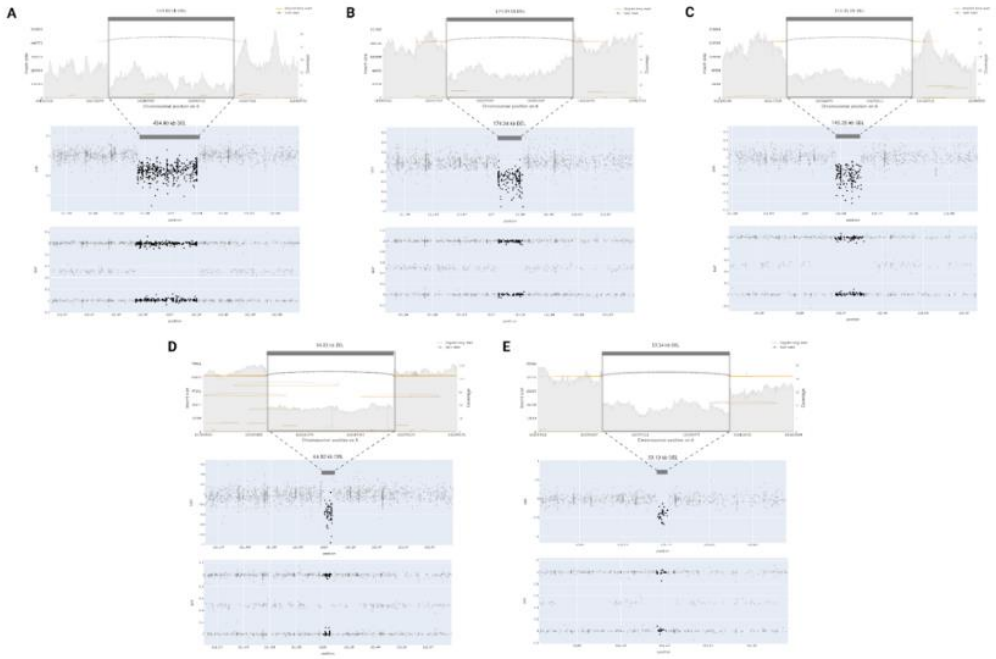
0.813%
0.542%
0.407%
MAPT/17q21.31
PD
Control
Mix
PSP
DLB
Undetermined-MCI
Other
MSA
Prodromal
AD

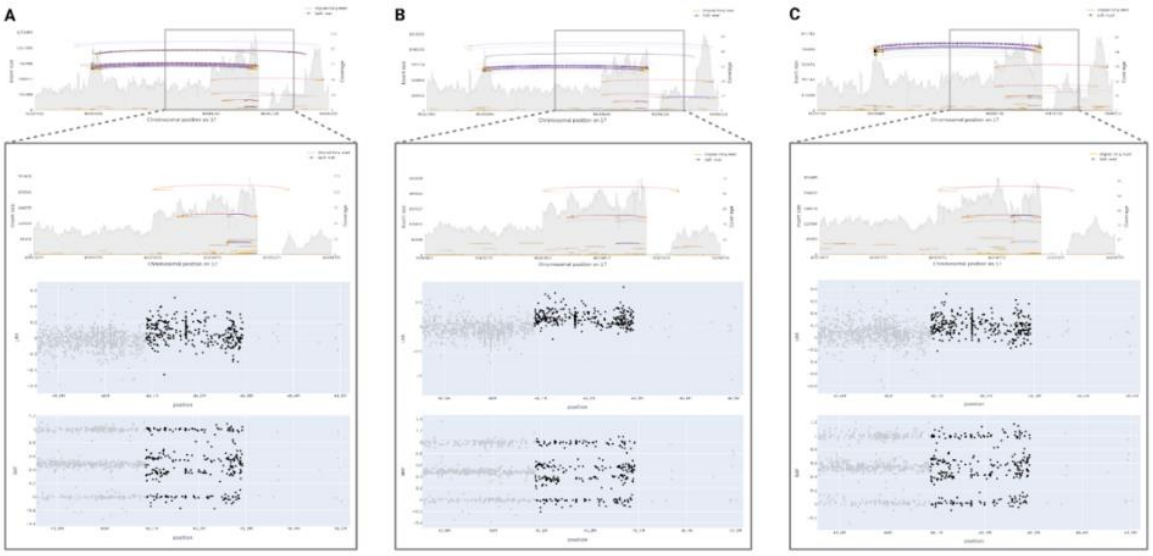
In one cohort, long-read sequencing confirmed 5 *PRKN* deletions (Figure 3) and 3 17q21.31/*MAPT* duplications (Figure 4), while short-read sequencing validated samples with varying prediction values (Figure 5).

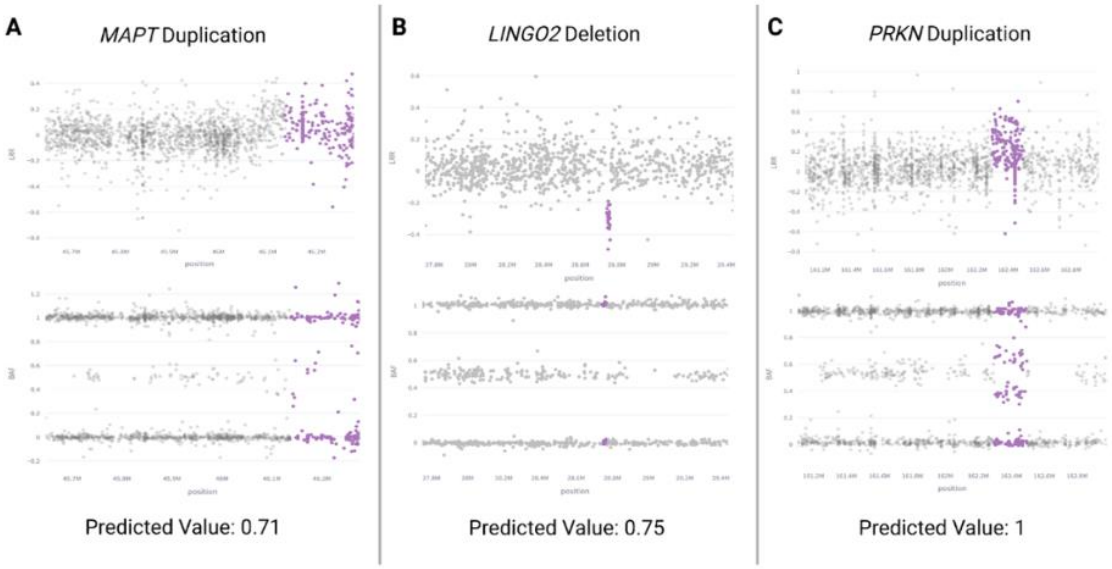




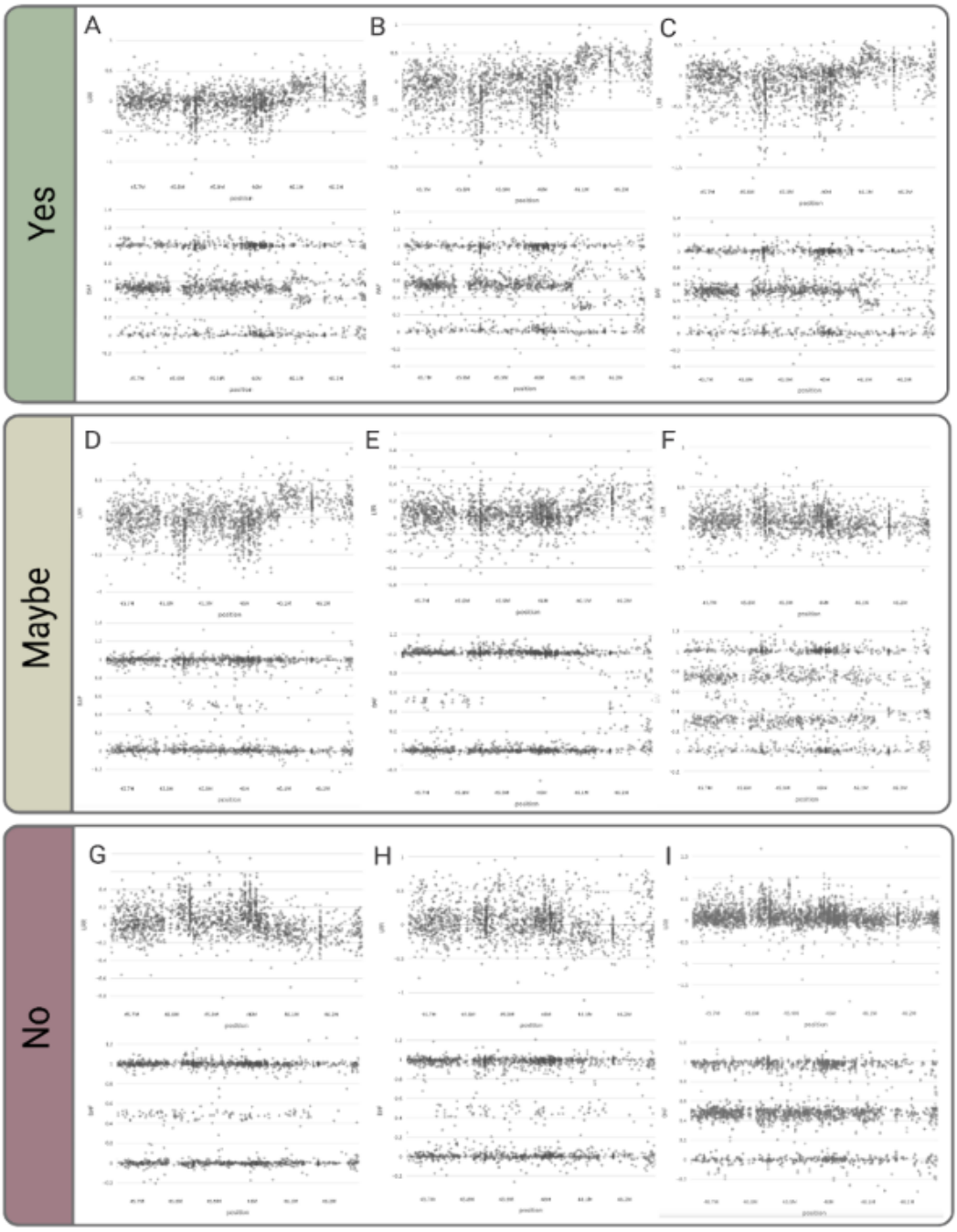

A
MAPT Duplication
Predicted Value: 0.71
B
LINGO2 Deletion
Predicted Value: 0.75
C
PRKN Duplication
Predicted Value: 1


A
B
C
D
E





Further examining the 17q21.31 region, a logistic regression on 1,151 samples using H2 haplotype-carrier status as the only feature, achieved 97% accuracy and an AUC of 0.95 in predicting a 'Yes' annotated duplication near *MAPT* (Figure 6).



Conclusions: CNV-Finder demonstrates robustness across multiple use cases, reducing the manual burden of CNV validation and supporting large-scale genomic studies.

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Virtual OO - 210

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SINGLE-CELL ATLAS OF THE TRANSCRIPTOMIC LANDSCAPE IN PARKINSON'S DISEASE PROGRESSION ACROSS MULTIPLE BRAIN REGIONS

Tereza Clarence[1,2,3], Prashant N.M.[1,2,3], John Fullard[1,2,4], Nicolas Masse[1,2,3], Donghoon Lee[1,2,3], Jaroslav Bendl[1,2,3], Vahram Haroutunian[1,2], Sabina Berretta[5], William Scott[6], Panos Roussos[1,2,4,7,8]
[1]Icahn School of Medicine at Mt Sinai, Department Of Psychiatry, New York, United States of America, [2]Friedman Brain Institute, Icahn School Of Medicine At Mount Sinai, NEW YORK, United States of America, [3]Center for Disease Neurogenomics, Icahn School of Medicine at Mount Sinai, NEW YORK, United States of America, [4]Center for Disease Neurogenomics, Icahn School of Medicine at Mount Sinai, New York, United States of America, [5]Broad Institute of MIT and Harvard, Stanley Center For Psychiatric Research, Cambridge, United States of America, [6]Brain Endowment Bank, University of Miami Miller School of Medicine, Department Of Neurology, Miami, United States of America, [7]Icahn School of Medicine at Mt Sinai, Department Of Genetics And Genomic Sciences, NEW YORK, United States of America, [8]Mental Illness Research Education and Clinical Center (VISN 2 South), James J. Peters Va Medical Center, New York, United States of America

Aims: This study seeks to create a comprehensive single-cell transcriptomic atlas of Parkinson's disease (PD), capturing gene expression patterns across different brain regions and disease stages. By systematically categorizing transcriptomic variations, the study aims to uncover region-specific molecular signatures and cellular behaviors, offering insights into PD progression and potential therapeutic targets.
Methods: Samples from 100 donors were utilized for single-cell RNA sequencing (scRNA-seq), yielding over 2 million nuclei across multiple brain regions, including the Dorsal Motor Nucleus of the Vagus (DMNX), Globus Pallidus Internus (GPI), Primary Motor Cortex (PMC), Prefrontal Cortex (PFC), and Primary Visual Cortex (PVC). The downstream analysis involved identifying transcriptomic signatures, performing differential gene expression analysis, cell-type compositional explorations and examining cell-cell interactions, combined with machine learning predictions to uncover gene expression patterns across different brain regions and stages of Parkinson's disease.
Results: The largest single-cell transcriptomic atlas of Parkinson's disease (PD) across 5 brain regions reveals distinct, region-specific transcriptomic changes and establishes a comprehensive region-specific taxonomy. Our study identified critical molecular signatures and pathways, particularly in microglia, which exhibit altered activation states and functions with advancing disease. Additionally, we uncovered differential cell-cell interactions and specific gene expression patterns associated with neurodegeneration. These findings provide a detailed understanding of the cellular and molecular landscape of PD, offering new insights into the spatial and temporal dynamics of disease progression.
Conclusions: In conclusion, the multi-regional single-cell transcriptomic atlas of Parkinson's disease (PD) reveals distinct, region-specific gene expression patterns and cellular behaviors that evolve as the disease

progresses. The study highlights key molecular signatures and phenotypic changes, particularly in microglia, offering a valuable resource for advancing therapeutic strategies that target the spatial and temporal dynamics of PD.

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METABOLOMIC PROFILING OF NINE PARKINSON'S DEMENTIA DISEASE BRAIN REGIONS

Melissa Scholefield[1], Stephanie Church[1], George Taylor[2], David Knight[3], Richard Unwin[1], Garth Cooper[4]
[1]University of Manchester, Division Of Cardiovascular Sciences, Manchester, United Kingdom, [2]University of Manc, Biological Mass Spectrometry Core Research Facility, Manchester, United Kingdom, [3]University of Manc, Biological Mass Spectrometry Core Research Facility, PT, United Kingdom, [4]University of Auckland, School Of Biological Sciences, Auckland, New Zealand

Aims: To date, there have been very few metabolomics analyses simultaneously investigating several regions of the Parkinson's disease dementia (PDD) brain, with most studies either focusing on regions with high levels of neurodegeneration such as the substantia nigra alone, or on PD without cognitive decline. This study aimed to fill this gap in knowledge in order to provide a more extensive metabolic profile of the PDD brain.
Methods: Semi-targeted metabolomics was carried out on nine confirmed PDD cases and nine age, sex, and post-mortem delay-matched controls using high-performance liquid chromatography–mass spectrometry (HPLC–MS) across nine brain regions including the cerebellum, cingulate gyrus, hippocampus, medulla, middle temporal gyrus, motor cortex, pons, and substantia nigra. Case–control differences were determined by multiple t-test, followed by 10% FDR correction.
Results: Of 64 identified metabolites, 49 were found to be altered in PDD cases in at least one brain region. Affected metabolic pathways included glucose metabolism, purine metabolism, and the TCA cycle, with widespread alterations in fructose, ribose-5-phosphate, inosine, proline, serine, and deoxyguanosine. Regions of the brain affected earlier in PDD according to traditional α-synuclein Braak staging appeared to show more metabolic alterations, although the cerebellum also showed an unexpectedly high number of changes.
Conclusions: The PDD brain shows extensive alterations in glucose metabolism, purine metabolism, and energy production pathways, affecting not only regions with high levels of neurodegeneration but showing a wider distribution across the brain. This study shows how extensive metabolic dysregulation is within the PDD brain and highlights many alterations not previously observed, such widespread fructose and serine elevations.

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Virtual OO - 212

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UREA ELEVATIONS PRESENT IN EVERY INVESTIGATED REGION OF THE PD, PDD, AND DLB BRAIN

Melissa Scholefield[1], Stephanie Church[1], Richard Unwin[1], Garth Cooper[2]
[1]University of Manchester, Division Of Cardiovascular Sciences, Manchester, United Kingdom, [2]University of Auckland, School Of Biological Sciences, Auckland, New Zealand

Aims: In untreated chronic kidney disease, urea elevations in the brain can lead to uremic encephalopathy, in which accumulation of urea in the brain leads to cognitive dysfunction, delirium, confusion, and emotional volatility, among other symptoms. Unexpectedly, investigations of the Alzheimer's and Huntington's disease brain revealed widespread elevations in urea, similar to those seen in uremic encephalopathy. In light of this, our group aimed to determine whether such urea elevations are also present in the brains of those with Parkinson's disease with (PDD) or without (PD) dementia, and dementia with Lewy bodies (DLB).
Methods: Urea concentrations were quantified in 20 DLB cases, nine PD cases, nine PDD cases, and matched controls using ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS), investigating multiple brain regions simultaneously. Case–control differences were determined for each condition using Mann–Whitney U tests, and observed urea alterations were compared across conditions.
Results: Urea was found to be elevated in every investigated brain region for all three conditions. The degree of elevation was similar to that seen in uremic encephalopathy; the highest average increase was 4.3-fold in PDD, followed by 3.9-fold in PD, and 3.0-fold in DLB. The level of increase was not correlated with α-synuclein Braak stage in PD.
Conclusions: It is possible that urea levels reach toxic levels in the brains of those with PD, PDD, and DLB. This may contribute to pathogenesis in these conditions. Future research should determine the source of this elevated urea and its downstream effects in the brain.

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CELL-TYPE SPECIFIC EPIGENETIC ALTERATIONS IN LEWY BODY DISEASES

Jennifer Imm[1], Joshua Harvey[1], Adam Smith[1], Barry Chioza[1], Ehsan Pishva[2], Byron Creese[3], Leonidas Chouliaras[4], Emma Dempster[1], Clive Ballard[1], John O'Brien[5], Dag Aarsland[6], Jonathan Mill[1], Katie Lunnon[1]
[1]University of Exeter, Department Of Clinical & Biomedical Sciences, Exeter, United Kingdom, [2]Maastricht University, Department Of Psychiatry And Neuropsychology, Maastricht, Netherlands, [3]Brunel University London, Department Of Life Sciences, London, United Kingdom, [4]University of Cambridge, Cambridge, United Kingdom, [5]Cambridge University, Department Of Psychiatry, Cambridge, United Kingdom, [6]King's College London, Psychological Medicine, London, United Kingdom

Aims: The Lewy body diseases (LBDs), Dementia with Lewy bodies (DLB), Parkinson's disease (PD) and Parkinson's disease dementia (PDD) are all neurodegenerative diseases classified by the accumulation of alpha-synuclein in neurons, forming Lewy bodies (LB). We hypothesise that these LBs cause epigenetic changes within neurons and surrounding cells, that these changes are cell type specific and can be used to distinguish the different diseases from one another.
Methods: We generated a cohort of cingulate gyrus tissue to investigate the cell type specific epigenetic changes across the LBDs and control tissues (n=20 per group). Fluorescent-activated nuclei sorting was used to isolate populations of neurons, oligodendrocytes and microglia from each tissue sample. DNA from these populations was then analysed using the methylation EPIC array generating a quantitative measure of DNA methylation for over 850,000 CpG sites. Analysis of Variance, followed by a post-hoc Tukey test, was used to identify significantly differentially methylated loci between disease groups in each cell type individually, alongside the cellular pathways these correspond with. We also compared these loci with bulk methylation data from the same individuals to identify which cell types are driving the bulk methylation signature.
Results: We have identified significant differentially methylated loci within each cell type across the different LDBs and control samples. These loci include genes that have been previously associated with synucleinopathies and neurodegenerative diseases previously including *ANK1, BDNF* and *ABCA13*.
Conclusions: We have collated a well characterised cohort to interrogate the epigenetic basis of clinical diagnosis within distinct cell types. Cell type specific analyses have revealed disease associated changes across the LBDs. Work is underway to compare these changes to bulk methylation data and to generate modules of co-methylated loci using Weighted gene co-expression network analysis.

Virtual OO - 214

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BRADYKINESIA AND POSTURAL INSTABILITY IN A MODEL OF PRODROMAL SYNUCLEINOPATHY WITH A-SYNUCLEIN AGGREGATION IN THE GIGANTOCELLULAR NUCLEI

Vasileios Theologidis[1], Sara Ferreira[2], Poul Henning Jensen[3], Nanna Møller Jensen[4], Marina Romero-Ramos[5], Wilma Van De Berg[6], Asad Jan[2]
[1]Aarhus University, Department Of Clinical Medicine, Aarhus, Denmark, [2]Aarhus University, Aarhus, Denmark, [3]Aarhus University, Dandrite, Biomedicine, Aarhus, Denmark, [4]Aarhus University, Dandrite, Dept. Of Biomedicine, Aarhus C, Denmark, [5]Aarhus University, Dept. Of Biomedicine, Aarhus C, Denmark, [6]Vrije Universiteit Amsterdam1081 HZ Amsterdam, Department Of Anatomy And Neurosciences, Amsterdam, Netherlands

Aims: α-Synuclein (aSyn) accumulation within the extra-nigral neuronal populations in brainstem, including the gigantocellular nuclei (GRN/Gi) of reticular formation, is a recognized feature during the prodromal phase of Parkinson disease (PD). Accordingly, there is a burgeoning interest in animal model development for understanding the pathological significance of extra-nigral synucleinopathy, in relation to motor and/or non-motor symptomatology in PD. Therefore, we hypothesized that direct induction of aSyn aggregation within GRN of rodents will lead to the emergence of unique sensorimotor phenotypes, which could potentially be relevant to PD symptomatology. In particular, we wanted to study the patterns of locomotion, movement coordination and nociception in relation to the emergence and propagation of aSyn pathology in brainstem, with GRN as the initial nidus of aSyn aggregation
Methods: Steretoaxic Surgeries, Survival analyses, Motor Performance, Histopathology
Results: In transgenic mice expressing the human mutant Ala53Thr aSyn ((M83 line), we observed that *de novo* induction of aSyn aggregation in GRN, -by stereotaxic delivery of pre-formed fibrillar (PFF) aSyn-, was associated with progressive reduction in spontaneous locomotion and subtle defects in postural motor coordination, long before phenotypes reflecting motor weakness were seen. With the progression of aSyn pathology into additional nuclei in the brainstem, the animals exhibited worsening deficits in movement coordination and defective response in tests of nociception, with consequent decline in survival.
Conclusions: Collectively, our observations suggest an experimental framework for studying the pathological significance of aSyn aggregation in GRN in relation to features of movement disability in PD. With further refinements, we anticipate that this model holds promise as a test-bed for translational research in PD and related disorders.

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Virtual OO - 215

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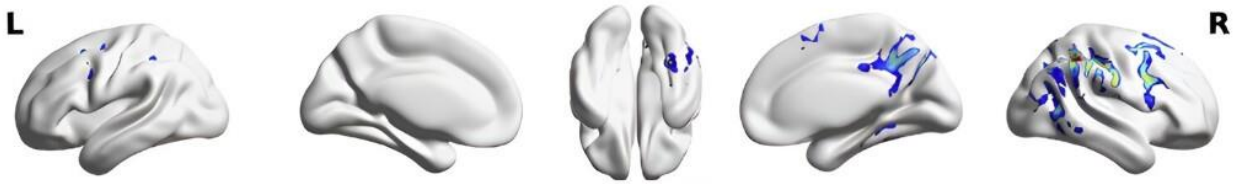
DISTINCT TAU DEPOSITION PATTERNS IN PRECLINICAL ALZHEIMER'S DISEASE ARE ASSOCIATED WITH COGNITIVE PHENOTYPES

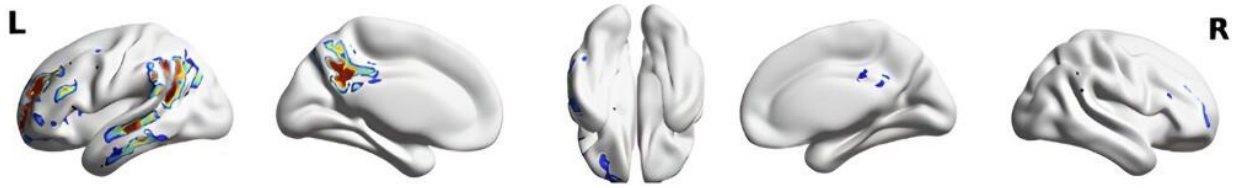
Seyed Hani Hojjati[1], Qolamreza Razlighi[1], Tracy Butler[1], Mony De Leon[1], Jose Luchsinger[2], Yaakov Stern[2], Nancy Foldi[1], Yi Li[1], Kewei Chen[3], Gloria Chiang[1]
[1]Weill Cornell Medicine, New York, United States of America, [2]columbia university irving medical center, New York, United States of America, [3]Arizona State University, Phoenix, United States of America

Aims: This study aimed to identify tau deposition patterns in the preclinical stages of Alzheimer's disease (AD) and their cognitive implications.
Methods: We leveraged positron emission tomography (PET) data from a second-generation tau tracer (18F-MK6240) in a large sample of 590 cognitively healthy older individuals (mean age 66.58 ± 5.13 years; 340 females). Independent Component Analysis (ICA) was applied to identify distinct tau deposition patterns. Tau uptake within each pattern was quantified using a voxel-wise threshold of Z-score>6. Finally, linear regression analyses were conducted to assess the associations between tau uptake in each pattern and three cognitive phenotypes (memory, language, and reasoning). We focused on the top quartile of individuals with the highest expression of each tau pattern while controlling for age, gender, and APOE-ε4.
Results: Seven distinct tau patterns were identified (**Figure 1**) and associated with unique cognitive phenotypes (**Table 1**). Only the tau uptake in the subcortical medial temporal lobe (MTL)-sparing pattern (IC6) was significantly associated with worse memory performance ($t=-2.64$, $p<0.01$). Conversely, tau uptake in unique patterns involving neocortical regions, particularly asymmetric left frontal-temporoparietal (IC2) and bilateral temporoparietal (IC5), was strongly associated with deficits in language ($t<-3.13$, $p<0.002$) and reasoning ($t<-2.63$, $p<0.01$).

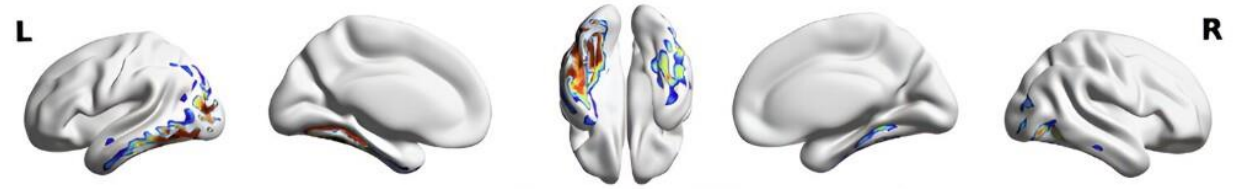
IC1: Asymmetric right parietal



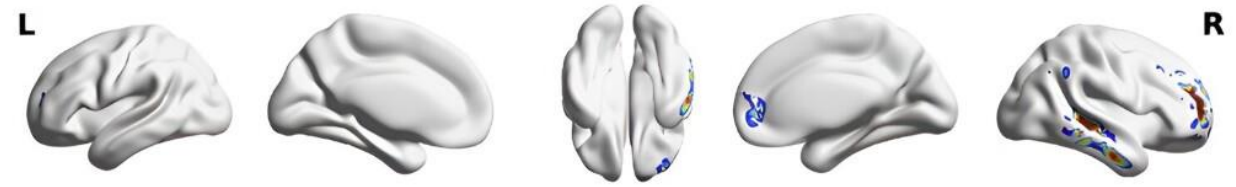
IC2: Asymmetric left frontal-temporoparietal



IC3: Bilateral temporal-occipital



IC4: Asymmetric right frontal-temporoparietal



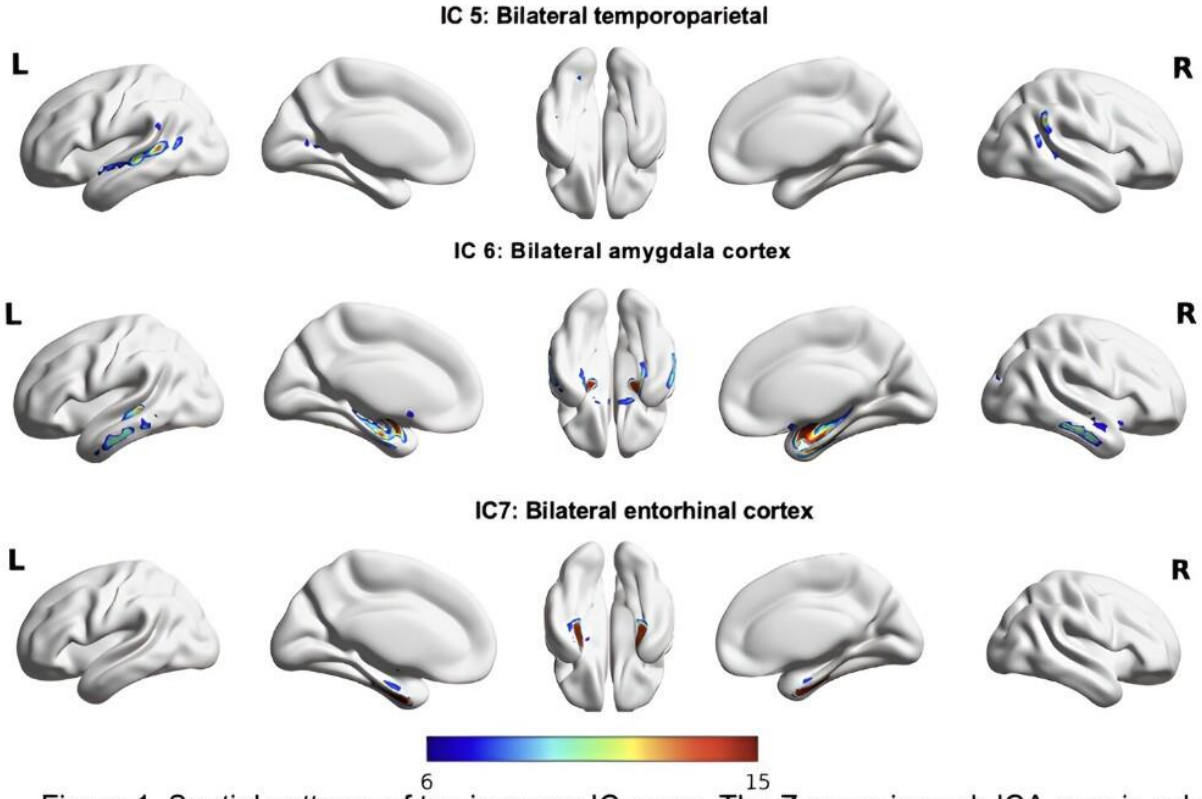


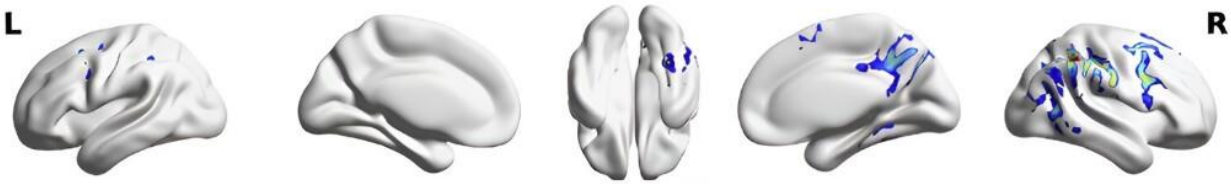
Figure 1. Spatial patterns of tau in seven IC maps. The Z-score in each ICA map is color-coded, with blue indicating a Z-score of 6 and red indicating a Z-score of 15 or higher.

Table 1. Associations between tau uptake in each IC map and cognitive phenotypes

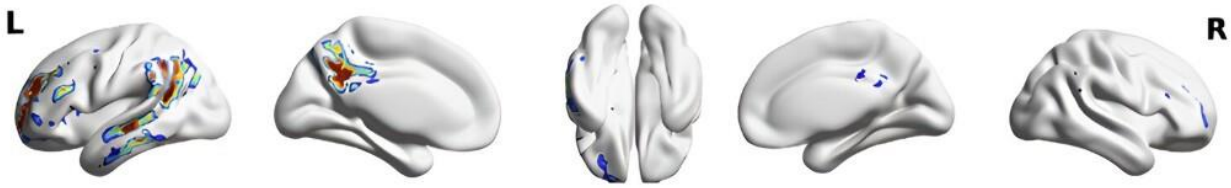
Cognitive assessments	IC1	IC2	IC3	IC4	IC5	IC6	IC7
Memory: Selective reminding test (total recalls)	*N.S*	*N.S*	*N.S*	*N.S*	*t= -2.23 p<0.02*	***t= -2.64 p<0.01[a]***	*N.S*
Language: Category fluency	*N.S*	***t= -3.26 p<0.002***	*N.S*	*t= -2.47 p<0.015*	***t= -3.33 p<0.001***	*N.S*	*N.S*
Language: Letter fluency	*N.S*	***t= -3.14 p<0.002***	*t= -2.24 p<0.027*	*t= -2.30 p<0.024*	***t= -3.13 p<0.002***	*N.S*	*N.S*
Reasoning: Identities and oddities	***t= -2.63 p<0.01[a]***	*N.S*	***t= -3.55 p<0.001***	*N.S*	***t= -3.064 p<0.003***	*N.S*	*N.S*

N.S: Not significant, Bold font: Survived after FWER, a: Marginally survived after FWER

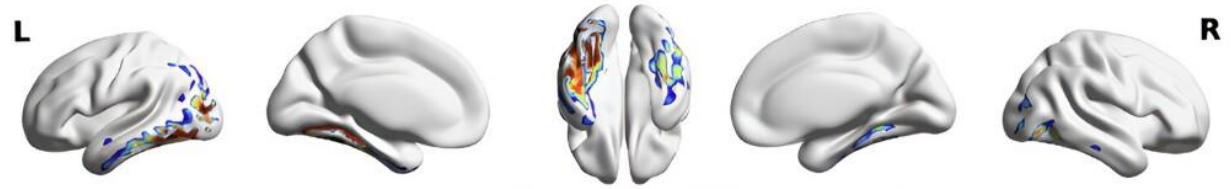
IC1: Asymmetric right parietal



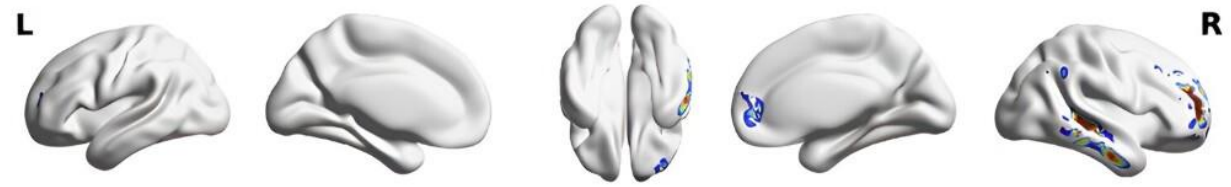
IC2: Asymmetric left frontal-temporoparietal



IC3: Bilateral temporal-occipital



IC4: Asymmetric right frontal-temporoparietal



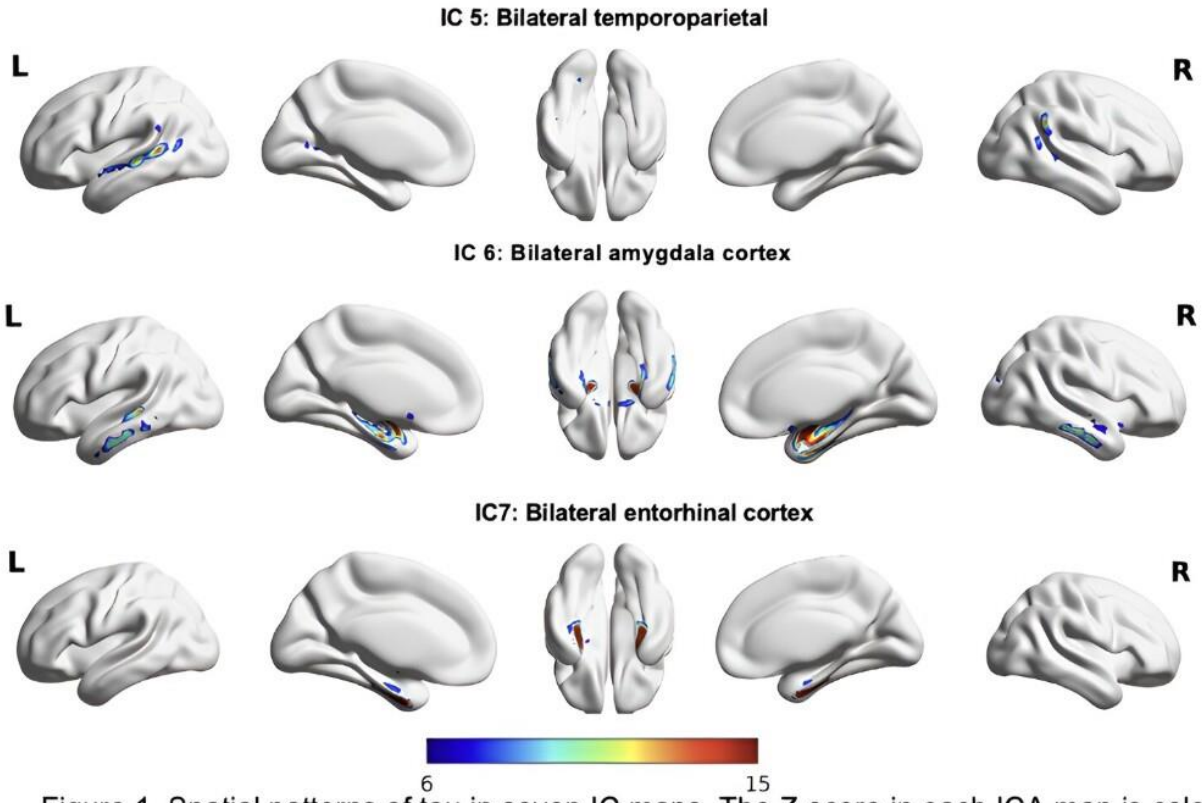


Figure 1. Spatial patterns of tau in seven IC maps. The Z-score in each ICA map is color-coded, with blue indicating a Z-score of 6 and red indicating a Z-score of 15 or higher.

Table 1. Associations between tau uptake in each IC map and cognitive phenotypes

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Language: Category fluency	*N.S*	***t= -3.26 p<0.002***	*N.S*	*t= -2.47 p<0.015*	***t= -3.33 p<0.001***	*N.S*	*N.S*
Language: Letter fluency	*N.S*	***t= -3.14 p<0.002***	*t= -2.24 p<0.027*	*t= -2.30 p<0.024*	***t= -3.13 p<0.002***	*N.S*	*N.S*
Reasoning: Identities and oddities	***t= -2.63 p<0.01[a]***	*N.S*	***t= -3.55 p<0.001***	*N.S*	***t= -3.064 p<0.003***	*N.S*	*N.S*

N.S: Not significant, Bold font: Survived after FWER, a: Marginally survived after FWER

Conclusions: Unique tau patterns can be detected in the preclinical stages of AD and are strongly linked to domain-specific cognitive deficits. These findings highlight the importance of identifying tau patterns early in the disease process, which may have implications for future spread of tau and the development of non-amnestic forms of AD.

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Virtual E-Posters and Oral On-Demand
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LEVERAGING GENETIC DIVERSITY IN AFRICAN ANCESTRY POPULATIONS FOR ENHANCED UNDERSTANDING OF ALZHEIMER DISEASE GENETICS

Joshua Akinyemi[1], Farid Rajabli[2], Larry Adams[3], Scott Kyle[3], Motunrayo Coker[4,5], Kazeem Akinwande[4], Samuel Diala[4], Patrice Whitehead[3], Mayowa Ogunronbi[4], Kara Hamilton-Nelson[3], Albertino Damasceno[6], Andrew Zaman[3], Yared Zeble[7], Gary Beecham[8], Biniyam Ayele[9], Allison Caban-Holt[10], David Ndetei[11], Anthony Griswold[2,3], Fred Sarfo[12], Susan Blanton[3], Albert Akpalu[13], Michael Cuccaro[2,3], Kolawole Wahab[14], Katalina Mcinerney[15], Reginald Obiako[16], Olusegun Baiyewu[17], Pedro Mena[3], Njideka Okubadejo[18], Izri Martinez[3], Adesola Ogunniyi[4], Brian Kunkle[3], Raj Kalaria[19], Jeffery Vance[3,15], Christiane Reitz[20], Giuseppe Tosto[21], William Scott[22], William Bush[23], Jonathan Haines[24], Goldie Byrd[10], African Dementia Consortium (Afdc)[25], Rufus Akinyemi[4], Margaret Pericak-Vance[2,3]
[1]College of Medicine, University of Ibadan, Department Of Epidemiology And Medical Statistics, Ibadan, Nigeria, [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, John P. Hussman Institute For Human Genomics, Miami, United States of America, [4]Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria, [5]University of Ibadan, Cell Biology And Genetics Unit, Department Of Zoology, not applicable, Nigeria, [6]Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique, [7]College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia, [8]Wake Forest School University of Medicine, Department Of Biostatistics And Data Science, Winston-Salem, United States of America, [9]College of Health Sciences, Addis Ababa University, Addis Ababa, Nigeria, [10]Wake Forest School of Medicine, Maya Angelou Center For Health Equity, Winston-Salem, United States of America, [11]Africa Institute of Mental and Brain Health, Nairobi, Kenya, [12]Komfo Anokye Teaching Hospital, Kumasi, Ghana, [13]University of Ghana, Accra, Ghana, [14]University of Ilorin Teaching Hospital, Ilorin, Nigeria, [15]University of Miami Miller School of Medicine, Department Of Neurology, Miami, United States of America, [16]Ahmadu Bello University, Zaria, Nigeria, [17]University College Hospital, Ibadan, Nigeria, [18]University of Lagos, Lagos, Nigeria, [19]Newcastle University, Newcastle, United Kingdom, [20]College of Physicians and Surgeons, Columbia University, Gertrude H. Sergievsky Center, Taub Institute For Research On The Aging Brain, Departments Of Neurology, Psychiatry, And Epidemiology, New York, United States of America, [21]Columbia University, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, College Of Physicians And Surgeons, New York, United States of America, [22]University of Miami, John P. Hussman Institute For Human Genomics, Miami, United States of America, [23]Department of Population and Quantitative Health Sciences, Institute for Computational Biology, Case Western Reserve University, Cleveland, United States of America, [24]Case Western Reserve University, Institute For Computational Biology, Department Of Population & Quantitative Health Sciences, Cleveland, United States of America, [25]University of Ibadan, College Of Medicine, Ibadan, Nigeria

Aims: Genetic studies in Alzheimer disease (AD) show that ancestral background may modify the effects of genetic risk factors, such as the *APOE e4* allele. In this study, we leverage DAWN Study (READD_ADSP) datasets ascertained through the Africa Dementia Consortium (AfDC) to explore ancestral heterogeneity across five countries, spanning West (WA) to East Africa (EA), and among African Americans (AA).
Methods: We performed whole genome sequencing (WGS) on 434 Africa individuals from WA (Nigeria and Ghana) and EA (Kenya and Ethiopia) and 355 AAs (US). Population substructure was assessed using PC-AiR. ADMIXTURE analysis (AdMIX_An) with K=2 up to 8 (using African (AF), European (EU), Middle Eastern (ME), Central-South Asian and Native American populations from the HGDP reference panel) was conducted to estimate underlying population substructure.
Results: AdMIX_An revealed distinct ancestral patterns among AF and AA. In WA, Nigeria (99%) and Ghana (97%) showed almost entirely. EA populations demonstrated substantial admixture with ME ancestry: Kenya (78% AF, 22% ME) and Ethiopia (38% AF, 62% ME). AdMIX_An results for K=8 differentiated the African ancestral backgrounds of WA from EA. Principal component analysis identified significant differences in population substructures driven by admixture levels and distinct African backgrounds. AA closely aligned with WA populations.
Conclusions: The ancestral heterogeneity between WA and EA provides the potential to identify novel genetic loci, enriching our understanding of AD genetics. The shared ancestral backgrounds of WAs and AAs, alongside their differing environmental and social factors, enable study of how these factors and their interaction with genetics, influence AD risk. These insights inform research on precision medicine therapies that are globally tailored to the unique genetic profiles in all populations.

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Virtual OO - 217

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NON-CODING RNA CHANGES ASSOCIATED WITH ALZHEIMER'S DISEASE PATHOLOGY IN SINGLE NUCLEI DATA

Eric Alsop[1,2], Jerry Antone[1], Elizabeth Hutchins[1,2], Qi Wang[3], Rebecca Reiman[4], Winnie Liang[4], Geidy Serrano[5], Thomas Beach[6], Diego Mastroeni[3], Ben Readhead[3], Andrew Singleton[1], Michael Nalls[1,2], Eric Reiman[7], Kendall Van Keuren-Jensen[1]
[1]National Institute of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [2]DataTecnica, Washington, United States of America, [3]Arizona State University, Asu-banner Neurodegenerative Disease Research Center, Tempe, United States of America, [4]TGen, Neurogenomics, Phoenix, United States of America, [5]Brain and Body Donation Program Banner Sun Health Research Institute, Civin Laboratory For Neuropathology, AZ, United States of America, [6]Brain and Body Donation Program Banner Sun Health Research Institute, Civin Laboratory For Neuropathology, Sun City, United States of America, [7]Banner Alzheimer's Institute, Phoenix, United States of America

Aims: We performed single nuclei sequencing using a gene annotation reference expanded for additional non-coding RNA on post-mortem samples from a total of 102 individuals from the following groups: AD (35 individuals), MCI (15 individuals), clinical controls with AD pathology (15 individuals) and age matched controls with normal age-related pathology (36 individuals) across three brain regions (frontal cortex, visual cortex and posterior cingulate cortex). We then leveraged our expanded reference to explore novel disease and cell type associations.
Methods: Single nuclei sequencing was performed using 10X Genomics Chromium Next GEM Single Cell 3' v3.1 kits. For analysis, a custom reference was built using cellranger which included all genes in gencode v46 and additional non-overlapping lncRNAs from lncBook. In addition, we did not remove biotypes (such as pseudogenes) which are filtered from the standard 10X Genomics reference. Single nuclei analysis was done separately on all brain regions in scanpy.
Results: In comparison to the standard reference used by 10X genomics, with our custom reference we detected an average of 39,136 additional genes per sample. Using these additional genes, we found RNAs that uniquely identified with cell type and disease. Interestingly, we found layer 5 extratelencephalic neurons contain a more diverse transcriptome than other cell types. In frontal cortex, for genes detected in >50% of cells in the cluster, we found 343 lncRNAs and 586 protein coding genes that are unique to this cell type. Our previous data, and data from other groups, have shown that this cell type is potentially more vulnerable to disease.
Conclusions: Our expanded single nuclei reference allowed for the detection of additional cell type and disease-enriched genes which may be used to further classify cell types and cell states.

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

Boyi Hu[1], Badri N. Vardarajan[1,2,3], Yuanjia Wang[4], Annie Lee[1,2,3]
[1]Columbia University, Department Of Neurology, New York, United States of America, [2]G.H. Sergievsky Center, Columbia University, New York, United States of America, [3]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, United States of America, [4]Columbia University, Biostatistics, New York, United States of America

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%)

	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)
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Figure 1. Trajectories of global cognitive function by group

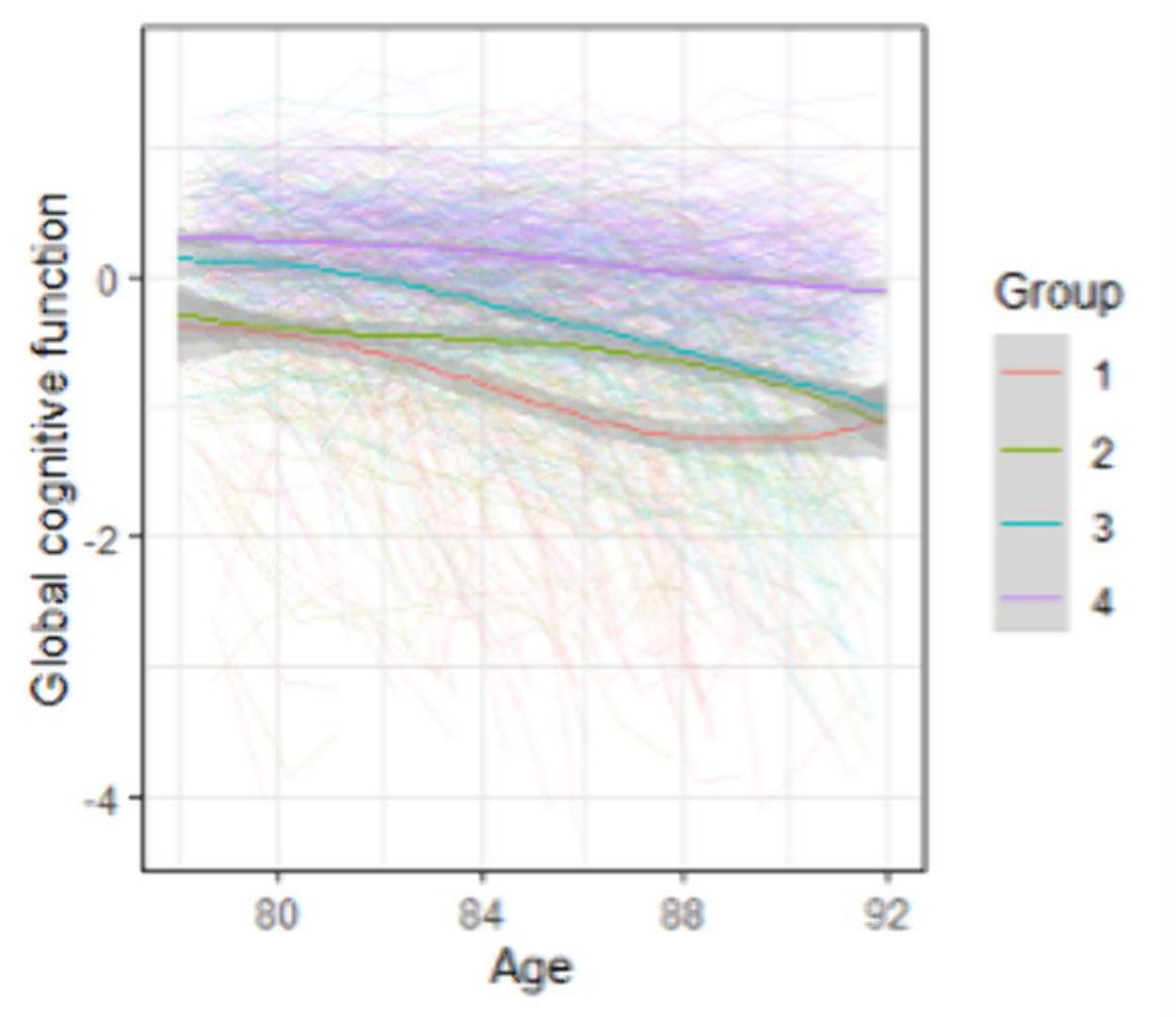
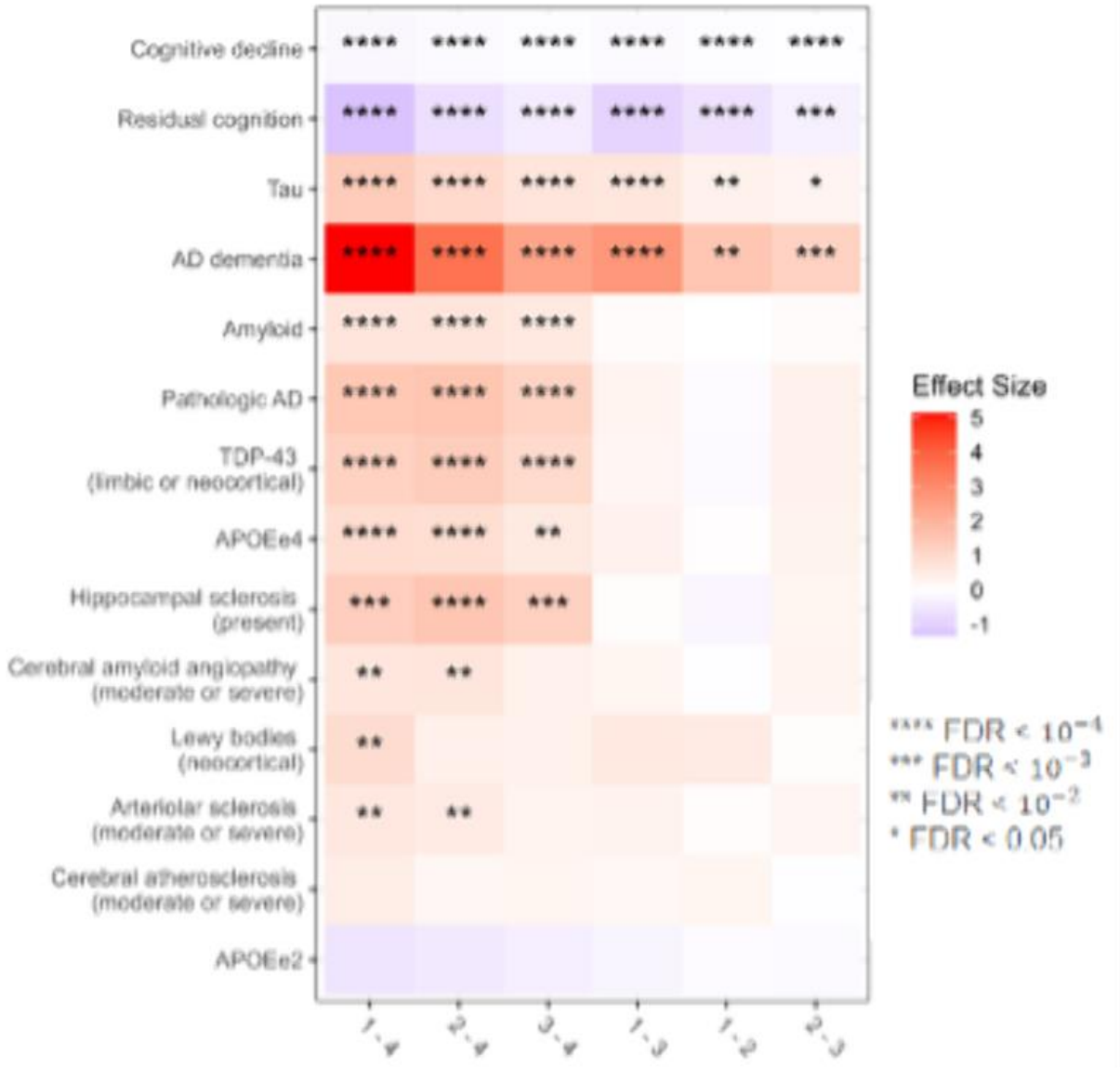


Figure 2. Clinico-pathological differences among groups


Cognitive decline
Residual cognition
Tau
AD dementia
Amyloid
Pathologic AD
TDP-43 (limbic or neocortical)
APOEe4
Hippocampal sclerosis (present)
Cerebral amyloid angiopathy (moderate or severe)
Lewy bodies (neocortical)
Arteriolar sclerosis (moderate or severe)
Cerebral atherosclerosis (moderate or severe)
APOEe2
Effect Size
5
4
3
2
1
0
-1
**** FDR < 10^-4
*** FDR < 10^-3
** FDR < 10^-2
* FDR < 0.05

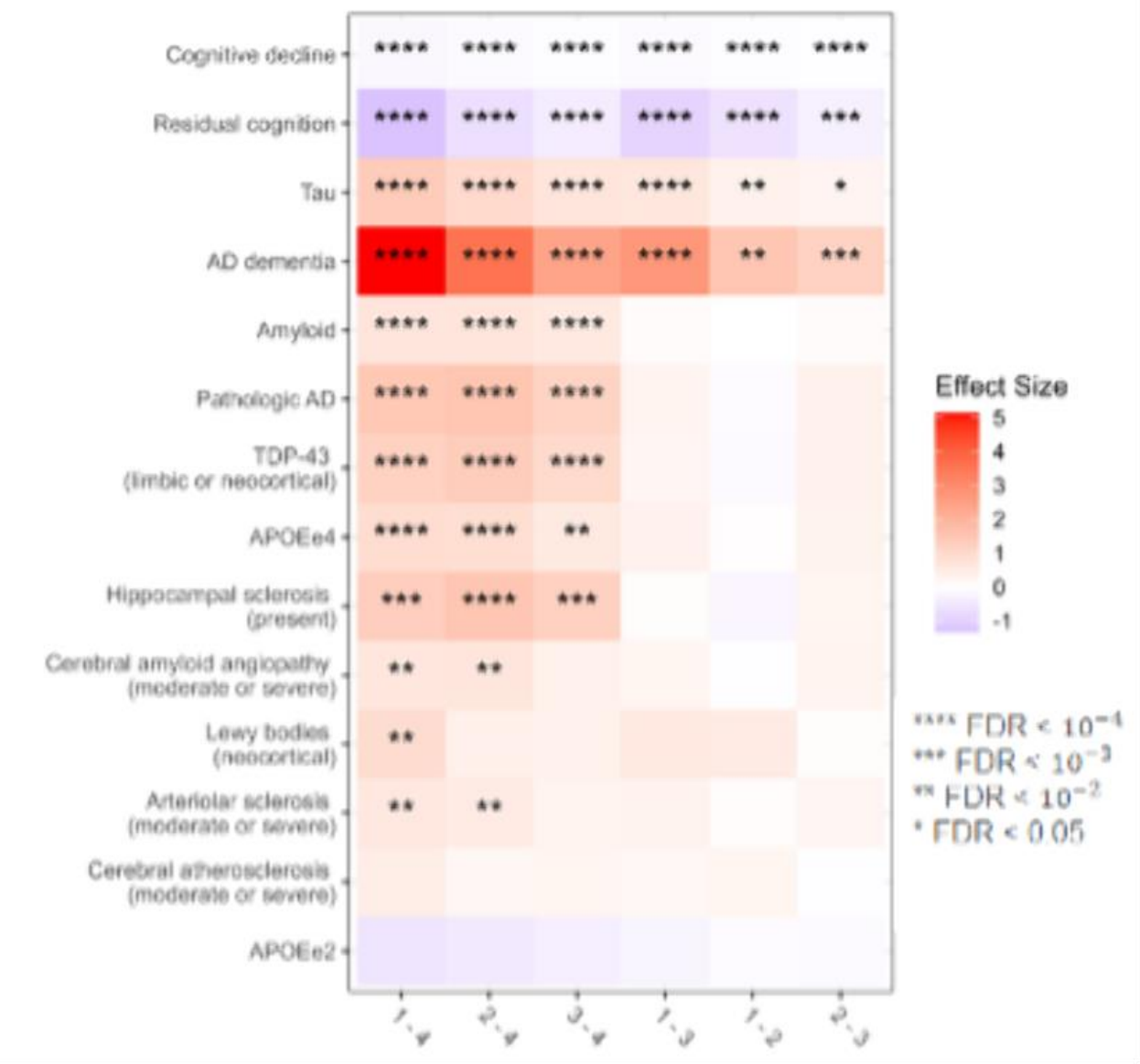
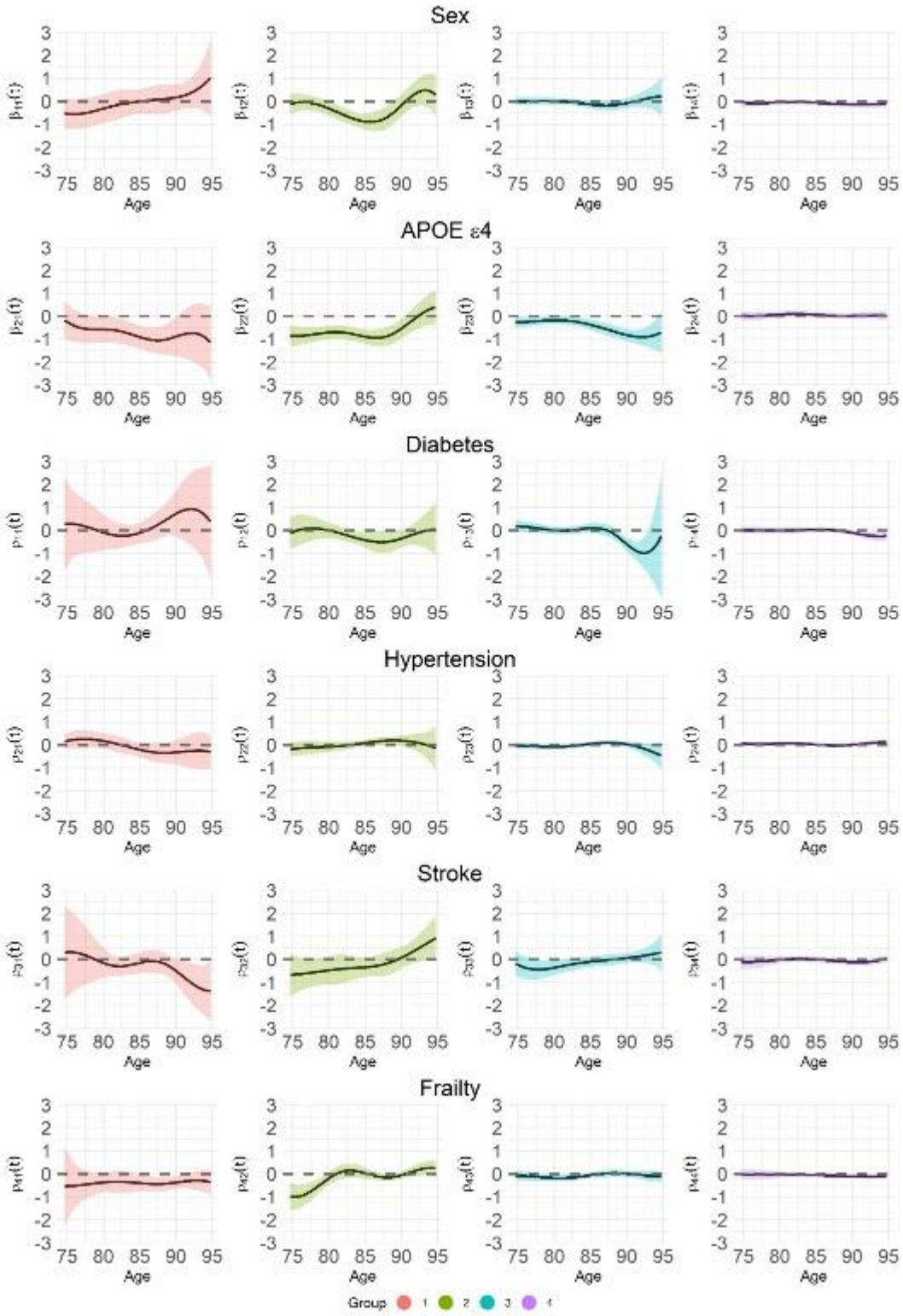


Figure 3. Effect of time-varying risk factors on global cognitive function for each group.



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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ASSOCIATION BETWEEN BRAIN GLYMPHATIC DYSFUNCTION AND INFLAMMATION IN ALZHEIMER'S DISEASE

Min Chu[1], Liyong Wu[1], Pedro Rosa-Neto[2]
[1]Xuanwu Hospital, Capital Medical University, Neurology, Beijing, China, [2]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: To explore the characteristics of glymphatic function across the AD spectrum using the diffusion tensor image analysis along the perivascular space (DTI-ALPS) index and to investigate its relationships with inflammatory parameters.
Methods: A cohort of AD, mild cognitive impairment (MCI), and cognitively normal (CN) individuals were enrolled. Participants underwent cognitive assessments, ^{18}F-AZD4694 PET, ^{18}F-MK6240 PET, MRI and DTI image evaluations, and pathological, inflammation biomarker analyses from blood and cerebrospinal fluid (CSF). DTI-ALPS index was calculated and partial correlation and mediation analysis were conducted to evaluate the association and mediators.
Results: ALPS was decreased in both AD and MCI groups after being corrected for age, sex, and white matter hyperintensity. ALPS was correlated with Aβ, Tau, neurodegeneration, disease severity, and cognition. Notably, the ALPS index is correlated with biomarkers of inflammation. Inflammation mediates the relationship between ALPS and AD-related markers including Aβ, Tau, neurodegeneration, and clinical outcomes (cognition and disease severity). Inflammation and glymphatic function interact to influence Tau PET.
Conclusions: This study provides compelling evidence that glymphatic dysfunction is a significant factor in the pathophysiology of AD, influencing pathological protein clearance and associated with inflammation.

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ACTIVATION OF AMPK BY GLP-1R AGONISTS MITIGATES ALZHEIMER-RELATED PHENOTYPES

Yun Zhang[1,2,3], Huaqiu Chen[3], Yijia Feng[2], Weihong Song[2,4]
[1]Nanjing Drum Tower Hospital, Department Of Neurology, Nanjing, China, [2]Wenzhou Medical University, Institute Of Aging, Ouijang Laboratory, Wenzhou, China, [3]Xuanwu Hospital, Beijing, China, [4]University of British Columbia, Psychiatry, Vacouver, Canada

Aims: Dysregulation of energy metabolism is linked to Alzheimer's Disease (AD). Glucagon-like peptide-1 receptor agonists (GLP-1RAs), primarily used for glycemic control in diabetes, have shown neuroprotective properties and may reduce AD risk, though the underlying mechanisms remain poorly understood. This study aims to investigate the role of GLP-1R in AD and the effects of its agonist on Alzheimer-related phenotypes.
Methods: Plasma GLP-1 levels between wild-type (WT) mice and the AD transgenic mice APP23/PS45 was analyzed. Western blot and Elisa methods were applied to examine the level of AMPK, BACE1, APP processing and Aβ level. Immunohistochemical staining and behavioral tests were used to analyze AD-related neuropathologies and cognitive impairments
Results: In this study, we found that plasma GLP-1 levels decreased in AD, correlating negatively with neuropathological features. Enhancing GLP-1 signaling by GLP-1RAs upregulated CaMKK2, which subsequently activated 5' AMP-activated protein kinase (AMPK) signaling, a key regulator of energy metabolism. GLP-1RA-induced AMPK activation further reduced BACE1-mediatd cleavage of APP and Aβ generation by modulating BACE1 transcription via NF-κB signaling. Additionally, GLP-1RAs increased AMPK activity in microglia, inhibiting neuroinflammation and promoting Aβ phagocytosis. Consequently, GLP-1RAs inhibited neuritic plaque formation and improved memory deficits in AD mice.
Conclusions: Our findings indicate that AMPK activation mediates the effect of GLP-1RAs on AD progression, demonstrating the therapeutic potential of GLP-1RAs for AD treatment.