Proceedingsbook

Table of content

Speaker Lectures

Opening Lecture - The International DLB Consortium reaches thirty

Opening lecture by Ian McKeith (Newcastle, UK)

The first DLB Consortium meeting was held in Newcastle upon Tyne in October 1995, thirty years before the 2025 meeting in Amsterdam. In this opening lecture, Ian McKeith will recap some of the events that have shaped DLB over three decades during which DLB has progressed from being a relatively unknown cause of dementia, into a disorder which is now recognised by the two most significant clinical diagnostic systems used worldwide, (DSM5 and ICD11). He will demonstrate that a lot has changed over that time, and will ask whether a lot has also stayed the same. To what extent can lessons learned from DLB's past inform its future development?

Plenary I - Autonomic dysfunction in alpha-synucleinopathies

Alessandra Fanciulli (Innsbruck, Austria)

This talk will discuss the principles of the diagnosis and stepwise treatment of cardiovascular dysautonomia in people with Lewy Body dementia. It will further address the implications of cardiovascular dysautonomia for an early diagnosis, symptom burden and prognostic outcome in people living with Lewy Body dementia.

Plenary II - Pathogenesis of α-synuclein strains in disease

Amanda Woerman (Colorado, USA)

Synucleinopathies, including multiple system atrophy (MSA) and the Lewy body diseases (LBDs) – Parkinson's disease, Parkinson's disease with dementia (PDD), and dementia with Lewy bodies – are caused by misfolding of the protein a-synuclein into multiple conformations, or strains. Experimental data investigating these two strain types demonstrate distinct biological and structural differences between MSA and LBDs, including the ability of MSA patient samples to readily transmit neurological disease to TgM83$^{+/-}$ mice, which express human a-synuclein with the A53T mutation, following intracranial (i.c.) inoculation. By comparison, i.c. inoculation using LBD patient samples has only been shown to induce pathology in the absence of clinical disease. Unexpectedly, we recently identified one PDD human patient sample that induced neurological signs following i.c. inoculation with an incomplete attack rate over an extended incubation period. Intriguingly, the tissue sample used to generate our inoculum, the substantia nigra, contained Lewy bodies as well as glial cytoplasmic inclusions, suggesting the patient had both PDD and MSA. Hypothesizing that the prolonged incubation period was a result of low titer MSA present in the patient sample, we performed secondary passage using two of the terminal mouse samples. While both

samples transmitted disease with a shortened incubation period, consistent with increased titer, subsequent analysis of frozen tissue from secondary passage using our panel of mutant a-syn140-YFP biosensor cells showed the strain isolated from passaging the PDD human patient sample has unique biological properties compared to the a-synuclein strain(s) present in MSA patient samples. These data provide evidence for the isolation of a distinct a-synuclein strain and raise important questions about the clinical consequences arising from the interaction between two a-synuclein strains in a single human patient.

Plenary III - Alpha-synuclein seeding assays

Alison Green (Edinburgh, UK)

This talk will review the diagnostic utility of alpha-synuclein seeding amplification assays (α-syn SAA) in Parkinson's disease and related disorders. The analytical performance of the α-syn SAA using different biological samples will discussed and the challenges to implementing α-syn SAA into clinical practice reviewed.

Plenary IV - Co-pathology in DLB

David Irwin (Philadelphia, USA)

While the main neuropathologic substrate for the core clinical symptoms of Lewy body dementias (LBD) is alpha-synuclein inclusions in Lewy bodies (LBs) and Lewy Neurites (LNs), there is considerable clinical and pathological heterogeneity that is less understood. Indeed, there is increasing recognition of the contribution of multiple age-related neuropathologies in the development of cognitive impairment of aging, including LBD. Most notably, there is significant genetic and pathologic overlap of LBD with Alzheimer's disease neuropathologic change (ADNC; i.e. tau neurofibrillary tangles, threads and amyloid-beta plaque pathology). Moreover, in most autopsy cohorts, ~70% of Dementia with Lewy bodies (DLB) and ~40% of Parkinson's' disease with dementia (PDD) patients, have sufficient plaque and tangle pathology for a secondary diagnosis of medium-to-high levels of ADNC. The presence of significant ADNC co-pathology in LBD postmortem is associated with a higher burden of neocortical LBs/LNs and confers a worse prognosis with a shorter time to develop dementia and shorter overall survival, suggesting synergy between alpha-synuclein and ANDC pathology, as observed in experimental cell/animal model systems. Further, ADNC co-pathology in LBD is also associated with impairment in specific non-core cognitive domains of episodic memory and language, as well as greater motor postural instability. These retrospective postmortem observations are largely recapitulated in living LBD cohorts with the use of established biofluid and imaging biomarkers of amyloid and tau pathology. Thus, ADNC co-pathology is common in LBD and has a strong clinical influence on the heterogeneity of LBD. Other age-related pathologies likely also contribute to clinical heterogeneity and prognosis in LBD, including limbic-predominant age-related TDP-43 encephalopathy (LATE), chronic cerebrovascular brain injury and neuroinflammation. Future work with autopsy-confirmation will help establish new biomarkers that are sensitive and specific to these multiple age-related

pathologies. The use of multiple markers for these various co-pathologies will further help biologically characterize living LBD patients for improved clinical diagnosis/prognosis and inform clinical trial designs for both symptom-based and disease modifying therapeutics.

Plenary V - Brain first vs body first in LBD

Per Borghammer (Aarhus, Denmark)

Lewy body diseases (LBDs) are heterogeneous disorders characterized by motor symptoms and a multitude of non-motor symptoms including autonomic, sleep, psychiatric symptoms, and dementia. LBDs are special among the neurodegenerative diseases, since the defining pathology (Lewy pathology) involves not only the CNS but also the peripheral autonomic nervous system. Mounting evidence support that the first Lewy pathology arises outside the brain, in either the enteric nervous system of the gut or in the olfactory epithelium – perhaps induced by external triggers such as toxins or infections.

This lecture covers recent evidence supporting that Lewy pathology commonly originates in the gut (body-first) or the olfactory bulb/amygdala (brain-first). The pathology then spreads through the neural connectome and leads to different clinical subtypes of the disease. Body-first PD shows early, marked involvement of the autonomic nervous system before diagnosis, whereas brain-first patients typically do not develop autonomic dysfunction until after diagnosis. Other factors, such as genetic risks and the presence of co-pathologies (especially Alzheimer-type pathology) also influence the clinical phenotype and progression rates. It is argued that that clinical DLB phenotype often arises as a consequence of body-first Lewy body disease with concomitant Alzheimer's co-pathology.

The implications of this novel understanding for future research will be discussed.

Plenary VI - Drug trials and novel targets in DLB

Dag Aarsland (Stavanger, Norway)

The presentation will review recently published and ongoing clinical trials in prodromal and manifest DLB. A systematic review will be conducted by examining relevant literature databases and 3 international trial registries: ClinicalTrials.gov, the European Union Drug Regulating Authorities Clinical Trials Database, and the International Clinical Trials Registry Platform, to identify drugs in trials in DLB. Trials will be categorized according to trial phase, and the compounds according to disease modifying or symptomatic, and specific mechanisms listed.

Challenges in conducting clinical trials will be briefly discussed, including the need for disease-specific outcome measures and biomarkers, and improving representation of global and diverse populations.

Abstracts

Prodromal Lewy body disease

Oral Abstracts

Cognitive and Neuroimaging Outcome of Prodromal Dementia with Lewy Bodies

Frédéric Blanc [1, 2], Vincent Bouteloup [3], Claire Paquet [4], Benjamin Cretin [2], Jean-François Mangin [5], Carole Dufouil [3]

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Background:

The cognitive and neuroimaging evolution over the course of dementia with Lewy bodies (DLB) from prodromal stage -Pro-DLB- (subjective (SCI) to mild cognitive impairment (MCI)) is poorly understood. The aim of this study was to analyse from 5 years longitudinal data, the trajectories of Pro-DLB patients.

Methods:

The "Lewy- MEMENTO" prospective clinical cohort recruited 773 patients for either SCI or MCI. The Pro-DLB group was compared to a group with prodromal Alzheimer's disease (Pro-AD), a group with "prodromal DLB and AD" (Pro-DLB+AD), and a group without prodromal DLB and AD (no symptom [NS]). We modelled the 5 years evolution of cognitive functions and the 2 years evolution of brain MRI volumetry on MRI and brain metabolism (FDG PET).

Results:

The Pro-AD and Pro-DLB+AD groups had more cognitive and functional decline than the Pro-DLB and NS groups (P<.001). The Pro-DLB group had more cognitive decline than the NS group (P<.004). Incident dementia during the follow-up was higher in the Pro-AD (13.0 per 100 person-years) and Pro-DLB+AD (10.3) groups than in the Pro-DLB (1.02) and NS (0.44) groups (P<.001). The decline in the metabolism of the left orbitofrontal cortex was greater in the Pro-DLB+AD group. The volume decrease of hippocampi, entorhinal cortices, amygdalae, and left insula was higher in the Pro-AD and the pro-DLB+AD groups.

Conclusion:

Patients in the pro-DLB group had less cognitive, functional, brain volume and metabolism decrease than patients in the Pro-AD and pro-DLB+AD groups. DLB would therefore be a less degenerative disease at the prodromal stage.

Clinical utility of skin biopsy for cutaneous phosphorylated alpha-synuclein in cognitive manifestations of Lewy body disease

Michael Rigby [1], Stuart McCarter [1] Hugo Botha [1], Leland Barnard [1], Aaron Switzer [1], Vijay Ramanan [1], Bryan Neth [1], Rodolfo Savica [1], David Jones [1], Toji Miyagawa [1], Erik St. Louis [1], David Knopman [1], Ronald Petersen [1], Jonathan Graff-Radford [1], Bradley Boeve [1]

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Background:

The clinical presentation of dementia with Lewy bodies (DLB) is complex and diagnostically challenging. Immunohistochemically detected cutaneous phosphorylated alpha-synuclein was reported in 96% of DLB cases in a prior study limited to those meeting strict consensus criteria for DLB. The utility of this test in clinical practice and those with prodromal DLB (mild cognitive impairment, MCI-LB) is unknown. We aimed to evaluate the frequency of positive skin biopsies for alpha-synuclein in patients with cognitive symptoms in an academic memory clinic.

Methods:

Forty-nine patients presenting with cognitive symptoms underwent commercially available skin biopsy at three sites (posterior cervical, distal thigh, distal leg) for cutaneous phosphorylated alpha-synuclein as part of their clinical evaluation. Retrospective chart review determined if individuals met published criteria for probable DLB or MCI-LB, blinded to skin biopsy result. Descriptive statistics are reported by diagnostic subgroups.

Results:

Average age at skin biopsy was 70.0±1.4 years, with 80% being male. Thirty-two patients (65%) had a positive skin biopsy (at least one of three sites). Of the 39 patients who met blinded clinical criteria for DLB/MCI-LB, 27 (69%) had a positive skin biopsy with similar frequency between subgroups (DLB 65%; MCI 78%). Of the 31 patients who were determined to have DLB/MCI-LB by the treating physician, 27 (87%) had a positive skin biopsy, with the 3 of 4 negative tests having FDG-PET hypometabolism supportive of DLB. In 80% of cases, the skin biopsy result supported the initial suspected diagnosis. Of 18 patients thought not to have synucleinopathy, 5 (28%) had a positive skin biopsy. Alternative diagnoses in biopsy positive cases were anti-DPPX autoimmunity, anti-GFAP autoimmunity, hydrocephalus/epilepsy, OSA/anxiety, and refractory depression.

Conclusion:

The phosphorylated alpha-synuclein skin biopsy can be positive at any point along the cognitive spectrum of Lewy body disease, but our data shows a lower positivity rate in clinical practice than previously reported.

Genome-wide association study of REM-sleep behaviour disorder identifies new risk locus.

Emma N. Somerville [1, 2] Lynne Krohn [1, 2], Farnaz Asayesh [1, 3], Jamil Ahmad [1, 3], Dan Spiegelman [1, 3], Isabelle Arnulf [4], Michele T.M. Hu [5], Yo-El Ju [6], Jacques Y. Montplaisir [7], Jean-François Gagnon [7, 8], Alex Desautels [7, 9], Yves Dauvilliers [10], Abubaker Ibrahim [11], Ambra Stefani [11], Birgit Hogl [11], Monica Serradell [12], Gian Luigi Gigli [13, 14], Mariarosaria Valente [13, 14], Francesco Janes [13, 14], Andrea Bernardini [13, 14], Karel Sonka [15], David Kemlink [15], Gültekin Tamgüney [16, 17], Michael Sommerauer [18, 19, 20], Michela Figorilli [21], Monica Puligheddu [21], Brit Mollenhauer [22, 23], Claudia Trenkwalder [22, 23], Friederike Sixel-Doring [22, 24], Giuseppe Plazzi [25, 26], Francesco Biscarini [27], Elena Antelmi [25, 28], Valerie Cochen De Cock [29, 30], Wolfgang Oertel [24], Annette Janzen [24], Petr Dusek [15], Michele Terzaghi [31], Giuseppe Fiamingo [31, 32], Anna Heidbreder [33], Christelle Charley Monaca [34], Luigi Ferini-Strambi [35], Matej Skorvanek [36, 37], Femke Dijkstra [38, 39, 40], Viaene Mineke [38, 39], Jitka Bušková [41, 42], Beatriz Abril [43], Beatrice Orso [44], Pietro Mattioli [44], Dario Arnaldi [44], Bradley F. Boeve [45], Guy A. Rouleau [1, 2, 3], Ronald B. Postuma [1, 3, 7], Cornelis Blauwendraat [46, 47], Ziv Gan-Or [1, 2, 3]

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Background:

RBD is a parasomnia characterized by abnormal dream enactment behaviour. The vast majority of RBD individuals will eventually phenoconvert to a neurodegenerative disorder. Moreover, most individuals with a synucleinopathy have RBD, including roughly 80% of DLB (dementia with Lewy bodies) patients. Clinical diagnosis of DLB and related synucleinopathies typically occurs long after neurodegeneration has progressed substantially, with RBD presenting a unique prodromal timepoint where intervention could be most effective for these disorders.

Methods:

We aim to replicate the largest RBD genome-wide association study (GWAS) performed to date from Krohn et al. 2022, by incorporating the summary statistics with 802 new European RBD patients and 810 new healthy controls to discover new associated loci. In total, 13,154,277 variants with a minor allele frequency greater than 0.01 were analyzed, with a total cohort count of 3645 RBD patients and 140,446 healthy controls.

Results:

We replicated signals in *SNCA*, *GBA1* p.E326K and p.N370S, *TMEM175*, *INPP5F*, *SCARB2*, with all but *TMEM175* increasing in association strength. Additionally, we identified a novel associated locus in the *RCOR1* region (rs35785423, beta = 0.164, OR = 1.18, se = 0.0298, p = 3.792e-08). In an analysis of PD loci identified in the Nalls et al. 2019 PD GWAS, we identified potential associations in *FAM47E*, *STK39*, *SIPA1L2*, and in the *MAPT* locus. We also conducted a GWAS analysis to investigate common variants associated with RBD phenoconversion to synucleinopathies, and found no associations in the genome-wide or PD loci analyses.

Conclusion:

Our results shed new light on the genetic landscape underlying early neurodegeneration in synucleinopathies with the discovery of a new genome-wide significant risk locus. With the addition of genetic data from more RBD patients and controls in the near future, we aim to elucidate even more common risk loci.

The prodromal presentation of dementia with Lewy bodies: experience from an Australian longitudinal cohort study

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Background:

Prodromal dementia with Lewy bodies (DLB) is challenging to recognise leading to delayed diagnosis and limiting prospective research into this disease stage. Research criteria for prodromal DLB diagnosis propose mild cognitive impairment with Lewy bodies (MCI-LB), delirium-onset or psychiatric-onset presentations. We aimed to [1] classify the prodromal stage of DLB in an Australian research cohort against the proposed research criteria, and [2] describe the frequency of DLB clinical features in the prodrome.

Methods:

Participants with probable DLB were enrolled in a longitudinal cohort study. Retrospective file review by 3 independent assessors, followed by expert consensus discussion, classified participants against the research criteria and identified the presence or absence of clinical features during the prodrome (cognitive, gait/motor, autonomic, sleep, psychiatric, loss of smell or taste).

Results:

Of 45 participants (median age 74 [interquartile range 70-78] years, 38 (84%) male), 36 (80%) were MCI-onset, five (11%) delirium-onset, three (7%) psychiatric-onset and one (2%) unclear. Within the MCI-onset group, 24 (54%) had probable MCI-LB, 8 (18%) had possible MCI-LB and four (9%) were unclear.

Cognitive fluctuation was the commonest (n=36, 80%) core DLB clinical feature in the prodrome, followed by REM-sleep behaviour disorder (n=31, 69%), motor parkinsonism (n=21, 47%) and visual hallucinations (n=5, 11%).

All participants had cognitive features during the prodrome. Sleep (n=36, 80%), psychiatric (n=33, 73%) and gait/motor (n=30, 67%) symptoms were also common.

Conclusion:

MCI-LB was the most common prodromal presentation in this study. The small number of delirium-onset or psychiatric-onset participants potentially reflects the bias of research cohorts recruited from memory clinics. Clinical evaluation and research recruitment should consider ways to identify non-cognitive DLB prodromes, including sleep disturbance, which were prevalent in our cohort. Detection of prominent DLB-associated symptoms could alert clinicians to proactively monitor for emerging DLB.

Core clinical features and depressive symptoms have different impacts on cognitive decline in MCI-LB

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Background:

People with mild cognitive impairment (MCI) with Lewy bodies (MCI-LB) may present with differing combinations of core clinical features and other non-cognitive symptoms. As the underlying disease progresses, this initial presentation may also change, with new features emerging. We examined how this evolution of clinical phenotype, including emergent core clinical features and transient changes in symptoms of depression, was associated with progression of cognitive symptoms in MCI-LB.

Methods:

Longitudinal data were incorporated from n=69 MCI-LB cases, and n=54 MCI due to Alzheimer's disease (MCI-AD). Clinical phenotype was assessed annually by a three-person expert panel for up to 9 years. Accumulation of core clinical features was examined using multi-state Markov modelling. Cognitive performance was assessed using the Addenbrooke's Cognitive Examination – Revised. Rate of decline in cognitive performance was examined with multi-level models incorporating time-varying clinical features. Depressive symptoms were assessed annually with the 15-item Geriatric Depression Scale (GDS). Between- and within-person effects of depressive symptoms on cognitive function were examined with a novel Bayesian hierarchical model incorporating 387 paired ACE-R and GDS observations.

Results:

Approximately 25% of MCI-LB cases gained an additional core clinical feature over one year. The presence of more core features - in particular, fluctuations and visual hallucinations - was associated with faster cognitive decline (B = -2.8 [-4.1 to -1.5]). When assessed during periods where they reported more depressive symptoms, people with MCI had worse concurrent cognitive performance (B = -0.6 [-1.1 to -0.1]), but this performance deficit did not extend beyond this period.

Conclusion:

Differences in core clinical features and depressive symptoms may account for individual differences in severity and progression of cognitive impairments in MCI-LB. Emergence of hallucinations or fluctuations may correspond to a worse prognosis. Targeting mood symptoms may have the potential to improve cognition, though this requires further investigation.

Preliminary Longitudinal Data on the Prodromal Synucleinopathy Rating Scale Among Patients with REM Sleep Behavior Disorder in the North American Prodromal Synucleinopathy (NAPS) Consortium

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Background:

The Prodromal Synucleinopathy Rating Scale (PSRS) has been developed to capture the breadth and evolution of clinical burden in those with REM sleep behavior disorder (RBD).

Methods:

Ratings on the PSRS range from no symptoms/signs (score of 0) to more severe symptoms/signs (max score of 2-4 depending on the domain) based on clinical judgement for the cognitive (COG), neuropsychiatric (NP), motor-axial (MAX), motor-appendicular (MAP), autonomic (AUT), sleep (SLP), and sensory (SEN) domains. Ratings were generated on all participants (pts) in NAPS conducted 8/22 to 7/24 who have been evaluated twice. Wilcoxon signed-rank test was used to compare the difference in PSRS sum score (SUM) and its domains between visit 1 (V1) and visit 2 (V2).

Results:

Data from 129 pts (78% male, mean age 66±10 yrs) were analyzed. The median (IQR) duration between V1 and V2 was 12 (10-12) months. From V1 to V2, the score increased for COG ($p<0.0001$), NP ($p=0.0006$), MAX ($p<0.0001$), MAP ($p<0.0001$), AUT ($p=0.0001$) and SLP ($p=0.0038$) but not for SEN. Comparing V1 to V2, the frequency of an increased/stable/decreased score for each domain were COG: 39%/47%/14%, NP: 41%/42%/17%, MAX: 42%/50%/8%, MAP: 42%/47%/11%, AUT: 44%/36%/19%, SLP:

17%/50%/33%, and SEN: 19%/64%/17%. The SUM increased (mean 7.5±4.4 to 9.5±4.8, $p<0.0001$) and the frequency of an increased/stable/decreased SUM score were 60%/10%/30%.

Conclusion:

These data suggest that in most RBD pts, mild but variable increasing clinical burden on the PSRS evolves over one year. Additional longitudinal work is needed in a larger number of pts - including those who phenoconvert to dementia with Lewy bodies, Parkinson's disease or multiple system atrophy - to determine if the PSRS will be a useful marker of synucleinopathy clinical burden for future disease-modifying therapies in those with RBD.

Poster Abstracts

Cognitive Performance in Early Neuronal alpha-Synuclein Disease

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Background:

The NSD biological definition and Integrated Staging System (NSD-ISS) provide a research framework to identify individuals with underlying Lewy body pathology (based on alpha-synuclein seed amplification assay [SAA] and dopamine transporter scan [DaTscan]) and stage them based on underlying biology and increasing degree of functional impairment. Stage 2 (2A is SAA+/DaTscan-; 2B is SAA+/DaTscan+) is meant to capture persons with subtle clinical symptoms in cognitive, motor and/or non-motor domains, prior to the onset of slight functional impairment.

Methods:

Using PPMI baseline data, cognitive performance was assessed globally with the MoCA and in detail with a cognitive summary z-score (CSS) developed from a multi-cognitive domain battery. Performance was compared between participants classified as Stage 2A or 2B at baseline and a robust healthy control group (HC) defined based on intact MoCA performance longitudinally. CSS norms were regression-based internal norms based on HC performance and adjusted for age, sex and education.

Results:

The cohorts were Stage 2A (N=175), Stage 2B (N=318) and SHC (N=158). Stage 2 participants were older than the SHC. Although less than 20% of Stage 2 participants met the criteria to be included in the cognitive domain for this stage and on average had intact MoCA scores (Stage 2A mean (SD) =26.9 (2.3); Stage 2B mean (SD) =27.1 (2.3)), Stage 2A had worse global cognitive performance numerically (z-score mean difference =0.10, p-value NS; effect size=0.16), and Stage 2B had worse global cognitive performance statistically (z-score mean difference =0.26, p-value <0.05; effect size=0.40) compared with SHC. In addition, Stage 2B performed worse statistically than Stage 2A (z-score mean difference =0.15, p-value <0.05).

Conclusion:

Early-stage NSD is associated with detectable cognitive deficits compared with a SHC group, particularly when dopamine system impairment is superimposed, supporting the inclusion in NSD-ISS of a cognitive domain for symptom progression and functional impairment across all disease stages.

Faster Decline of Very Prodromal Dementia with Lewy Bodies When Amyloid Positive

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Background:

The cognitive and neuroimaging evolution over the course of dementia with Lewy bodies (DLB) from prodromal stage -Pro-DLB- (subjective (SCI) to mild cognitive impairment (MCI)) is poorly understood. The aim of this study was to analyze from 5 years longitudinal data, the trajectories of Pro-DLB patients, according to the amyloid status (A).

Methods:

The "Lewy-Memento" prospective clinical cohort with a recruited 342 patients for either SCI or MCI. The A was measured either using amyloid PET or ABeta-42 in CSF. The decline was compared according to the A in four groups: Pro-DLB, prodromal Alzheimer's disease (Pro-AD), "prodromal DLB and AD" (Pro-DLB+AD), and a group without prodromal DLB and AD (no symptom [NS]). We observed the evolution of cognitive, functional, and quality of life measures every year and of brain volumetry on MRI every two years.

Results:

In the Pro-DLB and Pro-DLB+AD groups, amyloid positive (A+) patients had more cognitive and functional decline than the amyloid negative patients. In the Pro-AD group, A+ patients had more functional decline. For cognitive aspects, Mini-Mental Status Examination (MMSE) had faster decline but not the memory and executive functions. In the NS group, A+ patients had more decline in the functional measure, and some cognitive tests but not the MMSE. For brain MRI, only the A+ Pro-AD showed a greater volume decline of the left insula.

Conclusion:

The presence of amyloid lesions worsens very prodromal DLB patients over time, both cognitively and functionally, but without increasing atrophy.

Are fibromyalgia and obsessive personality disorder related with lewy body dementia?

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Background:

Recent reports have suggested that attention-deficit/hyperactivity disorder (ADHD) is related to the emergence of Lewy body disease (LBD). Fibromyalgia and Obsessive Personality Disorder (OCPD) are associated with ADHD in adults. We aimed to determine to what extent the presence of these 2 entities increases the risk of LBD or any of its clinical features.

Methods:

The prospective observational cohort study with a 15-year follow-up compared a group of adults with ADHD, meeting the DSM-IV-TR criteria for ADHD with a healthy control group. All subjects were evaluated at baseline and follow-up for the diagnosis of fibromyalgia using American College of Rheumatology criteria and OCPD according to DSM criteria. Univariate analysis and multiple logistic regression were performed to examine the association of Fibromyalgia and OCPD with LBD features, adjusting for multiple variables.

Results:

The baseline sample consisted of 161 subjects with ADHD and 109 without ADHD. At the end of the follow-up, 31 subjects developed dementia, 27 cases in the ADHD group and 4 in comparison group controls. Dementia with Lewy bodies (DLB) was the most frequent type (N:20) of which 19 corresponded to the ADHD group. Features of LBD were significantly more common in the ADHD group. The most frequent were cognitive fluctuations and RBD. Adjusted multivariate logistics showed that those with fibromyalgia had increased odds of developing certain LBD features (odds ratio (95% confidence interval)) including fluctuations (1.46 (.6-3.57)), REM sleep behavior disorder (1.29 (.56-3.02)), visuospatial dysfunction (1.56 (.65-3.73)) and depression (2.25 (.89-5.7). The presence of OCPD increased the odds of fibromyalgia (3.73(1.59-8.8) and depression (1.6 (0.88-2.88) but not with other variables.

Conclusion:

Fibromyalgia in ADHD patients may increase the risk of presenting features of LBD cognitive fluctuation, RBD, VD, and depression in LBD. Future studies should clarify these findings to understand the physiopathology of the association

Viral Infections or Chemical Exposure and their Association with Parkinson's Disease or Lewy Body Dementia in the United States (2000-2010) in Older Adults

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Background:

Parkinson's disease (PD) and Lewy body dementia (LBD) are degenerative neurological diseases primarily affecting older adults. LBD includes dementia with Lewy bodies (DLB) and PD dementia (PDD). The exact causes of these illnesses are still unknown, but they progressively debilitate due to brain nerve damage caused by decreasing dopamine levels and the aggregation of alpha-synuclein (αSyn) protein.

Methods:

Quantitative cross-sectional research measured the effect of viral infections and chemical exposure on PD and LBD in older U.S. adults. Age, sex, race, pneumonia, and other diseases were considered. Data were collected from the Utah Department of Health Office of Health Care Statistics Hospital Healthcare Facility Discharge Database. Multiple logistic regression analysis helped determine if a relationship exists between the variables.

Results:

The study included 6,413 U.S. older adults aged 50 to 99, with the largest group aged 50–60 (n = 2,977; 46.4%). Male majority (n = 3,465; 54%) white race majority (n = 3,208; 50%).

Four separate Chi-square tests of independence determined the relationship between independent variables on PD. Results - significant difference for all four predictors: IAV (p < .001), HCV (p < .001), EBV (p = .001), and toxic chemicals (p =.01). The null hypothesis was rejected (statistically significant).

Minimal subjects with IAV and none with HCV, EBV, or chemical exposure developed PD.

Given the small number of subjects with both PD and IAV, HCV, EBV, or chemical exposure, drawing clear conclusions is difficult.

Four Chi-square tests of independence determined the relationship between independent variables on LBD. Results- significant difference between IAV (p <.001) and HCV (p <.001) predictors. Thus, the null hypothesis was rejected (statistically significant) relationship between the two predictors and LBD appears to exist.

Conclusion:

None of the individuals with IAV, HCV, EBV, or chemical exposure developed LBD. Due to the low prevalence of LBD, the findings are inconclusive.

Alpha-synuclein pathology identified among individuals with REM sleep Behavior Disorder induced by a selective serotonin reuptake inhibitor.

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Background:

Under normal physiological conditions, REM sleep is characterized by vivid dream mentation combined with skeletal muscle paralysis. In REM sleep Behavior Disorder (RBD), normal REM atonia is lost and patients exhibit dream enactment, frequently with thrashing, punching and kicking behaviors. Isolated RBD (iRBD) is a prodromal syndrome of Dementia with Lewy bodies with evidence of systemic alpha-synuclein pathology noted on skin biopsy. However, the dream enactment of RBD also frequently presents after initiating an SSRI antidepressant medication (5-HT RBD). 5-HT RBD is more likely to present in younger individuals and women compared to iRBD. It is uncertain whether 5-HT RBD, like iRBD, is a prodromal syndrome of Dementia with Lewy bodies. This project tested for the presence of abnormally phosphorylated alpha-synuclein aggregates on targeted skin biopsy among individuals with 5-HT RBD.

Methods:

We performed skin biopsies with immunostaining for pathological evidence of phosphorylated alpha-synuclein deposition in cutaneous nerve fibers among 10 individuals with 5-HT RBD.

Results:

We identified systemic alpha-synuclein pathology on skin biopsy in half (5) of the individuals with 5-HT RBD. 5-HT RBD Individuals with a positive biopsy were older (60.6, SD +/- 11.1) and less likely to be female (1/5) compared to 5-HT RBD individuals with a negative biopsy who were younger (54.0, SD +/- 8.5) and more likely to be female (4/5).

Conclusion:

This study demonstrated the presence of systemic alpha-synuclein pathology among a subgroup of 5-HT RBD patients indicating that 5-HT RBD does frequently represent a prodromal syndrome of Lewy body pathology. Further investigations are needed to characterize the natural history of 5-HT RBD, the relationship between positive biopsy findings and clinical phenomena, and whether interventions can prevent the development of Lewy body disease.

Sex effect on cortical neurodegeneration associated with isolated REM sleep behavior disorder

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Background:

Isolated REM sleep behavior disorder (iRBD) is the early manifestation most strongly associated with the development of dementia with Lewy bodies (DLB). This sleep disorder, occurring mostly in males, is characterized by muscle atonia loss and the onset of abnormal movements during REM sleep. Individuals with iRBD already exhibit brain atrophy and clinical abnormalities, although sex-specific differences in structural brain changes remainl unclear. The objective of this study was to investigate, for the first time, the effect of sex on brain atrophy in iRBD and the brain correlates of motor abnormalities in the largest neuroimaging dataset worldwide with polysomnography-confirmed iRBD.

Methods:

A total of 888 individuals underwent brain MRI acquisition (T1-weighted scans), including 408 individuals with iRBD and 480 healthy controls. Vertex-based cortical surface reconstruction and segmentation were conducted using FreeSurfer. General linear models were used vertex-wise to quantify brain atrophy and assess the sex effect on cortical thickness in iRBD compared to controls, while controlling for age. General linear models were also used to investigate sex-specific associations between cortical thickness and Parkinsonian motor symptoms (UPDRS-III). Clusters were considered significant when $P<0.05$ after Monte Carlo permutations.

Results:

Cortical thinning was found in males compared to females with iRBD in left postcentral and superior frontal regions, and in right precentral and paracentral regions. This difference was absent in controls, supporting the idea that sex exerts a specific effect on neurodegeneration associated with iRBD. Furthermore, whereas males did not show any significant correlations between cortical thickness and UPDRS-III scores, more pronounced motor symptoms in females were associated with cortical thinning in prefrontal regions.

Conclusion:

In addition to previously identified sex-specific clinical abnormalities in iRBD, these new findings suggest distinct differences in brain atrophy between male and female individuals. These results emphasize the potential need for developing sex-specific neuroprotective treatments during the prodromal stages of DLB.

Delirium incidence in alzheimer's disease and dementia with Lewy bodies before and after dementia diagnosis

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Background:

Delirium is reported to be more common in Dementia with Lewy bodies (DLB) than in Alzheimer's disease (AD). Delirium is proposed to be one presentation of prodromal DLB, in addition to neuropsychiatric and mild-cognitive impairment onset. However, the frequency is unknown and symptoms of DLB resemble those of delirium. The aim was to analyze differences in incidence of delirium in DLB and AD patients before and after dementia diagnoses in a dementia cohort in Norway.

Methods:

The Dementia Study of Western Norway included 247 persons with mild dementia (MMSE ≥ 20 and/or Clinical Dementia Rating Scale ≤1), who were followed annually until death. 181 subjects with DLB (n=75) and AD (n= 106) were included in this analysis. Delirium was retrospectively diagnosed through chart review assessing all available information in 732 acute or planned hospital admissions into psychiatric and somatic wards from 5 years before dementia diagnosis until death.

Results:

Delirium was recorded in 221 (30,2 %) hospital admissions. 49 (65,3 %) DLB patients and 71 (67,0 %) AD patients had at least one delirium episode. There was a significant difference in the number of DLB patients with at least one delirium episode before diagnosis compared to the AD group (p.023), and the incidence rates of delirium after diagnosis were higher in DLB than AD, 20 vs 15 per 100 person-years respectively (p.033).

Conclusion:

Delirium seems to be more common in DLB patients than in AD patients both before and after diagnosis. This holds true when delirium diagnoses are made by chart review by dementia specialists, thus reducing the risk of misinterpreting DLB symptoms as delirium. More studies are needed to establish the frequency and trajectory of delirium-onset DLB.

Neuropsychological test performance in mild cognitive impairment with Lewy bodies: a meta-analysis.

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Background:

Prodromal dementia with Lewy bodies (DLB) diagnostic criteria were recently published and further work is needed to further inform and refine clinical criteria. We performed a meta-analysis to compare the cognitive performance of mild cognitive impairment with Lewy bodies (MCI-LB) groups to controls, MCI due to Alzheimer's disease (MCI-AD), and DLB.

Methods:

We performed a systematic review and meta-analysis including studies with cognitive data for MCI-LB from PubMed, EMBASE, Web of Science, and PsycINFO (January 1990 to March 2023). Neuropsychological test performances for MCI-LB were compared to controls, MCI due to Alzheimer's disease (MCI-AD), and dementia with Lewy bodies (DLB) groups with random-effects models.

Results:

We included 26 studies with 2823 participants. Individuals with MCI-LB performed worse across all cognitive domains relative to controls. Compared to individuals with MCI-AD, the MCI-LB group performed worse in attention/processing speed (g = -0.35, 95% CI: -0.12,-0.42) and attention/executive domains (g = -0.42; 95% CI: -0.56, -0.28), but better in verbal immediate recall (g = 0.37; 95% CI: 0.15, 0.59) and delayed memory (g=0.40; 95% CI: 0.22, 0.58). There were no significant differences in visuospatial or language domains between MCI-LB and MCI-AD. The MCI-LB group performed worse than the MCI-AD group on Trail Making Test Part A (g = -0.37; 95% CI: 47.25, 68.24) and Part B (g= -0.41,95% CI: 109.53, 176.34). The MCI-LB group performed worse than the DLB group across all cognitive domains.

Conclusion:

Consistent with the 2020 McKeith criteria, this meta-analysis provides evidence of impaired attention, processing speed, and executive functions in MCI-LB. Neuropsychological evaluation may be useful in the differential diagnosis of MCI-LB from

MCI-AD, but screening measures appear to be insufficient in this regard. A high degree of heterogeneity across studies suggests the need for harmonized neuropsychological research batteries.

Delirium-onset Prodromal Dementia with Lewy Bodies: A series of 5 cases

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Background:

Delirium-onset prodromal dementia with Lewy bodies (DLB) has been proposed as one of the primary phenotypes of prodromal stages of DLB. The detailed clinical features and biomarker profiles of delirium-onset prodromal DLB have not been well characterized.

Methods:

Five consecutive cases of delirium-onset prodromal DLB were documented. The diagnosis of prodromal DLB was made based on neuroimaging biomarkers, including dopamine transporter single-photon emission computed tomography (SPECT), cardiac ^{123}I-metaiodobenzylguanidine scintigraphy, and/or brain perfusion SPECT, as well as clinical findings in the post-delirium follow-up periods.

Results:

In all cases, one or more of the core or supportive clinical features of DLB, including rapid eye movement sleep behavior disorder, minor hallucinations, hyposmia, or autonomic dysfunction, were present prior to the onset of delirium. The precipitating factors for delirium were diverse, including surgery, radiation therapy, chemotherapy, and infection. The duration of delirium was prolonged for several months in two cases, whereas it was resolved within a few weeks in the other cases. In most cases, persistent mild cognitive or behavioral symptoms were observed, which were improved with donepezil.

Conclusion:

Our observations suggest that delirium-onset prodromal DLB may represent the later stages of the prodromal DLB rather than its initial stages. It is possible that delirium in the prodromal stages of DLB may represent subthreshold cognitive fluctuations that are transformed into clinically detectable states by a variety of precipitating factors.

Delirium incidence in alzheimer's disease and dementia with Lewy bodies before and after dementia diagnosis

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Background:

Delirium is reported to be more common in Dementia with Lewy bodies (DLB) than in Alzheimer's disease (AD). Delirium is proposed to be one presentation of prodromal DLB, in addition to neuropsychiatric and mild-cognitive impairment onset. However, the frequency is unknown and symptoms of DLB resemble those of delirium. The aim was to analyze differences in incidence of delirium in DLB and AD patients before and after dementia diagnoses in a dementia cohort in Norway.

Methods:

The Dementia Study of Western Norway included 247 persons with mild dementia (MMSE ≥ 20, Clinical Dementia Rating Scale ≤1), who were followed annually until death. 181 subjects with DLB (n=75) and AD (n= 106) were included in this analysis. Delirium was retrospectively diagnosed through chart review assessing all available information in 732 acute or planned hospital admissions from 5 years before dementia diagnosis until death.

Results:

Delirium was recorded in 221 (30,2 %) hospital admissions. 49 (65,3 %) DLB patients and 71 (67,0 %) AD patients had at least one delirium episode. DLB patients had more delirium episodes both prior to and after diagnosis of dementia (p=0.024), and the incidence rates of delirium after diagnosis were higher in DLB than AD, 21 vs 15 per 100 person-years respectively (p=0.033). DLB patients had significantly shorter survival after diagnosis than AD patients, and thus shorter time at risk for both hospitalization and delirium.

Conclusion:

Delirium was more common in DLB than AD, both prior to and after diagnosis. This holds true when delirium diagnoses are made by chart review by dementia specialists, thus reducing the risk of misinterpreting DLB symptoms as delirium. More studies are needed to determine the frequency of delirium in DLB and the impact on disease trajectory.

Discordance between striatal dopaminergic imaging and motor performances in REM sleep behavior disorder

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Background:

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 each). 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.

Conclusion:

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.

Alzheimer’s disease and Lewy body disease biomarkers and conversion rate of late-onset psychosis to dementia : a retrospective cohort study.

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Background:

Although some psychotic disorders with onset at age 60 years (very late-onset schizophrenia-like psychosis: VLOSLP) have positive results for Lewy body disease (LBD) and Alzheimer’s disesase (AD) biomarkers, how these outcomes alter cognitive function over time is not yet known.

Methods:

Among patients who visited our clinic between 2018 and 2023, we retrospectively selected patients with VLOSLP meeting the 2000 diagnostic criteria who underwent at least once in two years and 1.5 months. Among them, those who could be classified into the following groups were taken as the participants: both Alzheimer’s disease (AD) and Lewy Body disease (LBD) biomarker-negative (BMs-neg), AD biomarker-positive and LBD biomarker-negative (AD-pos/LBD-neg), and LBD biomarker-positive (LBD-pos). The demographic data and the conversion rate to dementia were compared between the three groups using Kruskal-Wallis test and Fisher's exact test. We also compared changes in CDR sum of boxes (CDR-SB) from the initial to the follow-up assessments between the groups using mixed ANOVA with age as a covariate.

Results:

Among 66 patients with VLOSLP, 23 patients were followed up. After excluding 4 cases with no biomarker data, seven BMs-neg, six AD-pos/LBD-neg and six LBD-pos were finally selected. Baseline characteristics such as age, sex, education, time to follow-up, MMSE, CDR, and CDR-SB were not significantly different. The conversion rate was 14% in BMs-neg , compared to 67% and 50% in AD-pos/LBD-neg and LBD-pos , respectively, but the difference was not statistically significant (p=0.187). The mixed design ANOVA revealed significant group-by-time interaction in CDR-SB (p=0.004), with significant difference between groups at the follow-up assessment (p=0.007) in the post-hoc test.

Conclusion:

This study showed that VLOSLP patients who were positive for AD and/or LBD biomarkers may be more likely to progress to dementia within approximately two years than those who were negative.

Amyloid pathology in prodromal AD and DLB: an ADNI PET study

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Background:

Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB) are two commonest types of dementia with distinct pathological mechanisms. The primary pathological features of AD are the accumulation of amyloid-beta plaques and tau tangles [1], whereas DLB is characterized by intracellular alpha-synuclein, causing the formation of Lewy bodies [2]. Despite some differences at the dementia stage, both conditions exhibit similar clinical features during the prodromal stage - mild cognitive impairment (MCI), making early differential diagnosis challenging. Therefore, developing biomarkers to differentiate these two diseases at the MCI stage is crucial for their early diagnosis and intervention.

Methods:

In this study, we re-examinmed the clinical data from the ADNI study using the recently published MCI due to Lewy bodies criteria [3], and identified 24 patients in the prodromal stage of DLB (MCI-LB), along with 400 age and sex matched patients in the prodromal stage of AD (MCI-AD) and 129 normal controls (NC). For amyloid PET images, we performed partial-volume correction with patient specific T1 MRI images and calculated standard uptake value ratio (SUVR) using PET12 toolbox. Then, we compared the SUVR among the three groups at voxel and global level.

Results:

We found that the SUVR in MCI-AD patients was significantly higher than in NC ($T = 3.29$, $p = 0.001$), but there was no significant difference between MCI-LB with NC and MCI-AD with MCI-LB. Further voxel-based analysis revealed that the differences in amyloid-beta deposition between MCI-AD and NC were widespread across the whole brain.

Conclusion:

In summary, our findings demonstrated a higher amyloid burden in the prodromal stage of AD compared with DLB. This is consistent with the previous literature that showed lower amyloid burden in prodromal DLB [4]. However, the current study is limited by the significant fewer number of patients with MCI-LB, thus reduced power to detect a difference.

REM-sleep behaviour disorder in Lewy body disorders: insights from polysomnography and high-field MRI

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Background:

REM-sleep behaviour disorder (RBD) is characterised by often violent dream enactments, following REM sleep without atonia (RSWA). RBD is strongly linked to Lewy body disorders, including Parkinson's disease (PD; estimated prevalence of RBD: 30-50%) and dementia with Lewy bodies (DLB; 76%). The current study aimed to explore polysomnographic and neuroimaging features of RBD in Lewy body disorders.

Methods:

We collected clinical, video-polysomnographic (PSG), and 7T MRI data from 31 participants (20 PD, 11 DLB; 87% male). RBD was diagnosed upon the presence of both dream enactment (interview or PSG) and increased RSWA (chin and flexor digitorum superficialis muscle activity), according to the ICSD-3. RBD diagnosis outcomes based on the interview and PSG were compared. Using diffusion-weighted MRI and the Brainstem-Navigator-Toolbox, we investigated the correlation of RSWA with structural connectivity between brainstem nuclei implicated in RBD (locus subcoeruleus with pedunculotegmental nucleus and paramedian nucleus).

Results:

Of the 31 participants with Lewy Body disorder, 24 reported a history of dream enactment. An increased amount of RSWA (>31.7%) was observed in 16 out of those 24 participants, leaving 6 participants with unconfirmed RBD (RSWA 9-27%). One DLB case without history of dream enactment showed increased RSWA (46%) and dream enactment, and was diagnosed with RBD. In the MRI analysis, no significant correlations were identified between RSWA and brainstem structural connectivity.

Conclusion:

The findings from the current study emphasise the variability of the amount of RSWA across individuals with Lewy body disorders. The discrepancy between interview and PSG outcomes in some participants challenges the existing dichotomous criteria for diagnosis. In the MRI analysis, we showed that tracts connecting brainstem nuclei that are thought to be involved in RBD's pathophysiology can be successfully identified using 7T MRI. Follow-up analysis in a larger sample is planned to test the robustness of these effects.

Gait alterations in prodromal and early clinically evident stages of Parkinson's Disease: a mobile health technology multi-center study

Andrea Pilotto [1, 2, 3], Cinzia Zatti [4] Andrea Rizzardi [4], Clint Hansen [5], Marcello Catania [4], Robbin Romijnders [5], Leandro Purin [4], Maria Pia Pasolini [4], Eva Schaeffer [5], Andrea Galbiati [6], Luigi Ferini Strambi [6], Maria Cristina Rizzetti [7], Daniela Berg [5], Walter Maetzler [5], Alessandro Padovani [4]

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Background:

Gait abnormalities are a prominent feature of Parkinson's disease (PD), but the onset and spatio-temporal characteristics of gait in different stages of the disease are still not clearly defined. Idiopathic REM sleep behavioral Disorder (iRBD) is a marker of early neurodegenerative synucleinopathy, and may present with subtle gait alterations. Aim of the study was to analyze spatio-temporal parameters of gait from the prodromal to the early stages of PD.

Methods:

The prospective multicentre study enrolled participants with PSG-confirmed iRBD without parkinsonism, drug-naïve PD (nPD) and early-stage treated PD (tPD) patients, and healthy controls (HC). All participants underwent a supervised gait assessment using mobile health technology (MHT) at normal and fast pace and during dual-tasking.

Results:

The study included 208 participants, 60 nPD, 60 tPD, 23 iRBD and 65 age-matched HC. In normal gait, nPD and iRBD, but not tPD, showed longer step time than HC. In fast gait, nPD and tPD, but not iRBD, showed longer step time than HC. In dual task gait, iRBD, nPD and tPD showed longer step time than HC. In all different gait tasks, both nPD and tPD, but not iRBD, had a shorter step length than HC.

Conclusion:

This study suggests that temporal gait parameters, especially in dual-task conditions, are more sensitive to change than spatial parameters in prodromal and early clinically evident stages of PD.

Prevalence of isolated REM-sleep behavioral disorder in Idiopathic Polyneuropathy with cardiac sympathetic denervation: A Cohort Study.

Naja Helt Andersen [1] Casper Skjærbæk [1], Stig Holt Bøgh [1], Janne Kærgård Mortensen [1, 2], Jenny-Ann Phan [2, 3], Marit Otto [2, 4], Per Borghammer [1, 5], Astrid Juhl Terkelsen [1, 2, 6]

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Background:

The prevalence of polyneuropathy (PN) in patients with Parkinson's Disease (PD) is estimated to be 4-55% compared to 9% in the background population. PD is a Lewy body disease (LBD), which also includes Dementia with Lewy Bodies (DLB) and Pure Autonomic Failure (PAF). In LBD, non-motor symptoms include dysautonomia, hyposmia and REM-sleep behavioral disorder (RBD). Hyposmia and isolated RBD (iRBD) can occur decades before the diagnosis of LBD. Whether idiopathic PN (iPN) with dysautonomia is an early manifestation of Lewy Body Disease remains to be elucidated.

Hypothesis: iRBD is more prevalent in patients with iPN and abnormal cardiac MIBG-scintigraphy as compared with normal cardiac MIBG-scintigraphy. Patients with iPN and cardiac sympathetic denervation (assessed by 123I-MIBG scintigraphy) are hypothesized to progress to iRBD, PD or DLB.*Primary outcome:* iRBD. *Secondary outcome:* DLB, PD or MSA.

Methods:

Material: A prospective cohort study. Aim: n=81 patients diagnosed with iPN confirmed by nerve conduction studies (large fiber PN) or skin biopsy (small fiber PN).

Methods: Phenotypic characterization of autonomic dysfunction: Autonomic symptom scores (Composite Autonomic Symptom Score-31 (COMPASS-31), scales for outcomes in Parkinsons' Disease - Autonomic Dysfunction (SCOPA-AUT), international index of erectile function-5 (IIEF-5) combined with functional autonomic testing (Tilt-table test, Valsalva maneuver, deep breathing, quantitative sudomotor axon reflex test). Cognitive screening tests (Montreal Cognitive Assessment, Trail Making Test B (Executive function)), depression (Beck Depression Inventory-II), olfactory testing (16-item sniffin' Stick), motor function (MDS-UPDRS-III), rating of parasomnia (REM Sleep Behavior Disorder Screening Questionnaire), daytime sleepiness (ESS) combined with video-polysomnography. Multimodal imaging including brain MRI, 18F-PE2I-PET, cardiac 123I-MIBG-Scintigraphy). Diagnosis of iRBD, DLB or PD in collaboration with specialists in dementia, PD, and sleep disorders. *Visits:* baseline, 5-year follow-up.

Results:

Ongoing inclusion. Enrolment status: 30 participants.

Conclusion:

Expected outcome: To improve the understanding of early onset symptoms compatible with Lewy Body Disease.

Clinical Features

Oral Abstracts

Autonomic and neurosensory disorders in dementia with Lewy bodies patients: characteristics, follow-up and neural basis

Morgane Linard [1] Olivier Bousiges [1, 2], Mary Mondino [1], Léa Sanna [3], Benjamin Cretin [1, 3], Candice Muller [3], Catherine Demuynck [3], Nathalie Philippi [1, 3], Frédéric Blanc [1, 3]

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Background:

In dementia with Lewy bodies (DLB), autonomic (AUD) and neurosensory (NSD) disorders can precede neurocognitive symptoms by several years. Improving knowledge of these symptoms is essential to avoid associated complications, and could shed light on the pathophysiological mechanisms involved at an early stage in the disease.

Methods:

Within the AlphaLewyMA cohort, nine AUD and three NSD were repeatedly screened at 0, 6, 12, 18, 24, 36, 48, 60, 72, 84 and 96 months of follow-up using a standardized questionnaire and a search for neurogenic orthostatic hypotension (NOH). Among 142 probable DLB patients, we described the prevalence and fluctuations of these symptoms and the impact of an Alzheimer's co-pathology (51% of our sample). In order to explore the neuroanatomical correlates of these AUD/NSD, we performed whole-brain Voxel-Based Morphometry analyses on gray matter volumes in 116 participants with MRI data.

Results:

At 24 months of follow-up, the six most frequently reported AUD/NVS were rhinorrhea, constipation, dry mouth, photophobia, lacrimation and sexual dysfunction with prevalences of 47%, 40%, 38%, 37%, 33% and 32%, respectively. Due to their highly fluctuating nature, repeated screening of these symptoms had a major impact on their prevalence: over the entire follow-up, the six most frequently reported AUD/NVS were rhinorrhea, lacrimation, constipation, sexual dysfunction, photophobia and NOH with prevalences of 78%, 67%, 65%, 63%, 60% and 58%, respectively. The presence of an Alzheimer's co-pathology had no major impact on symptom prevalences. DLB patients with i) nasal, ocular or oral dryness and ii) severe taste disorders had significantly lower gray matter volumes in the left insula and the left putamen, respectively.

Conclusion:

AUD/NSD are highly prevalent and fluctuating in probable DLB patients, highlighting the need for regular, systematic screening. Insula, a key region of the central autonomic network, may be involved in the occurrence of some of these symptoms.

Circadian Rhythm disruption as a biomarker to differentiate between Dementia with Lewy Bodies and Alzheimer's Disease

João Durães [1, 2, 3] Elza Rocha [2, 4], Marisa Lima [1, 2, 5], Catarina Carvalhas-Almeida [2, 4, 6], Bárbara Santos [2, 4, 6], Laetitia S. Gaspar [2, 4], Inês Baldeiras [2, 3], Miguel Tábuas-Pereira [1, 2, 3], Cláudia Cavadas [2, 4, 6], Ana Rita Álvaro [2, 4, 7], Isabel Santana [1, 2, 3]

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Background:

Pathological disruptions in circadian system structures and clinical circadian rhythm changes are common in both Dementia with Lewy Bodies (DLB) and Alzheimer's Disease (AD). However, knowledge regarding circadian rhythm in these diseases and its role in differentiating them is very limited. Our aim was to investigate whether circadian rhythm biomarkers can differentiate DLB from AD.

Methods:

We included patients with DLB (n=18) or AD (n=18), diagnosed according to the most recent international criteria, who underwent CSF-AD biomarker analysis. Circadian rhythm was assessed through 14-day actigraphy and clock gene expression profile (5 assessments in a 24-hour period) in peripheral blood cells. Brief cognitive assessment (MMSE) and cognitive fluctuation scales (DCFS-R and MFCS) were also performed.

Results:

Patients with DLB had significantly lower mean values of circadian rhythm amplitude (1261±839.0 vs 1984±828.5,p=0.01), M10 (activity levels in the most active 10h, 2432±1366 vs 3555±1396,p=0.02) and MESOR (midline-estimating statistic of rhythm, 1401±695.1 vs 1981±814.2,p=0.03), and higher inter-daily variability (0.883±0.323 vs 0.669±0.121,p=0.02). Although there were no significant differences between DLB patients with or without amyloid co-pathology, amplitude, M10 and MESOR values had a positive correlation with CSF tau and p-tau values, and a negative correlation with DCFS-R and MFCS values. The 24-hour expression profiles for clock gene had less amplitude in DLB than in AD. Average expression levels were also decreased in DLB for the *BMAL1* (p=0.008), *CLOCK* (p=0.008) and *CSNK1E* (p=0.02) genes.

Conclusion:

There was a broader and more severe circadian disruption in DLB than AD, with lower activity levels and more inter-daily variability. There was also less amplitude of both rest-activity and clock gene expression rhythms, providing a biological support for the clinical findings in DLB. Circadian dysfunction appears to be unrelated to amyloid co-pathology. A better comprehension of circadian rhythm in DLB could lead to interesting diagnostic and therapeutic options.

Developing a digital delirium framework for continuous monitoring of rest-activity and sleep in inpatients with Parkinson's disease and Parkinson's disease dementia.

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Background:

Delirium is an acute neuropsychiatric syndrome associated with altered levels of consciousness, confusion, impaired attention and sleep-wake-cycle disruption. Delirium is associated with poor outcomes, and patients with Lewy body disease (LBD) are at increased risk of delirium. However, delirium may be missed due to overlapping symptoms. Wearable devices can provide continuous objective activity and sleep measures and may facilitate identification and monitoring of delirium inpatients. However, identifying which digital measures to use is unclear. This study aimed to determine differences in digital rest-activity measures in LBD with and without delirium and to propose a digital framework to aid clinical interpretation.

Methods:

Inpatients with Parkinson's disease (PD) and PD-dementia (PDD) who were admitted to hospitals in Newcastle-upon-Tyne, wore an Axivity Ax6 wrist-worn device in parallel to daily delirium assessments based on the DSM-5 criteria. Recorded sensor signals were processed using open-source software (GGIR) to provide 70 separate rest-activity and sleep measures averaged over the admission period. Measures showing differences between cases with and without delirium ($p<0.05$) were entered into a Principal Component Analysis (PCA).

Results:

Digital measures were derived for 54 participant admissions (47-PD, 7-PDD). Delirium was identified in 36 admissions (all cases with PDD). Seventeen digital measures were significantly different in participants with delirium compared to those without. The PCA identified four components: daytime activity/daytime rest/sleep fragmentation/24-hour rhythm. Delirium was associated with disrupted rest-activity patterns with increased daytime rest and increased night-time wake duration.

Conclusion:

We identified digital measures that were significantly different in PD and PDD inpatients with delirium compared to those without. The digital framework aids clinical interpretation and provides a foundation to explore the delirium profile across the admission period. The framework could facilitate the monitoring of inpatient recovery and establish common objective endpoints in future clinical trials. Replication in a larger study, including participants with DLB, is warranted.

Core Clinical Features Associated with Survival in Dementia with Lewy Bodies (DLB)

Stuart McCarter [1] Tanis Ferman [2], Kiera Grant [1], Jeremiah Aakre [1], David Knopman [1], Neill Graff-Radford [2], Leah Forsberg [1], Julie Fields [1], Gregory Day [2], Rodolfo Savica [1], Hugo Botha [1], David Jones [1], Vijay Ramanan [1], Christian Lachner [2], Aivi Nguyen [1], Melissa Murray [2], Ronald Petersen [1], Dennis Dickson [2], Ross Reichard [1], Kejal Kantarci [1], Bradley Boeve [1], Jonathan Graff-Radford [1]

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Background:

The core clinical features of DLB include REM sleep behavior disorder (RBD), fluctuations, parkinsonism, and visual hallucinations (VH). How these clinical features influence mortality risk is unknown.

Methods:

A clinical cohort of 484 probable DLB participants were followed annually in the Mayo Clinic Alzheimer's Disease Research Center. A subset of 187 participants with autopsy-confirmed DLB were examined. Cox proportional hazards models were carried out from the time patients met criteria for probable DLB (cognitive impairment + 2 core clinical features) to death utilizing time-dependent covariates and age as the time scale. Deaths occurring more than 2 years from last visit were censored at the time of last visit.

Results:

Clinical and autopsy-confirmed cohorts had similar sex distribution (76% male), age of cognitive symptom onset (69.6±8 years), and age of meeting probable DLB criteria (71.9±8 years). Shorter survival was associated with VH (HR 3.22, 95%CI 2.45-4.26) and parkinsonism (HR 2.26, 95%CI 1.52-3.35) but not fluctuations (HR 1.41 95%CI 1.05-1.88) or RBD (HR 1.25 95%CI 0.92-1.71). More core features (4 vs. 2 core, HR 3.62 95%CI 2.70-4.86, 4 vs. 3 core, HR 2.46, 95%CI 1.86-3.25, 3 vs. 2 core, HR 1.47, 95%CI 1.07-2.03) were also associated with shorter survival. More years from cognitive symptom onset to DLB diagnosis was associated with shorter survival in both models (HR 1.06-1.08, 95%CI 1.02-1.12). Findings were similar between sexes. In autopsy-confirmed DLB, shorter survival was associated with VH (HR 2.80, 95%CI 1.95-4.02), parkinsonism (HR 2.11, 95%CI 1.26-3.52), more years from cognitive onset to meeting DLB criteria (HR 1.08, 95%CI 1.03-1.13), and 4 core features (4 vs. 2 core, HR 2.72, 95%CI 1.86-3.99, 4 vs. 3 core, HR 2.46, 95%CI 1.70-3.57).

Conclusion:

Shorter survival in clinically-probable and autopsy-confirmed DLB was associated with VH, parkinsonism, greater number of core features, and longer time to meeting DLB criteria from cognitive symptom onset.

Comparison of clinical and neuropathologic features in probable dementia with Lewy bodies with cognitive symptom onset before and after age 65

Koji Kasanuki [1, 2, 3], Hiroaki Sekiya [3], Tanis Ferman [9] Jonathan Graff-Radford [4], Stuart McCarter [4], Shunsuke Koga [3], Neil Graff-Radford [5], Gregory Day [5], Julie Fields [6], Rodolfo Savica [4], David Jones [4], Vijay Ramanan [4], Aivi Nguyen [7], Melissa Murray [3], Ronald Petersen [4], Kejal Kantarci [8], Bradley Boeve [4]

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Background:

Little is known about whether clinical or neuropathologic features differ between dementia with Lewy bodies (DLB) with early and late onset of cognitive symptoms.

Methods:

Participants included 488 probable DLB patients prospectively followed in the Mayo Clinic Alzheimer's Disease Research Center. The early-onset DLB (EODLB) group developed cognitive symptoms < age 65 (n=129), and the late-onset DLB (LODLB) group developed cognitive symptoms ≥ age 65 (n=359). Dementia severity at the initial visit, presence/absence of each core feature, and time from cognitive symptom onset to each core feature were compared between groups. A subset of n= 191 with gross neuropathology and n= 65 with digital pathology were compared based on early vs. late cognitive symptom onset.

Results:

The EODLB and LODLB groups did not differ in sex (76% men) or MMSE score at the first visit (23.5±5). EODLB exhibited a longer disease duration (11.3±4 vs. LODLB 8.3±4 years, $p<0.001$), higher rates of REM sleep behavior disorder (RBD) (90% vs. LODLB 72%, $p<0.001$), more frequent 3+ core DLB features (80% vs. LODLB 70%, $p=0.034$). The time from cognitive symptom onset to the development of visual hallucinations, fluctuations, and parkinsonism was longer in the EODLB ($p<0.001$) compared to the LODLB group. Autopsy-confirmed EODLB (n=88) and LODLB (n=103) showed no difference in the severity of cortical Lewy-related pathology, amyloid plaque distribution, or Braak neurofibrillary tangle stage. Digital pathology of 20 EODLB and 45 LODLB showed no difference in cortical Lewy body counts or cortical burden of alpha-synuclein, amyloid-beta, and tau.

Conclusion:

Clinically probable EODLB had higher rates of RBD, more core DLB features, a longer disease duration, and longer time to develop visual hallucinations, fluctuations, and parkinsonism from cognitive symptom onset compared to LODLB. No significant differences were found in neuropathological features between the groups.

Why do visual hallucinations happen in Lewy body dementia?

Rimona Weil [1]

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Hallucinations are common in Lewy body dementia, and can be challenging to treat.

Professor Weil will present data examining mechanisms for hallucinations from studies in people with Parkinson's disease and Lewy body dementia.

She will focus on 3 linked mechanisms:

These are evidence for impaired visual processing, and how this relates to poor outcomes in Parkinson's disease; evidence for over-reliance on visual priors and expectations in people with Lewy body dementia; and evidence for changes in functional connectivity between relevant brain regions.

Finally she will consider how these mechanisms fit into recent models for hallucinations in Lewy body disorders.

Poster Abstracts

Profound impairment of spatial navigation skills in Lewy body disease using the real-space environment and its computerized version

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Background:

We have previously demonstrated spatial navigation (SN) impairment in the Alzheimer's disease (AD) continuum using real-space and computerized tests, which may address SN abilities more comprehensively than paper-and-pencil-based neuropsychology. Visuospatial impairment is prominent in dementia with Lewy bodies (DLB), but studies other than pencil-and-paper-based are scarce. We assessed the pattern and magnitude of SN impairment using real-space and computerized SN environments in DLB compared to AD, including prodromal patients, and controls.

Methods:

Biomarker-based prodromal AD (MCI-AD-n=14) and overt AD dementia (n=6) grouped as AD (n=20); n=8 prodromal DLB (MCI-LB), n=8 overt DLB, and n=8 MCI-Parkinson disease (MCI-PD) grouped as LBD (n=24), and cognitively unimpaired controls (n=33) underwent detailed evaluations. SN was assessed by a human analog of the Morris water maze called the Hidden Goal Test as participants were searching for a goal that shifted its position across several trials utilizing various SN strategies in both real space and its 2D computerized environment: 1. solely using their own body position (no external cues, egocentric), 2. using solely external cues (allocentric), 3. mixed (allo-egocentric) and 4. delayed recall allocentric.

Results:

LBD patients scored the poorest using allocentric and mixed strategies (p's<0.0001) in both real-space and computerized environments (p's<0.0001). AD scored the worst in the real-space delayed allocentric recall (p=0.00179). Adjusting for age, education, and clinical status (normal/MCI/dementia), findings remained consistent. MCI-LB tended to perform worse than MCI-AD in most tests and were similar to MCI-PD. DLB tended to perform worst when accounting for age, education, and status, though given small subgroup numbers, p-values are unreported.

Conclusion:

Overall, LBD patients showed the most prominent SN impairment, potentially interfering with everyday functioning. Patterns of SN impairment may be differential in LBD vs AD patients. Associations of SN with regional brain atrophy and overlapping AD pathophysiology in LBD are currently underway.

The cognitive connectome in the continuum of Dementia with Lewy bodies

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Background:

Cognition has a central role in the diagnosis and characterization of dementia with Lewy bodies (DLB) and its prodromal stage of mild cognitive impairment with Lewy bodies (MCI-LB). While cognition is traditionally investigated using a univariate approach, the complex associations among cognitive deficits along the DLB continuum are still unknown. We used a multivariate method based on graph theory to investigate the so-called cognitive connectome in participants with MCI-LB and DLB compared with healthy controls (HC) and participants with mild cognitive impairment due to Alzheimer's disease (MCI-AD) and Alzheimer's Disease dementia (AD).

Methods:

We included participants with MCI-LB (n=88), DLB (n=104), HC (n= 3703), MCI-AD (n=1789) and AD (n=1985) from the National Alzheimer's Coordinating Center (NIA/NIH Grant U24-AG072122). We built cognitive connectomes using Spearman correlations between pairs of 24 cognitive measures, and computed global and nodal graph measures of centrality, integration and segregation to characterize the connectome differences.

Results:

For global measures, both MCI-LB and DLB showed lower transitivity (segregation) when compared with HC. MCI-LB did not differ significantly from MCI-AD. DLB showed higher global efficiency (integration) and lower transitivity than AD. MCI-LB showed lower global efficiency and higher transitivity than DLB. Nodal measures showed differences in executive functions when comparing MCI-LB and DLB with HC. Additionally, DLB showed nodal differences in visuoconstructive functions, memory, processing speed/attention, language and orientation compared with HC. DLB showed nodal differences in memory compared with AD, and MCI-LB in executive functions, processing speed/attention and language compared with DLB.

Conclusion:

The cognitive connectome is impaired in the DLB continuum, showing a loss of cognitive specialization already detectable at the prodromal stage and becoming more pronounced at the dementia stage. These findings inform on the complex associations among cognitive deficits in MCI-LB and DLB, which may have implications for the differential diagnosis of these populations.

Main Effects of post-mortem confirmed Lewy-Body pathology status on antemortem MRI Grey Matter Volumes and interaction effects with associated cognitive domain scores

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Background:

Lewy Body Dementia (LBD) involves the neurotoxic aggregation of α-synuclein proteins, forming Lewy Bodies (LB) that can lead to neuropathology (NP) associated with cognitive impairment (CI) common with Alzheimer's disease (AD) mechanisms. These clinically important effects are still under investigation and remain differentially elusive to AD, but by combining measures of cognition (MoCA), with antemortem brain MRIs and post-mortem LB pathology status, the present study aimed to study these effects in subjects covering the cognitive spectrum.

Methods:

Subject-specific antemortem MoCA scores and T1-MRI's closest to time of death were identified and based on the ADNI-NP dataset, which contained post-mortem confirmation of LB-NP status for n=46 subjects, and probable diagnosis of cognitively normal (CN), mild (MCI), or AD. MRI's pre-processed in SPM12/CAT12, extracting grey matter volumes (GMVs) and smoothing to $8mm^3$. Full factorial voxel-wise models examined the significance (t-values) and magnitude (β-values) for the main effects of LB status on GMV, and then for interactions with LB status associated MoCA subscores.

Results:

The sample consisted of CN (21.74%), MCI (56.52%), and AD: (21.74%), with 47.83% as LB+, was ~79.55 years at MRI, mainly male (76.09%), with less of the females having LB+ (18.18%), hence sex was adjusted for. This study identified significant (height threshold: $p \leq 0.10$; cluster threshold: $k \geq 5$ voxels) negative main effects on GMV for LB+ status (β_{max}=-0.09: T_{max}=3.34; K_{max}=1930; #*cluster*s=114) focused posteriorly on the cortex surrounding the parietal, calcarine, fusiform, and middle temporal regions, and positive main effects for LB- status (β_{max}=0.11: T_{max}=4.65;K_{max}=20,017; #*cluster*s=96) focused mainly around the parietal, temporal, limbic, frontal, and cerebellar regions. Interaction effects for LB status associated MoCA subscores, highlighted topologically distinct negative effects on GMV.

Conclusion:

These results highlight that LB status and associated neurocognitive correlates can be topologically distinguished, improving our understanding in how to differentially diagnose those with and without LB.

Clinical and genetic predictors of dementia in Parkinson's Disease

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Background:

Dementia affects nearly 50% of people with Parkinson's disease (PD) within ten years of their diagnosis. There is wide variability in dementia onset, which is underpinned by heterogeneity in pathophysiology and genetic factors. Increasing evidence suggests that the presence of visual dysfunction in PD is associated with a higher risk of developing dementia, and a wide range single nucleotide polymorphisms such as *APOE4* are associated with a more aggressive dementia phenotype. We aimed to investigate whether visual dysfunction interacts with genetic factors to increase progression to dementia in a large longitudinal cohort of patients with PD.

Methods:

This was a prospective cohort study of PD patients and age-matched controls from 35 UK centres. Patients with dementia at baseline were excluded. Tests of visual perception were performed using a web-based platform, and blood samples obtained for all participants. Global cognition was tested using the Montreal Cognitive Assessment (MoCA) at baseline and annually for three years. Individual SNPs were analysed, and a polygenic risk score for PD and Lewy Body Dementia created. Progression to dementia was defined as MoCA<=25.

Results:

661 participants were included, of which 541 had PD. Median disease duration at baseline was 2.7 years. In a multivariate model adjusted for participant age, baseline visuo-perceptive test scores below the median in at least two of the four visual tests was associated with progression to dementia (Hazard ratio=2.2, p=0.0174). Survival analysis demonstrated participants with at least one *APOE4* allele had worse dementia outcomes within their respective visuo-perceptive groups.

Conclusion:

Our large prospective study has demonstrated a strong association with visual dysfunction and future progression to dementia, with an interaction with genetic factors. Tests of visuo-perception and genetic screening may help identify patients for targeted therapies in future.

Clinical and Neuropathologic features of Capgras syndrome in Dementia with Lewy Bodies

Hiroyuki Watanabe [1], Hiroaki Sekiya [2], Tanis J Ferman [2] Neill R Graff-Radford [2], Gregory S Day [2], Owen Ross [2], Christian Lachner [2], Dennis W Dickson [2], Kejal Kantarci [1], Bradley F Boeve [1]

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Background:

Capgras syndrome refers to a delusion that a person close to the patient has been replaced by a duplicate. Little is known about the phenomenology or neuropathology of Capgras syndrome in dementia with Lewy bodies (DLB).

Methods:

Participants included 69 prospectively followed patients from Mayo Clinic Florida with autopsy-confirmed DLB. Immunohistochemistry and regional quantitative digital assessment of α-synuclein, tau, and amyloid-β pathology, with correction for multiple comparisons, was obtained.

Results:

Capgras syndrome occurred in 29% (20/69) and did not differ from the those without this clinical feature in age at baseline visit (72±7 years), sex (84% men), education (15±3 years), follow-up (mean 4.5±2.8 years), death age (77±7 years), or baseline dementia severity (MMSE 24±4, Dementia Rating Scale 120±15). Capgras occurred a mean of 4±2 years after cognitive symptom onset and later than each of the four core clinical features ($p<0.01$). Of those with Capgras, 100% had visual hallucinations compared to 63% without Capgras ($p<0.001$), with no group difference in fluctuations, parkinsonism, or RBD. In the Capgras group, 95% had diffuse Lewy body disease, 5% had transitional Lewy body disease, and 75% had neocortical neurofibrillary tangles, resulting in 80% with diffuse neocortical α-synuclein and tau co-pathology. Thal amyloid phase was higher in the Capgras group, with no difference in brain weight, TDP-43 pathology, vascular disease, or APOE e4 status. The Capgras group had greater α-synuclein and tau burden in cingulate, parahippocampal, frontal, inferior temporal, occipitotemporal, and parietal regions, greater α-synuclein burden in Brodmann area 18, and greater tau burden in CA1, CA2/3 and subiculum ($p<0.05$) compared to the non-Capgras group with no group differences in amyloid-β burden.

Conclusion:

In DLB, Capgras syndrome developed well after the other core features, in a subset who already had visual hallucinations, and was associated with greater regional burden of α-synuclein and tau pathology.

The prevalence of apathy in Lewy body dementia: a systematic review and meta-analysis

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Background:

Apathy is an important feature of Lewy body dementias (LBD). Existing data on the prevalence of apathy in LBD is heterogenous. Therefore, we aim to estimate the prevalence of apathy in LBD through systematic review and meta-analysis.

Methods:

Five databases (Embase, Medline, PsycInfo, Web of Science and CINAHL) were searched for relevant articles using key terms including "lewy body", "Parkinson's disease dementia", "mild cognitive impairment (MCI)", "neuropsychiatric symptoms", "apathy", and their synonyms. The last search was performed on the 1st of February 2023. Articles reporting prevalence of apathy in dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), LBD and mild cognitive impairment (MCI) DLB and PDD were included. Random effect meta-analysis was performed to determine prevalence of apathy.

Results:

The search identified 7477 articles, 47 met the inclusion criteria. The pooled prevalence of apathy in LBD (DLB and PDD, n = 3940) was 58% (95% confidence interval (CI) 51 – 64%, I^2 = 95.3%), in DLB (n = 2169) 58% (95% CI 52 – 64%, I^2 = 86.5%) and in PDD (n = 1557) 56% (95% CI 43 – 70%, I^2 = 97.6%). The pooled prevalence of apathy in combined MCI groups (total participants n = 653) was 45% (95% CI 34 – 57%, I^2 = 85.51%), in LB-MCI (n = 316) 49% (95% CI 34 – 65%, I^2 = 88.4%) and PD-MCI (n = 337) 40% (95% CI 29 – 51%, I^2 = 51.1%).

Conclusion:

Apathy is an important and prevalent feature of LBD throughout the disease continuum. The high prevalence of apathy in prodromal disease supports its utility in early LBD diagnosis. Future research should aim to prospectively validate apathy as a component of diagnostic criteria in prodromal disease as well as focus on earlier identification and management strategies for this common feature of LBD.

The Effect of Amyloid and Tau Co-pathology on Disease Progression in the Lewy body Dementias: A Systematic Review

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Background:

A proportion of people with Lewy body dementia (LBD) have co-morbid Alzheimer's disease (AD) pathology (amyloid-beta and tau), which may affect clinical outcomes. Here we review the effects of AD co-pathology on longitudinal clinical outcomes in LBD.

Methods:

A systematic search of MEDLINE and EMBASE (April 2024) yielded *n*=3332 records that were screened by two independent reviewers. Included studies assessed AD co-pathology in LBD by different methods: neuropathologic examination, positron emission tomography (PET) imaging, cerebrospinal fluid (CSF) and/or plasma biomarkers; and reported longitudinal clinical outcomes including cognitive and functional decline, mortality, or treatment response. The risk of bias was assessed with the Quality in Prognosis Studies tool. Heterogeneity among studies precluded a formal meta-analysis.

Results:

Twenty-nine studies met inclusion criteria (neuropathology = 10, PET = 7, CSF = 8, plasma = 4). All studies rated as low risk of bias (*n*=12) reported that increased AD co-pathology (LBD+AD) was associated with accelerated cognitive decline (*n*=7/7), accelerated functional decline (*n*=3/3), greater mortality (*n*=2/2) and/or poorer response to treatment (*n*=1/1). Among these studies, the mean differences in cognitive decline between LBD+AD and LBD without co-pathology ranged from -0.85 to -2.2 MMSE points/year, while one study reported an adjusted hazard ratio for mortality in LBD+AD as 3.70. Studies rated as moderate to high risk of bias found mixed results, with 9/17 reporting evidence for poorer prognosis in LBD+AD while 8/17 found no association between AD co-pathology and clinical outcomes. No study reported better outcomes in LBD+AD.

Conclusion:

AD co-pathology is associated with worse clinical outcomes in LBD. This is an important consideration in the design of clinical trials, subject stratification and in the clinical provision of new treatments for dementia. Further work is needed to understand the relative contribution of individual pathologies (alpha-synuclein, amyloid-beta and tau) to disease progression in LBD.

Catatonia and dementia: a case series

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Background:

Catatonia is a syndrome combining a variety of psychomotor and behavioural symptoms. It is under-diagnosed in the elderly and associated with significant morbidity and mortality. Little is known about the links between catatonia and dementia.

Methods:

We propose a "real-life" case series of 5 patients with dementia and catatonia, in order to explore the links between catatonia and dementia, and potentially guide future research on this topic.

Results:

In our cases, major depression was strongly associated with catatonia (4/5) and two patients had bipolar disorder Iatrogenicity was linked to catatonia in three patients, particularly with antipsychotics. Two patients had dementia with Lewy bodies and one was suspected with frontotemporal degeneration. These are the two dementia most frequently associated with catatonia. Catatonia had been mistaken for confusional syndrome in one of our patients. It is important to look for it and treat it, even in a confusional state. The differential diagnosis between catatonia and frontotemporal lobe degeneration (FTLD) was difficult in one of our case because the chronic behavioural symptoms of FTLD can mimic catatonic symptoms. In this case response to symptomatic treatment, symptom fluctuations and sudden onset of atypical symptoms for FTLD may support catatonia.

Conclusion:

Dementia is a direct and indirect risk factor (via iatrogenesis, general médical or psychiatric pathologies) for catatonia. Screening for catatonia using scales should be systematically carried out in wards caring for people with dementia, as this is a treatable syndrome.

Investigating Early Clinical Risk Factors of Dementia in Parkinson's disease: A Ten-Year Prospective Study

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Background:

Clinical features in Parkinson's disease (PD) that accurately predict the risk and timing of dementia are crucial for early treatment and better patient outcomes. This study aims to identify key clinical features in newly diagnosed patients with PD that predict dementia within the first ten years of PD diagnosis.

Methods:

We included 190 new-onset, non-demented PD patients from the population-based Norwegian ParkWest cohort. Clinical data, including motor symptoms, cognitive function, and non-motor symptoms, were collected at baseline. Patients were followed with two annual clinical evaluations for up to ten years, and mild cognitive impairment (MCI) and PD dementia diagnosed according to the MDS criteria. Univariate and multivariate Cox models correcting for age, sex and education were used to analyze potential clinical risk factors of dementia.

Results:

Of the 190 patients, 67 (35,3 %) developed dementia. Univariate analyses revealed that more severe motor symptoms (HR 1.06, 95 % CI 1.04 to 1.09, $p < 0.001$), abnormal olfaction (HR 2.05, 95 % CI 1.17 to 3.58, $p = 0.013$), higher systolic orthostatic blood pressure drop (HR 1.02, 95 % CI 1.01 to 1.03, $p = 0.009$), MCI (HR 4.16, 95 % CI 2.52 to 6.88, $p < 0.001$), and probable REM sleep behavior disorder (HR 2.48, 95 % CI 1.29 to 4.74; $p = 0.006$), all each associated with an increased risk of developing dementia within 10 years. In a multivariate analysis, more severe motor symptoms (HR 1.05, 95 % CI 1.02 to 1.07, $p < 0.001$) and MCI (HR 3.75, 95 % CI 2.18 to 6.45, $p < 0.001$) remained the strongest predictors.

Conclusion:

Our study highlights MCI and increased motor severity at time of diagnosis as important risk factors of dementia in PD. These findings can guide early identification and management of high-risk individuals.

Physical Activity and Sleep Biomarkers associated with Cognitive Fluctuation in Dementia with Lewy Bodies

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Background:

Cognitive fluctuation (CF) is a key diagnostic criterion of dementia with Lewy bodies (DLB). Although CF can be measured using one of several validated assessment instruments, including the Mayo Fluctuations Composite Scale (MFCS), CF prevalence varies widely across studies. Given that this may reflect challenges in objectively characterizing CF, we sought to learn how MFCS ratings of CF correlate with objective measurements of actigraphy and sleep in participants with probable DLB and Alzheimer's disease (AD).

Methods:

Participants wore wGT3X-BT actigraphy devices (DLB n=12; AD n=8) for 2 weeks to obtain daily activity counts and Sleep Profiler X8 devices (DLB n=9; AD n=7) for 2 nights to obtain auto-staged measurements of rapid eye movement (REM) sleep and non-REM with hypertonia (NRH), which were verified by a sleep physician. CF status was characterized using the MFCS.

Results:

At baseline, 9 (75%) participants with DLB were classified as CF+, whereas only 2 (25%) participants with AD were classified as CF+. Our preliminary analyses suggest that CF+ participants with DLB and AD exhibited fewer daily activity counts than CF- participants [mean (in millions) =1.16 for DLB/CF+, 2.07 for DLB/CF-, 1.31 for AD/CF+, 1.72 for AD/CF-]. Although there were no differences in the % REM in CF+ and CF- participants, CF+ participants with DLB had substantially higher % NRH than any of the other groups (mean=17% for DLB/CF+, 4% for DLB/CF-, 3% for AD/CF+, 6% for AD/CF-).

Conclusion:

Individuals with DLB and CF may be less physically active and may have higher NRH. However, larger studies of CF, physical activity, and sleep are necessary to confirm these findings and to further demonstrate the value of actigraphy and the Sleep Profiler in identifying CF in DLB.

Analysis of Parkinson's Disease Questionnaire-39 in Dementia with Lewy Bodies

Elizabeth Abrahamson [1] Kiera Grant [1], Jeremy Syrjanen [1], Tanis Ferman [2], Julie Fields [1], Leah Forsberg [1], Jonathan Graff-Radford [1], Rodolfo Savica [1], Neill Graff-Radford [2], Vijay Ramanan [1], Gregory Day [2], Philip Tipton [2], Hugo Botha [1], David Jones [1], Christian Lachner [2], David Knopman [1], Ronald Petersen [1], Kejal Kantarci [1], Bradley Boeve [1]

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[2] Mayo Clinic, Jacksonville, United States

Background:

The Parkinson's Disease Questionnaire-39 (PDQ-39) is a 39-question, participant-completed questionnaire used to evaluate their experience across 8 dimensions of daily living based on experiences form the prior month. Item responses are on a 5-point scoring system, and total scores in all domains range from 0 (no difficulty) to 100 (always have difficulty).

Methods:

Participants included clinically probable DLB, MCI-LB, and controls enrolled in the DLB research program as part of the Mayo Clinic Alzheimer's Disease Research Center. Baseline PDQ-39 responses were examined for each domain relative to disease severity based on CDR Sum of Boxes (CDR-SB)) scores using a Generalized Linear Model.

Results:

At baseline visit, 76 participants (mean age 68.8 $\pm$ 8 years, mean education level 15.9 $\pm$ 3 years, 83% male, mean CDR-SB = 4.2 $\pm$ 3) completed the PDQ-39. Mean total scores among the 8 domains were 24.08 $\pm$ 24.47 for mobility, 21.16 $\pm$ 23.95 for ADLs, 24.18 $\pm$ 19.02 emotional well-being, 9.05 $\pm$ 14.05 stigma, 8.59 $\pm$ 16.01 social support, 32.00 $\pm$ 18.74 cognitive impairment, 16.01 $\pm$ 17.47 communication, and 29.28 $\pm$ 23.31 bodily discomfort. A generalized linear model analysis shows a significantly worse mobility ($p=0.005$), ADLs ($p=0.0008$), social support ($p=0.0075$), and communication ($p<0.0001$) in relation to disease severity.

Conclusion:

In DLB and MCI-LB, greater disease severity (CDR-SB) was associated with the mean total domain scores of mobility, ADL, social support, and communication.

Establishing a worldwide consortium to assess cross-cultural differences in the presentation and measurement of social cognition in LBD, FTD, and HD

Rachel Fitzpatrick [1]

[1] School of Medicine, Trinity College Dublin, Dublin, Ireland

Background:

Social cognitive deficits are often an early indicator of Lewy body dementia (LBD). However, these deficits may manifest differently across cultures due to varying social norms. Consequently, social cognition assessments developed in one cultural context may lack relevance in others. We aimed to establish a worldwide consortium of researchers and healthcare professionals to enable cross-cultural comparison of the presentation and measurement of social cognition in LBD, Huntington's Disease (HD), and Frontotemporal Dementia (FTD).

Methods:

We developed our consortium through an expression of interest form disseminated to a worldwide network of researchers and health professionals. Consortium members then completed an online survey, outlining the participant groups (LBD, FTD and/or HD) for which they collected social cognition data, and the assessments they used for each group. This allowed us to identify the types of data each consortium member was contributing, and the cross-cultural differences in assessment tools being used. Finally, we hosted an online webinar to discuss strategies for cross-cultural comparisons of social cognition data for LBD, FTD, and HD, including setting up a data-sharing scheme between members.

Results:

Our consortium consists of 32 researchers and health professionals from 10 countries: Chile, Brazil, Peru, Argentina, Ireland, France, UK, Italy, USA, and Australia. Our survey revealed significant variability in the tests used to assess social cognition in individuals with LBD, FTD, and HD across participating countries. The mini-SEA was the most commonly used assessment (used in 6/10 countries). After this, the most used assessments (each used in 3/10 countries) were the Ekman 60-Faces and the Interpersonal Reactivity Index.

Conclusion:

The variability in assessment tools across cultures suggests that cross-cultural comparisons may need to focus on social cognition domains rather than specific measures. These findings are particularly relevant for migrant communities, emphasizing the need for culturally tailored assessments.

Proportion and Characteristics of DLB Patients Among Those Wishing to Receive Lecanemab Therapy

Hisatomo Kowa [1] Kohei Morimoto [1]

[1] Kobe University Hospital, Kobe, Japan

Background:

Since Lecanemab was introduced in Japan, we have seen a large number of patients coming to our specialized outpatient clinic. It has come to our attention that a significant number of those patients may have Dementia with Lewy Bodies (DLB). This study aimed to identify the percentage of DLB patients with those who seek Lecanemab treatment and to explain their clinical characteristics.

Methods:

From January to June 2024, 57 patients who wished to receive Lecanemab at our clinic were examined. Of these, 23 were suspected of having early-stage Alzheimer's disease (AD), with 18 testing positive for amyloid and 5 testing negative. We investigated the reasons behind the decision to exclude 34 patients from amyloid testing.

Results:

Eight patients were suspected of being other than AD and did not undergo amyloid testing. Six individuals were diagnosed with DLB or DLB-MCI through Dopamine transporter SPECT imaging. Four of these six patients had maintained an MMSE score of 22-23 for over two years and were on donepezil treatment. Additional indicators of DLB include vivid dreams, small figures in drawing tests, and constipation. Five cases showed mild rigidity as a symptom of Parkinsonism.

Conclusion:

According to our findings, there is a significant number of patients eligible for Lecanemab therapy who do not show typical DLB symptoms, including visual hallucinations. It is crucial to always consider DLB in the differential diagnosis. If any symptoms suggest DLB, it is important to conduct appropriate testing for DLB before proceeding with amyloid testing.

Investigating sensory impairments in people with dementia with Lewy bodies (DLB): a scoping review

Rachel Fitzpatrick [1] Sin Chai [1], Adam Roche [1], Iracema Leroi [1], Panos Alexopoulos [2]

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[2] University of Patras, Patras, Greece

Background:

Research has demonstrated a strong association between sensory impairment and dementia symptom severity. However, evidence of this link stems predominantly from Alzheimer's research. We aim to shed light on current evidence on the frequency of sensory impairments in DLB, and the relationship between sensory impairments and cognitive/non-cognitive symptoms of DLB.

Methods:

A scoping review was undertaken using Embase, CINAHL, PsychINFO and PubMed. Only papers discussing sensory impairments in DLB were included. Sensory impairment was conceptualized as the loss or reduction of vision, hearing, or olfaction, and did not include neuropsychiatric forms of sensory symptoms, such as auditory and/or visual hallucinations. Two reviewers independently assessed each study for inclusion. Disagreements were resolved by a third reviewer.

Results:

24 studies were included in this review: 8 focused on visual impairments; 2 on hearing impairments; and 14 on olfactory impairments. Strong associations were observed between sensory impairments and both cognitive and non-cognitive symptom severity. Visual hallucinations were positively associated with visual impairments and auditory hallucinations were positively associated with hearing impairments. Unsurprisingly, olfactory impairments were the most commonly assessed sensory impairment in DLB, and were associated with worse cognitive and non-cognitive functioning in DLB. Of note, no studies assessed social cognition as part of their cognitive batteries, despite social cognition being a core element of cognitive functioning that can be impacted by sensory impairments.

Conclusion:

This review underscores a substantial gap in research concerning the prevalence of sensory impairments in DLB and their association with DLB symptoms. Notably, there is a critical need for further investigation into the relationship between auditory function and DLB, particularly in light of the well-established connection between auditory impairments and symptom severity in other dementia subtypes. Future research should also integrate social cognitive assessments into cognitive batteries to better evaluate the interplay between cognitive and sensory impairments in DLB.

Establishing a worldwide consortium to assess cross-cultural differences in the presentation and measurement of social cognition in LBD, FTD, and HD

Rachel Fitzpatrick [1]

[1] Trinity College Dublin, Dublin, Ireland

Background:

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Conclusion:

The variability in assessment tools across cultures suggests that cross-cultural comparisons may need to focus on social cognition domains rather than specific measures. These findings are particularly relevant for migrant communities, emphasizing the need for culturally tailored assessments.

Exploring the longitudinal changes in digital rest-activity and sleep outcomes in inpatients with Parkinson's disease and Parkinson's disease dementia, with and without delirium.

Gemma Bate [1] Florence Gerakios [1], Sarah Richardson [1], Laura Wright [1], John-Paul Taylor [1], David Burn [2], Glenn Stebbins [3], Louise Allan [4], Alison Yarnall [1], Silvia Del-Din [1], Rachael Lawson [1]

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Background:

Delirium is an acute neuropsychiatric syndrome associated with altered levels of consciousness, confusion, impaired attention and sleep-wake-cycle disruption. Patients with Lewy body disease (LBD) are at increased risk of delirium. However, delirium may be missed due to overlapping symptoms. Most tools only provide information for a snapshot of time, which fails to show fluctuating delirium symptoms. This study aimed to explore the changes in digital rest-activity and sleep measures in LBD inpatients with and without delirium and between delirium subtypes over the hospital admission.

Methods:

In parallel to prospective delirium assessments based on the DSM-5 criteria, inpatients with Parkinson's disease(PD) and PD-dementia(PDD) wore an Axivity-AX6 wrist-device for up to seven days and processed using open-source software(GGIR). Seventeen digital measures based on a digital-framework were included and represented: daytime activity/daytime rest/sleep-fragmentation/night-to-day variability. Delirium subtypes were derived based on validated criteria(DMSS-4). Linear mixed-effects modelling was used to identify changes ($p<0.05$) in the digital measures over the hospital admission.

Results:

Digital measures were derived for 52 participant admissions (45-PD,7-PDD). Delirium was identified in 34 admissions (all cases with PDD) and included n=6 hyperactive, n=8 hypoactive, n=20 mixed. Daytime activity declined during the hospital stay in delirium and all delirium subtypes compared to cases without delirium ($p<0.05$). Daytime rest increased over time in hypoactive-delirium compared to those without delirium ($\beta=0.43$,$p=0.040$) and mixed-delirium ($\beta=0.44$,$p=0.039$). Night-time wake duration (sleep fragmentation) increased in mixed-delirium compared to those without delirium ($\beta=18.08$,$p=0.005$) or hyperactive-delirium ($\beta=24.12$,$p=0.031$); no further significant changes were found ($p>0.05$ for all).

Conclusion:

Digital measures may have clinical utility for monitoring change in daytime activity, daytime rest and sleep fragmentation over time in PD and PDD inpatients with delirium and delirium subgroups. This may be useful for establishing common objective endpoints in future clinical trials. Results are exploratory; replication in a larger study, including participants with DLB, is warranted.

The impact of sensory impairment on the cognitive and non-cognitive features of Lewy body dementia: Findings from the SENSE-Cog Lewy study

Adam Daniel Roche [1]

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Background:

Lewy Body Dementia (LBD), which includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), accounts for over 20% of the 65,000 people living with dementia in Ireland.

Sensory impairments may significantly contribute to cognitive deterioration and impact key clinical symptoms of LBD, though their role as early indicators of disease progression remains underexplored. The "SENSE-Cog Lewy" study seeks to further characterise the prevalence and impact of sensory losses (hearing, vision and olfaction) on LBD patients, in order to inform both diagnostic and management pathways and ultimately improve the lived experience of patients and their families.

Methods:

Twenty participants diagnosed with probable LBD (DLB or PDD) and their nominated care partner were recruited from a specialist memory outpatient clinic in our tertiary teaching hospital. Hearing assessment was performed with a Siemens HearCheck device, vision assessment was carried out using the Peek Acuity appliciation, olfactory examination was completed using the University of Pennsylvania Smell Identification Test (UPSIT). Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) and the Clinical Dementia Rating (CDR) scale. Neuropsychiatric assessments, motor and fuctional assessments were performed as well as measurements of quality of live and overall care burden.

Results:

Statistical analyses focused on correlating sensory impairments with cognitive performance, controlling for confounding variables such as age and disease duration revealed that the majority of participants exhibited significant sensory impairments in one or more modalities, with over two thirds of participants showing moderate to severe deficits in olfaction. A strong correlation was observed between olfactory dysfunction and lower MoCA scores. Participants with multisensory deficits demonstrated worse cognitive performance than those with single-modality impairments.

Conclusion:

These findings suggest sensory impairments, particularly olfaction are strongly correlated with cognitive decline in LBD, supporting the hypothesis that sensory deficits may serve as early indicators of disease progression and cognitive deterioration.

Neuropsychiatric symptoms in people with Lewy body diseases with and without dementia.

Panagiotis Alexopoulos [1], Adam Roche [2], Ella Caroll [2], Orla Keane [2], Ashay Panse [2], Iracema Leroi [2]

[1] University of Patras, Patras, Greece
[2] Trinity College Dublin, Dublin, Ireland

Background:

Individuals with Lewy body diseases (LBD), encompassing Parkinson's disease (PD) and cognitive disorders with parkinsonism, are often confronted with cognitive deficits and neuropsychiatric symptoms. They both pose a heavy burden for people with LBD and their care partners while the latter embody the main reasons for referral to old-age psychiatry services.

Methods:

This report refers to differences in the frequency of neuropsychiatric symptoms between individuals with dementia due to LBD and people with LBD but no dementia in a real life clinical setting.The analyses are based on a naturalistic cohort of 90 consecutive referrals to the 'Mind and Movement' clinic of the St. James's Hospital in Dublin, which is situated alongside Parkinson's and memory assessment services. Clinical diagnoses were established according to international diagnostic criteria for dementia due to PD (PDD), dementia with Lewy bodies (DLB) and mild cognitive impairment in PD (MCI-PD). Neuropsychiatric symptoms were captured with the widely employed Neuropsychiatric Inventory. The analyses considered the four-factor symptom clustering of neuropsychiatric symptoms, i.e. Hyperactivity, Affect, Apathy/vegetative and Psychosis. The statistical analyses relied on T-tests.

Results:

Of the 90 attendees of the Mind and Movement Clinic, 47 fulfilled the criteria for PDD or DLB, while the rest were diagnosed with MCI-PD or PD without cognitive impairment. Individuals with dementia were significantly older. Sex distribution did not differ across people with and without dementia. The former had significantly more psychotic symptoms. No significant differences were detected between the two groups in the other clusters of neuropsychiatric symptoms.

Conclusion:

As cognitive deficits advance and functional impairment surges, the frequency and severity of psychotic symptoms increase in people with LBD. This finding may be attributed to progression of the neurodegenerative changes but also to modifications of the antiparkinsonian medication due to increasing needs for dopamine substitution

Systematic Review of the Impact of Sex and/or Gender Considerations in Lewy Body Dementia (LBD).

Iracema Leroi [1, 2, 3], Gillian Daly [1, 3, 4] Heather Dignam [2, 4], Melanie Einsiedler [5], Isabelle Mastantuono [1], Mariapaola Barbato [5], Antonella Santuccione [5], Julie Martinkova [6], Anusha Mohan [2], Patrick Chirilele [2], Laura Castro [5]

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[4] University of Limerick, Limerick, Ireland
[5] Women's Brain Foundation, ., Switzerland
[6] Cognitive center, Department of Neurology, Charles University, Prague, Czech Republic

Background:

Dementia, particularly Lewy body dementia (LBD) is a global research priority in our ageing population. This systematic review aims to outline the impact of sex and gender on the wider dementia experience. It is known that sex and gender have an impact on many areas of medicine, and sex-based differences in biological processes have been shown to be estimated or assumed. The impact of sex and gender on symptoms and clinical manifestations has been seen in diseases such as Alzheimer's Disease (AD) for which 2 out of every 3 patients are female. This systematic review will look deeper into the role of sex and gender in LBD.

Sex and gender have an important role in the area of precision medicine, in a way that is not conceptualized by artificial intelligence (AI). This is because AI lacks the capacity to answer how or why questions and thus, will insert certain assumptions. Studies have shown that the analysis of sex and gender is something that will benefit the process of research, and this project will extend that benefit to dementia research with a focus on LBD.

Methods:

The protocol for this systematic review was registered with PROSPERO. A systematic review was completed following PRISMA guidelines. Covidence was used to complete title and abstract screening, data extraction was completed using an excel form, and risk of bias assessment was completed using the MMAT.

Results:

The differences seen by the process of this systematic review reinforce the importance of sex and gender based representation and considerations in LBD clinical trials, in order to best serve the LBD community.

Conclusion:

There is an important impact of sex and gender on many components of LBD. These impacts span a number of aspects of the LBD experience, and this should inform future research priorities.

Pathology in DLB

Oral Abstracts

GP2: enabling global genetics research

Andrew Singleton

Background:

defining the genetic basis of disease is a fundamental step in understanding the underlying disease mechanism(s) and, subsequently, in creating mechanistic-based therapeutics. Genetics is not only confined to understanding the basis of disease as a whole, but will also serve as a component of predicting disease, predicting course, and matching therapeutic to mechanism. While genetic factors play a significant role in neurodegenerative disease, the full spectrum of genetic risk remains unknown and our understanding of the genetic basis of neurodegenerative disease in populations outside those of Northern European ancestry has been limited. To realize the promise of precision therapeutics and to ensure equity, we must understand the genetics of neurodegenerative disease across ancestrally diverse populations

Methods:

The Global Parkinson's Genetics Program (GP2) is a large-scale international collaboration that aims to identify novel genetic risk factors for neurodegenerative disease. The program comprises an international collective of hundreds of researchers from around the World and includes major training, networking, and analytical components. The project leverages state-of-the-art genetics methods to uncover the basis of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome in ancestrally diverse populations worldwide. The program will generate and analyze data on more than 250,000 individuals.

Results:

GP2 has already generated and deployed data on more than 70,000 individuals. GP2 has successfully identified numerous new genetic loci associated with neurodegenerative disease, including variants largely unique to traditionally underserved populations. These findings have expanded our understanding of the genetic architecture of PD and provided insights into the biological pathways involved in disease pathogenesis.

Conclusion:

GP2 represents a significant step forward in understanding the genetic basis of PD and related neurodegenerative diseases. The findings from this project have important implications for developing new diagnostic tools, therapeutic interventions, and personalized medicine approaches for neurodegenerative disease.

Modeling Lewy Body Disease with SNCA Triplication iPSC-Derived Cortical Organoids and Identifying Therapeutic Drugs

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Background:

Aggregated α-synuclein (α-SYN) proteins, encoded by the *SNCA* gene, are hallmarks of Lewy body disease (LBD), affecting multiple brain regions. However, the specific mechanisms underlying α-SYN pathology in cortical neurons, crucial for LBD-associated dementia, remain unclear.

Methods:

We investigated two iPSC lines from LBD patients with *SNCA* triplication and two from healthy controls, differentiating them into cortical organoids. After 8 weeks of culture, we analyzed total and phosphorylated α-SYN levels using biochemical methods and size exclusion chromatography to determine the size distribution of α-SYN species. Single-cell RNA sequencing (scRNA-seq) identified molecular pathways linked to α-SYN pathogenesis in the organoids, while functional validation included mitochondrial stress testing with Seahorse and neuronal activity assessment using a multi-electrode assay (MEA). We further compared these findings to single-nucleus RNA sequencing (snRNA-seq) data from human superior temporal cortex samples from normal and LBD brains. Differentially expressed genes (DEGs) were validated in organoids from isogenic iPSC lines and postmortem human brains. Finally, we screened 1,280 FDA-approved drugs for their ability to inhibit α-SYN seeding activity in Real-Time Quaking-Induced Conversion (RT-QuIC) assays, testing promising candidates on *SNCA* triplication organoids.

Results:

We observed elevated soluble and phosphorylated α-SYN levels, along with insoluble α-SYN aggregates, in *SNCA* triplication organoids. Approximately 45% of α-SYN species were at 55 kDa, consistent with human brain samples. scRNA-seq revealed higher *SNCA* expression in excitatory neurons, with DEGs linked to synaptic and bioenergetic dysfunctions validated through Seahorse and MEA assays. Four drug candidates—Entacapone, Tolcapone, Phenazopyridine Hydrochloride, and Zalcitabine—reduced α-SYN aggregation and improved mitochondrial function in the *SNCA* triplication organoid models. Computational modeling showed that these four drugs inhibit α-SYN assembly by inducing conformational changes in key amino acids Lys43 and Tyr39 within the binding site.

Conclusion:

Our findings establish human cortical LBD models and suggest novel therapeutic drugs targeting α-SYN aggregation for LBD and its associated dementia.

Accumulation of Lewy-related pathology starts in middle age and may be more common than previously thought - lessons from neuropathological population studies

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Background:

Neuropathological population studies provide unbiased information on the frequencies of diseases in populations. When effective treatments against neurodegenerative diseases become a reality, it will be important to know the frequencies of diseases and their subtypes in different age groups and the age these pathologies begin to develop.

Methods:

To investigate the occurrence of Lewy-related pathology in the general population, we assessed two internationally unique population autopsy cohorts collected from Southern Finland: the Tampere Sudden Death Study (TSDS) and the Vantaa 85+ study. TSDS includes 600 unselected forensic autopsies on individuals aged 16–95 yrs living outside hospital institutions, representing 20% of all deaths in the region during the timeframe of the study collection. The Vantaa 85+ study includes all subjects aged 85 + living in the city of Vantaa in 1991, of whom 50% were autopsied (n=300). Alpha-synuclein immunohistochemistry (5G4 antibody) was performed on a large collection of tissue samples from the CNS and periphery.

Results:

In the forensic TSDS dataset, Lewy-related pathology was present in 9% of subjects aged 50+ without clinical Lewy Body Disease/ Parkinson's disease diagnosis. The youngest case was 54 years, and the frequency of Lewy-related pathology increased with age. In the population-based Vantaa 85+ study, Lewy-related pathology was present in 41% of the population aged 85+, and two common anatomically distinct subtypes, consistent with the body first vs. brain-first hypothesis, were seen: the body-first type was found in 27% and the brain-first type in 13% of the whole population.

Conclusion:

Accumulation of Lewy-related pathology starts in middle age and may be more common than previously thought. At least two common subtypes of Lewy-related pathology exist in the oldest old population.

Investigating the effect of mixed pathologies on neuropathological distribution in dementia with Lewy bodies

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Background:

Dementia with Lewy bodies (DLB) is neuropathologically defined by inclusions of α-synuclein (α-syn). However, concomitant Alzheimer's disease (AD) pathologies, hyperphosphorylated tau (HP-*T*) and β amyloid, are observed frequently at *post-mortem* examination, with 50-70% of DLB cases found to have medium to high- level of AD neuropathologic change. Mixed pathologies are associated with an accelerated cognitive decline, which can make diagnosis challenging. An increased burden of all three pathologies in end- stage dementia suggests a potential synergistic interaction between these proteins and is supported by studies that demonstrate α-syn and HP-*T* are co-localised. Proteins can undergo numerous alterations, which can affect their structure and enhance toxicity, however little is known regarding the distribution pattern of post-translational modifications (PTMs) of α-syn and tau and how this may affect disease progression.

Methods:

Using tissue microarray (TMA) slides that incorporate 15 anatomically distinct brain regions we investigated if a number of PTMs of α-syn and tau (i.e α-syn phosphorylated at serine 129, MC1, CP13, Alz 50 and PHF-1) are frequently co-localised and are predictors of neuropathological spread and clinical disease progression in DLB by using human *post-mortem* brain tissue.

Results:

Distribution and burden of a syn pSer129 and CP13 differ between DLB cases with low and high tau pathology. DLB cases with high NFT burden have significantly more a syn pSer129 in the amygdala and entorhinal cortex. CP13 load in the amygdala and entorhinal cortex are also increased in DLB with high NFT compared to AD cases.

Conclusion:

Different distribution patterns of a syn and tau in the brains of DLB patients with AD co pathology suggest discrete subtypes can emerge and will have important implications for patient stratification for clinical trials, biomarker assessment, and ultimately affect how we treat these patients when disease modifying therapies are available.

Substantia nigra iron deposition in Lewy Body disease: an imaging and neuropathology study

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Background:

Parkinson's disease and dementia with Lewy bodies are characterized by abnormal iron deposition in the substantia nigra (SN), which can be measured with quantitative susceptibility mapping (QSM) on MRI. However, neuropathologic validation of the increased QSM in the SN associated with Lewy body disease (LBD) is lacking. In this study we compared iron deposition in the SN as measured with quantitative susceptibility mapping (QSM) on antemortem MRI between individuals with and without Lewy-related pathology at autopsy.

Methods:

We performed a retrospective cohort study including 54 participants who underwent autopsy and antemortem MRI with QSM. Cases were classified as LBD-present (n=13) if they had Lewy-related pathology and LBD-absent (n=42) if they did not have Lewy-related pathology. QSM was calculated for the whole SN and the two sub-regions: pars compacta (SNc) and pars reticulata (SNr). Non-parametric Wilcoxon rank-sum tests were used to compare SN QSM values between LBD-present and LBD-absent cases. Area under the ROC curve (AUC) analyses tested the accuracy of SN QSM values to distinguish the two groups. Associations of QSM values in the SN and its sub-regions with clinical features were tested with Spearman's correlations.

Results:

The LBD-present group had higher QSM values in the SNc (p=0.008) than the LBD-absent group with no differences in SNr. QSM values of the SNc distinguished LBD-present and LBD-absent cases with good accuracy (AUC=0.74) and correlated with the presence of parkinsonism and parkinsonism severity.

Conclusion:

This study provides neuropathologic confirmation of the utility of SNc QSM as an in-vivo biomarker of Lewy-related pathology. Imaging evidence of abnormal iron deposition in the SNc could potentially serve as a biomarker for inclusion in emerging research frameworks aimed at defining individuals with LBD based on their biological characteristics. Ultimately, this could facilitate more precise diagnoses and guide treatment strategies in LBD.

Quantitative Analysis of Misfolded Alpha-Synuclein: A Biomarker for Synucleinopathies

Omar El-Agnaf

Diagnosing α-synucleinopathies and assessing target engagement in trials is hindered by the lack of reliable biomarkers. Here, we introduce a first-in-kind quantitative, highly sensitive, and disease-specific diagnostic assay, named Seeding Amplification mmunoAssay (SAIA), developed and validated to detect synucleinopathy-linked disorders. To this end, we used wide range of specimens, including 37 brain homogenates (BH) and 574 cerebrospinal fluid (CSF) samples from subjects with diverse synucleinopathy disorders, non-synucleinopathy diseases, idiopathic REM sleep behavior disorder (iRBD), and controls. SAIA generated robust amplification results detecting disease-related α-synuclein seeds in BH samples at attogram levels, as referenced to preformed fibrils of α-synuclein. Furthermore, we conducted side-by-side comparisons between SAIA and a traditional Seeding Amplification Assay (SAA), which revealed high concordance. Further, SAIA distinguished synucleinopathies from non-synucleinopathies and controls with sensitivities and specificities ranging between 80-100% and area under the curve values exceeding 0.9. Importantly, the assay revealed a positive correlation between CSF α-synuclein seeds and severity in motoric signs of Parkinson's disease (PD), as measured by scores on the Unified Parkinson's Disease Rating Scale (UPDRS-III) in two out of the three cohorts studied. SAIA also accurately identified 24/24 (100%) iRBD cases, considered a prodromal state of PD, with 100% sensitivity and 80% specificity. Further optimization of SAIA through timepoint analyses revealed that shorter incubation times enhanced the assay's specificity for distinguishing MSA from PD highlighting the potential for improved differentiation between specific synucleinopathies. In conclusion, SAIA represents a novel powerful high throughput method to screen, diagnose and monitor synucleinopathy disorders in living subjects, offering significant improvements over existing methods to assist clinical trials that aim to test disease modifying interventions.

Poster Abstracts

Alzheimer's co-pathology exacerbates disease severity in DLB but not in MSA: a comparative analysis

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Background:

Concomitant Alzheimer's disease (AD) pathology may contribute to disease severity in synucleinopathies, such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). This study aims to clarify the role of AD co-pathology in clinical and neuropathological severity in synucleinopathies.

Methods:

%Area of alpha-synuclein (KM51), amyloid-beta (6F/3D) and p-tau (AT8) pathology was assessed in pure DLB (n = 15), mixed DLB+AD (n = 35), pure MSA (n = 61) and mixed MSA+AD (n = 9) donors in limbic and neocortical brain regions using immunostaining and quantitative image analysis. Additionally, neuropathological staging and retrospective clinical characterization of the cohort was performed.

Results:

Co-pathology loads were higher in all regions in mixed DLB than in mixed MSA cases. Mixed DLB cases had a higher alpha-synuclein load in the amygdala than in pure DLB (p = 0.049), while no differences existed between MSA cases. In addition, alpha-synuclein load associated with amyloid-beta and p-tau loads, specifically in the amygdala, for DLB (p < 0.001), but not for MSA. A shorter disease duration was observed in mixed DLB than in pure DLB (p = 0.020), but was not associated with AD co-pathology load. Cognitive impairment associated mainly with amyloid-beta and p-tau pathology load in both synucleinopathies (p < 0.001). Concomitant pathology in MSA was related to age at onset in MSA (68±9 in mixed vs. 59±9 years in pure MSA cases, p = 0.005), but not in DLB. In addition, 90% of the mixed synucleinopathies were APOE-ε4-carriers, against 32% of the pure synucleinopathies (p < 0.001).

Conclusion:

Synergistic co-pathology in DLB contributes to disease severity, while co-pathology in MSA is less frequent and mainly related to age and APOE-ε4 genotype. The amygdala is most severely affected in mixed DLB+AD, but not in MSA. Our study highlights the regional differences in AD co-pathologies in the spectrum of synucleinopathies.

An epigenomic assessment of α-Synucleinopathy and co-pathologies in Lewy body dementias.

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Background:

Lewy body diseases (LBD) are a group of neurodegenerative disorders that are characterized by the presence of abnormal protein deposits called α-Synuclein in the brain. Epigenetic mechanisms, molecular processes that modify gene expression without changing the underlying genetic sequence, represent a potential area of contribution that has been under-researched to date.

Methods:

DNA methylation was profiled using the Illumina EPIC array for three independent cohorts in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC). The UK Brain Bank Cohort (UKBBN, n = 805; 419 donors; PFC and ACC), the Netherlands Brain Bank Cohort (NBB, n = 322; PFC) and the Brain's for Dementia Research Cohort (BDR, n = 124; PFC), to give a total sample size of 1,251. Epigenome wide association analyses were conducted in each cohort, controlling for confounding variation, ensuring no evidence of genomic inflation and meta analysed in a full cohort fixed-effect inverse weighted model for significant association with LB pathology.

Results:

Meta analyses identified three differentially methylated positions (DMPs) with genome wide significant association ($P < 9 \times 10\text{-}8$), including sites annotated to UBASH3B and PTAFR and an intergenic loci cg13847853. A further 20 DMPs were associated at a false discovery rate (corrected $P < 0.05$), including HDAC4, GRM1 and PTPRN2. Subsetting meta-analysis to samples with LB pathology in the absence of significant Alzheimer's pathology (n = 798) showed attenuated significance, with only cg13847853 passing multiple testing correction. However significant correlation of effects sizes (100% concordant effect direction) was observed between both analyses.

Conclusion:

We conducted the largest meta-analysis of DNA methylation changes related to LB pathology in brain to date, identifying several DMPs significantly associated with the pathology. We provide evidence for a number of previously associated genes, along with novel epigenetic associations.

The Syn-D Study: Detection of Cutaneous Phosphorylated Alpha-Synuclein in Patients with Mild Cognitive Impairment

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Background:

Dementia with Lewy bodies (DLB) is a neurodegenerative disease and is one of four "synucleinopathies"; diseases characterized by progressive accumulation of a misfolded protein, phosphorylated a-synuclein (PSYN). Alzheimer's disease (AD) is characterized by the progressive accumulation of beta-amyloid and tau proteins, but up to 30% of patients may exhibit synuclein co-pathology in the central nervous system. An important unmet need exists for a validated, simple, reproducible marker of synuclein pathology in neurogenerative diseases at the prodromal stage.

Objectives

To quantify the deposition of cutaneous PSYN in patients with suspected DLB and AD at the mild cognitive impairment (MCI) stage and track clinical and pathologic changes over time.

Methods:

After informed consent, detailed neurologic examinations, medical and neurological history review, cognitive evaluation, orthostatic vital signs and questionnaires were completed. An independent expert panel of reviewers, blinded to pathology, reviewed de-identified medical records to confirm clinical diagnoses. Skin biopsies at the distal leg, distal thigh and posterior cervical sites were performed. Phosphorylated alpha-synuclein immunostaining was performed blinded to any clinical data.

Results:

To date, 98 subjects have been enrolled (44 with MCI-AD and 54 with MCI-DLB) from 15 study sites across the United States out of an anticipated 100 subjects. The mean age of the enrolled subjects is 73.5±6.4 years. Of the 98 enrolled subjects, 57/98 are P-SYN positive (58%). Complete unblinded baseline data will be presented at the conference.

Conclusion:

Skin biopsies are a simple, low-risk outpatient procedure to test for phosphorylated alpha-synuclein as a diagnostic biomarker for the synucleinopathies. In this study of patients with suspected DLB and AD at the MCI stage, 55% of all subjects have MCI-DLB, and 58% of all subjects have PSYN on skin biopsy. Although still blinded the data suggest that skin biopsy is an early, sensitive marker of synuclein detection prior to a clinical diagnosis of dementia.

Cellular response to alpha-synuclein: Identification of cofactors of alpha-synuclein aggregation.

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Background:

The aggregation of alpha-synuclein (αSYN) is a fundamental process in the pathogenesis of Lewy body dementias. While recent studies have revealed key molecules that comprise end-stage Lewy pathology, the processes and players that drive the accumulation of αSYN into Lewy pathology remain undefined. The goal of this project is to advance the understanding of the role that αSYN plays in disease pathogenesis and progression of Lewy body dementias (LBD) by discovering molecular cofactors of αSYN and defining the αSYN aggregate interactome. We hypothesize that the αSYN molecular environment contributes to LBD processes and that proximity proteomics will capture the molecular microenvironment surrounding αSYN and reveal key players in pathological processes.

Methods:

Proximity-dependent biotin identification (BioID) technology fuses a promiscuous biotin ligase enzyme (BirA*) to a protein of interest in living cells, in this case αSYN. This facilitates biotinylation of proximal and interacting proteins that come within 100Å of αSYN as it undergoes the aggregation process. Cells expressing αSYN fused with the full-length BirA* enzyme (αSYN-BirA*), or inactive halves of BirA* (referred to as split-αSYN-BirA*) were treated with human αSYN PFFs and biotin. Proximal biotinylated proteins were then isolated via affinity purification and identified by mass spectrometry.

Results:

After filtering, a total of 1746 peptides corresponding to 708 distinct biotinylated proteins were identified. 108 peptides were identified to be significantly associated with full-length αSYN-BirA* and split-αSYN-BirA*, corresponding to 9 uniquely proximal to αSYN-BirA* and 17 uniquely proximal to split-αSYN-BirA*. The addition of PFFs identified 161 significantly associated peptides (31 proteins) uniquely associated with aggregating or aggregated αSYN.

Conclusion:

We have identified peptides uniquely associated with monomeric, oligomeric, and aggregating αSYN. This unbiased proteomics screen for biotinylated peptides has revealed potentially key cofactors in the aggregation process. Identified cofactors are currently undergoing validation.

Nuclear alpha-synuclein, DNA damage and damage derived cytoplasmic DNA in the pathology of Dementia with Lewy bodies.

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Background:

Alpha-synuclein, predominately a synaptic protein, is also present in the nucleus, where it may regulate DNA damage repair. Our prior work has demonstrated the pathological modification of nuclear aSyn as part of the cellular pathology of Dementia with Lewy bodies (DLB). Here we report on associated nuclear aSyn seed amplification, DNA damage, proteomic changes and provisional work into the pathological role of DNA damage derived cytoplasmic DNA (cytoDNA).

Methods:

Human post-mortem temporal cortex tissue from DLB and control cases were used throughout. Nuclear isolates, as per subcellular fractionation were subject to seed amplification assays (SAA) and protein analysis via western blot and label free proteomics. Fixed human and DLB mouse model (A30P) cortical tissue were probed for DNA damage and aSyn pathology via immunohistochemistry.

Results:

Nuclear fractionates from DLB cases demonstrated elevated phosphorylated aSyn compared to controls, alongside robust aSyn aggregation in SAA. Pathology coincided with increased DNA double strand breaks and marked overexpression of proteins associated with double strand break and base-excision repair pathways. Strikingly, multiple genomic DNA damage markers were enriched within cortical LBs and on-going work into DNA damage derived cytoDNA raise the potential for such DNA to facilitate aSyn aggregation. Critically, DNA damage markers were recapitulated in A30P mice, at a pre-symptomatic age, implicating genomic DNA damage as an early occurring disease mediated cellular insult.

Conclusion:

Combined the work highlights genomic DNA damage as a key pathological mediator in DLB neuropathology and calls for future investigation into relevant therapeutic interventions.

Insights into alpha-synuclein pathology from rare paediatric sphingolipid storage disorders

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Background:

Alpha-synuclein aggregation is thought to be a key pathogenic event in the aetiology of Lewy body diseases (LBD); however, the mechanisms underlying it remain unknown. A number of risk genes for LBD encode lysosomal enzymes that, when present in a bi-allelic state, underlie a range of predominantly paediatric lysosomal storage disorders characterised by the accumulation of sphingolipids. These include *GBA1* (Gaucher disease), *GALC* (Krabbe disease) and *ARSA* (metachromatic leukodystrophy; MLD). We sought to determine whether the association between these genes and LBD risk is mediated through an effect on alpha-synuclein aggregation by evaluating alpha-synuclein pathology in Krabbe disease and MLD.

Methods:

Post-mortem human brain tissue was obtained from Krabbe disease (N=4, age 10-15 months old) and MLD cases (N=5, aged 3-33 years old), in addition to those from age-, sex- and ethnicity- matched control cases. Immunohistochemistry against alpha-synuclein, amyloid-beta and tau pathology were performed for histological analysis and alpha-synuclein seeding aggregation assays (SAA) were performed on frozen tissues.

Results:

Krabbe disease and MLD cases manifested evidence of alpha-synuclein pathology, and this was primarily present as granular intraneuronal deposits and most commonly observed in older cases with MLD. SAA analysis indicated alpha-synuclein in Krabbe disease and MLD was seed-competent and generated fibrils reminiscent of those identified from LBD tissues.

Conclusion:

Alpha-synuclein pathology in such young cases indicates a direct relationship between alpha-synuclein aggregation and the sphingolipid dyshomeostasis associated with Krabbe disease and MLD. It is tempting to speculate that deficient lysosomal function and/or the accumulation of substrates that can potentiate alpha-synuclein aggregation could be responsible for alpha-synuclein aggregation. Our preliminary analysis of alpha-synuclein neuropathological burden in LBD cases with *GALC* and *ARSA* variants (N=37) indicates *ARSA* variants were associated with more widespread Lewy body pathology, suggesting these pathways may have important implications for alpha-synuclein aggregation in LBD.

Patterns of tau, amyloid and synuclein pathology in ageing, Alzheimer's disease and synucleinopathies

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Background:

Alzheimer's disease (AD) is defined by hyperphosphorylated tau (HP-tau) and β-amyloid deposition. Lewy body (LB) dementia, including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is characterised by α-synuclein aggregates. HP-tau and β-amyloid can also occur as copathologies in LB dementia, where a diagnosis of $_{mixed}$AD/DLB is made if present in sufficient quantities. We hypothesised the spread of these proteins selectively affects vulnerable areas that relates to pre-mortem clinical characteristics. Our aim was to investigate the spatial distributions of quantitative pathology from tissue microarray (TMA) post-mortem samples across healthy aging, AD and LB dementia.

Methods:

The study involved 159 diagnosed human post-mortem brains (48 controls, 47 AD, 25 DLB, 20 $_{mixed}$AD/DLB, 19 PDD). The burden of HP-tau, β-amyloid and α-synuclein was quantitatively assessed in selected areas. Principal components (PC) analysis was applied to determine the pattern nature of these pathologies. Further analyses explored associations of pathological patterns with cognitive and symptom variables.

Results:

Cortical ($^{tau}PC_1$) and temporolimbic ($^{tau}PC_2$) patterns were observed for HP-tau. For β-amyloid, a global brain pattern ($^{amyl}PC_1$) was identified. For α-synuclein, four patterns emerged: 'posterior temporal – occipital ($^{syn}PC_1$)', 'anterior temporal–frontal ($^{syn}PC_2$)', 'parieto–cingulate–insula ($^{syn}PC_3$)', and 'frontostriatal–amygdala ($^{syn}PC_4$)'. In dementia, cognitive measures correlated with $^{tau}PC_1$, $^{tau}PC_2$ and $^{amyl}PC_1$ pattern scores ($p \leq 0.02$) but not with α-synuclein parameters. Mediation analysis revealed that in the presence of $^{amyl}PC_1$, $^{tau}PC_1$ had a direct effect on global cognition in dementia ($n=65$, $p=0.04$), while $^{tau}PC_1$ mediated the relationship between $^{amyl}PC_1$ and cognition through the indirect pathway ($^{amyl}PC_1$ --> $^{tau}PC_1$ --> global cognition) ($p<0.05$). In synucleinopathies, $^{syn}PC_1$ and $^{syn}PC_4$ pattern scores were associated with visual hallucinations and motor impairment, respectively ($p=0.02$).

Conclusion:

In dementia, analyses revealed different pathways for HP-tau and β-amyloid on cognitive outcomes. Several core symptoms of LB dementia were correlated with specific α-synuclein topographies that may point to the clinical phenotype.

Investigation of the association between angiotensin receptor blocker (ARB) use and post-mortem dementia pathology using the UK Brain Banks Network (UKBBN) dataset.

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Background:

A recent international Delphi consensus by the RENEWAL study group identified angiotensin receptor blockers (ARB) as a potential drug class to be repurposed for Lewy body dementia treatment (O'Brien et al., 2022). ARBs and angiotensin-converting enzyme inhibitors (ACEI) are two drug classes with comparable efficacy in treating high blood pressure, but only ARBs are expected to protect against dementia. This study aimed to investigate whether ARB use during life is associated with lower post-mortem dementia neuropathology compared to ACEI use.

Methods:

All cases with a record of ACEI or ARB use, irrespective of dementia pathology (n=340) were extracted from the UKBBN dataset. Neuropathological staging systems were binarized into significant and non-significant neuropathology (Braak Lewy body stage >0, Thal amyloid phase >3, Braak neurofibrillary tangle stage >3, and CERAD neuritic plaque score 'moderate density' or 'high density'). Binomial logistic regression was carried out with age at death and sex as covariates. In 58 cases, alpha-synuclein, amyloid-beta, and tau in the entorhinal cortex and CA1 region of the diagnostic slides were quantified by % area stained using QuPath software.

Results:

In the UKBBN dataset, the ARB group had a numerically lower percentage of cases with significant neuropathology compared to the ACEI group in all dementia neuropathological staging systems (Any significant neuropathology 57.5% vs. 70.6%, p=0.025; Braak Lewy body stage 16.0% vs. 23.2%, p=0.170; Thal amyloid phase 42.4% vs. 51.9%, p=0.114; Braak neurofibrillary tangle stage 36.6% vs. 45.9%, p=0.122; CERAD neuritic plaque score 34.9% vs. 44.4%, p=0.126). For the image analysis, the mean percentage of alpha-synuclein stained area in the entorhinal cortex was lower in the ARB group compared to the ACEI group (2.39% vs. 5.59%, p=0.05).

Conclusion:

This study provides evidence that ARB use may be associated with lower levels of dementia neuropathology, particularly alpha-synuclein. These findings should be replicated in larger cohorts.

Beyond proteopathy: lipid dyshomeostasis in Lewy body dementia

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Background:

Lewy body dementia (LBD) is a relatively common form of dementia characterised by accumulations of the protein alpha-synuclein (αSyn) into intraneuronal deposits termed Lewy bodies. Sphingolipid dyshomeostasis has long been implicated in LBD as genes encoding sphingolipid catabolic enzymes are risk genes for LBD, and sphingolipids alter αSyn conformation and aggregation rate. However, it is not yet clear how changes in sphingolipid metabolism modulate αSyn deposition in LBD.

Methods:

We profiled 120 lipids spanning the entire sphingolipid degradation pathway, from globoside to ceramide, using LC-MS/MS in the cingulate cortex and lateral temporal cortex in post-mortem tissue from LBD patients (N=20) and controls (N=20). We interrogated the relationship between sphingolipid dyshomeostasis and αSyn, amyloid-beta (Aβ) and tau pathology by correlating abundance of sphingolipids with pathological burden in post-mortem brain tissue through immunohistochemistry, and quantified soluble and insoluble αSyn through Western blot.

Results:

After regression against age and sex, we identified a number of sphingolipid species were elevated, notably including many of those associated with LBD risk genes, such as hexosylceramides/hexosylsphingosines and sphingomyelins. Network analysis indicated these lipids are implicated in membrane dynamics, alterations in which have previously been shown to regulate the aggregation of αSyn. A number of sphingolipids were significantly correlated with αSyn pathological burden, including hexosylceramides and sphingomyelins. Consistent with previous studies in Alzheimer's disease, the abundance of GM3 ganglioside was significantly correlated with Aβ levels.

Conclusion:

These findings suggest, for the first time, that sphingolipid homeostasis is altered in LBD. Furthermore, LBD brains manifest changes to a number of sphingolipids associated with genetic risk of LBD and, in some cases, their abundance is correlated with the severity of αSyn pathology. Taken together, these findings suggest that sphingolipid dyshomeostasis is implicated in LBD, where it may be associated with αSyn pathology.

Alpha-Synuclein in the White Matter of Brains with Lewy Body Dementia

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Background:

Although Lewy body dementia (LBD) is a disease in which grey matter alpha-synuclein (αSyn) pathology is typically observed, a number of risk genes are predominantly expressed in oligodendrocytes, e.g. *GBA1*, *LRRK2*, *GALC* and *ARSA*. Some such genes, such as *GALC* and *ARSA*, whilst associated with LBD risk in heterozygosity also underlie paediatric white matter diseases in a bi-allelic state; notably, we have identified αSyn pathology with features reminiscent of that in LBD in such cases. Therefore, there are compelling reasons to indicate changes to oligodendrocytes could contribute to LBD aetiology.

Methods:

To evaluate αSyn pathology in LBD we performed quantitative analysis of αSyn and pS129 in cingulate cortex (CiCtx) and inferior temporal cortex (TCtx) from cases with LBD (n=20) and controls (n=20). Immunofluorescent analysis was performed to determine whether white matter αSyn pathology was observed within oligodendrocytes, and to examine whether it is associated with reduced expression of lysosomal enzymes and mitochondrial dysfunction associated with LBD.

Results:

αSyn and pS129 were present in white matter (CiCtx and TCtx) in variable quantities, significantly more than in controls, though less than in grey matter. Notably, the abundance of αSyn was not correlated between grey and white matter. Immunofluorescent analysis is on-going, though preliminary results indicate the abundance of arylsulphatase A (ASA; encoded by *ARSA*) is lower in LBD white matter compared to controls.

Conclusion:

These results constitute the first quantitative analysis of αSyn aggregates in the white matter of brains with LBD. The lack of correlation between αSyn in both regions suggests white matter pathology may occur independently of that in the grey matter. Although preliminary, lower abundance of ASA in oligodendrocytes in LBD could provide a tangible link between risk genes and αSyn pathology.

Impact of Alzheimer's Co-Pathology on Basal Forebrain Atrophy and Cognitive Decline in Dementia with Lewy Bodies

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Background:

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), with significant pathological overlap between the two conditions. The basal forebrain (BF), particularly the Nucleus Basalis of Meynert (NbM), is crucial for cholinergic activity and cognitive functions, and its atrophy has been documented in both DLB and AD. However, the impact of AD co-pathology on BF atrophy and its relationship with neurodegeneration and cognitive decline in DLB patients remains underexplored.

Methods:

This study included 40 DLB patients and 40 healthy controls (HC) from the Center for Neurodegenerative Diseases, University of Bari. Participants underwent neuropsychological evaluations, 3 Tesla MRI scans, and CSF biomarker or amyloid PET assessments. DLB patients were categorized based on the presence (DLB AD+) or absence (DLB AD-) of AD co-pathology. BF atrophy, along with hippocampal volume and mean cortical thickness, was analyzed using ANCOVA, adjusted for age, sex, and total intracranial volume. Mediation analysis assessed the indirect effects of AD co-pathology and BF atrophy on neurodegeneration (hippocampal volume and cortical thickness) and cognitive function.

Results:

DLB patients exhibited significant BF atrophy compared to HC ($p<0.001$), with DLB AD+ patients showing greater BF atrophy ($p=0.046$) and reduced mean cortical thickness ($p=0.017$) compared to DLB AD-, while hippocampal volumes did not significantly differ between groups. Significant correlations were found between BF volume and the pTau/Aβ42 ratio ($r=-0.468$, $p=0.005$), as well as between BF volume and MMSE scores ($r=0.624$, $p<0.001$). Mediation analysis revealed that BF atrophy mediated the relationship between the pTau/Aβ42 ratio and neurodegeneration, as well as the relationship between neurodegeneration and cognitive impairment.

Conclusion:

AD co-pathology in DLB exacerbates BF atrophy, correlating with cognitive decline. These findings emphasize the need to consider AD co-pathology in evaluating neurodegeneration in DLB, suggesting future studies should explore targeted interventions to address this pathological overlap.

Mayo Clinic brain bank for Lewy body disorders

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Background:

The brain bank at Mayo Clinic in Florida houses 1,957 brains with Lewy body pathology. All cases were evaluated by a single neuropathologist using a standardized protocol for tissue sampling and tissue processing. The majority of brains werefrom two states – Florida (>900) and California (>250) – but brains with Lewy body disorders were from every state in the USA . The majority (>90%) have fixed tissue, paraffin blocks and glass slides. The routine sampling includes 18 different brain regions. All cases undergo histologic studies, including immunohistochemistry with antibodies to phospho-tau, TDP-43 and α-synuclein.

Methods:

All cases have quantitative analyses of Alzheimer type pathology with thioflavin S fluorescent microscopy. Over 95% of the cases had at least some Alzheimer copathology. The majority (64%) were men. Only 6% were non-white. The average age at death was 82 ± 8 years. The average disease duration was 8 ± 6 years. Only 31% had a positive family history of neurologic disease. The most common antemortem clinical diagnoses were Parkinson disease (N=665), dementia with Lewy bodies (N=525), Alzheimer's disease (N=422) and Parkinson disease dementia (N=344). There were 90 cases with antemortem clinical diagnoses of multiple system atrophy.

Results:

The majority of cases (67%) had relatively mild Alzheimer type co-pathology with a median Braak neurofibrillary tangle Stage of IV and a Thal amyloid phase of 4 or less. There was evidence of cerebrovascular pathology in 30% of cases, and 33% had TDP-43 pathology most consistent with limbic predominant age-related TDP-43 encephalopathy.

Conclusion:

Of the 870 cases on which apolipoprotein E genotype data is available 52% were carriers of at least one E4 allele. Many of the cases have been part of multicenter genetic studies of Lewy body disorders, including genome wide association studies and whole genome studies that have implicated genes in the etiology of Lewy body disorders.

Profile of cerebral T cells in dementia with Lewy bodies

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Background:

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia, behind Alzheimer's disease (AD). Neuroinflammation has been implicated in the aetiology of AD, with involvement of innate and adaptive immunity. A potential role for adaptive immunity is supported by T cell recruitment into the AD brain, however, this has not yet been investigated in DLB.

Methods:

A human *post-mortem* brain study was conducted to characterise T cell populations in 30 DLB cases and 29 controls using immunohistochemistry. Specific markers were used to identify T cell populations: CD4 (helper), CD8 (cytotoxic), Foxp3 (Treg), Tbet (Th1/Tc1), and GATA3 (Th2/Tc2). T cells were quantified and categorised by location (grey matter or white matter) and compartment (parenchyma or perivascular). Markers of neuropathology and inflammation were correlated with T cell markers.

Results:

Increased CD4+ T cells ($p=0.041$) and Tbet+ T cells ($p=0.048$) were detected in the grey matter parenchyma in DLB. Tbet+ T cells were associated with increased expression of the inflammatory markers, CD64 and CD32b in DLB ($p<0.001$). Despite no change in CD8+ T cells between groups, their presence within grey matter in DLB was associated with increased expression of CD32b ($p<0.001$). No associations were found between T cell markers and markers of neuropathology. Analysis for GATA3 is in progress.

Conclusion:

The presence of CD4+ T cells in grey matter parenchyma suggests a role in DLB pathogenesis, with an increased Tbet+ T cell population supporting involvement of Th1 cells. Association with CD64 implies these T cells may communicate with microglia to induce proinflammatory responses. Interactions between T cells and neurons are inferred by associations with CD32b, potentially contributing to synaptic dysfunction. Further exploration of T cell subsets in the brain, cerebrospinal fluid and blood is warranted in DLB to improve our understanding of disease mechanisms and guide therapeutic strategies.

Markers of LRRK2 activity are associated with pathological protein aggregation in Dementia with Lewy Bodies and across neurodegenerative diseases

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Background:

Tau aggregation, in the form of neurofibrillary tangles and dystrophic neurites, is a commonly observed co-pathology in Dementia with Lewy Bodies (DLB). Recent evidence suggests leucine-rich repeat kinase 2 (LRRK2) may play a role in alpha-synuclein and tau pathology in DLB and other synucleinopathies, Mutations in the *LRRK2* gene cause autosomal dominant Parkinson's disease (PD), and both Lewy bodies and tau pathology are commonly observed in LRRK2 PD. To date, however, direct evidence linking LRRK2 to alpha-synuclein or tau pathology in human neurodegenerative diseases has not been described.

Methods:

Since PD-causing LRRK2 variants display increased kinase activity, we investigated whether levels of LRRK2 kinase activity markers correlate with alpha-synuclein and/or tau pathology by performing immunohistochemical labeling in brains from subjects with DLB, Alzheimer's disease (AD), and unaffected age-matched controls. We used phospho-LRRK2 S935 (pLRRK2) as a marker of LRRK2 levels, as well as phospho-Rab10 T73 (pRab10) and phospho-Rab12 S106 (pRab12) as markers of LRRK2 kinase activity.

Results:

We did not observe any significant change in pLRRK2-positive area in AD or DLB. However, we found that pRab12-positive area increases in AD and DLB, localizing to tau aggregates in AD and both tau aggregates and Lewy bodies in DLB. In addition, we observed labeling of granulovacuolar degeneration (GVD) in AD and DLB by both pRab10 and pRab12. We replicated this pRab12 GVD labeling in PS19 mice, which express human pathological P301S mutant tau that accumulates with age, demonstrating that pathological tau triggers GVD that is pRab12-positive.

Conclusion:

In conclusion, phosphorylation of Rab proteins by LRRK2 may play a role in GVD and Lewy body- and tau-associated neurodegeneration across neurodegenerative diseases. Future work will extend these findings to PD, test whether alpha-synuclein accumulation triggers pRab12-positive GVD in addition to tau, and perform double-labeling to confirm pRab12 localization to GVD, Lewy bodies and pathological tau in humans.

Interaction Between Phosphorylated Alpha-Synuclein and Cysteine String Protein Alpha in Synaptic Vesicle Dynamics

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Background:

Synucleinopathies are progressive neurodegenerative diseases that affect approximately 1% of people over the age of 60. These disorders are characterized by the presence of intracellular aggregates primarily composed of a small protein called alpha-synuclein (asyn). Within these Lewy bodies, the majority of asyn, roughly 90%, is phosphorylated at serine 129 (pS129) while in healthy brains, less than 1% of asyn is phosphorylated at this serine. These high levels of phosphorylation in brains of patients suggests that pS129 may play a critical role in pathology. Understanding the function of pS129-asyn in both healthy and diseased neurons is essential for unraveling the mechanisms of these disorders and developing effective interventions.

Methods:

To investigate this, I identified the protein interaction partners of pS129-asyn using co-immunoprecipitation and mass spectrometry.

Results:

Notably, clathrin and cysteine string protein alpha (CSPa), which is crucial for neuronal pre-synaptic maintenance, were among the main interacting proteins. Through immunohistochemistry and Airy Scan technology, we observed that pS129-aSyn and CSPa co-localize pre-synaptically in the brains of wild-type mice. We also found that reducing pS129-asyn levels led to a decrease in synaptic CSPa. Conversely, knocking down CSPa resulted in reduced levels of pS129-aSyn. Electrophysiological studies demonstrated that lower levels of pS129-asyn affect vesicle recovery after repeated firing, a finding corroborated by electron microscopy.

Conclusion:

Overall, our results reveal a significant correlation between CSPa and pS129-asyn in the regulation of pre-synaptic vesicle endocytosis. This data brings us closer to understanding the role of pS129-asyn in disease pathology.

The identification of alpha-synuclein pathology preceding clinical diagnosis of Lewy body disease – a systematic review

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Background:

The misfolding of α-synuclein (α-syn) is the pathological hallmark of synucleinopathies, encompassing Lewy body disease (LBD), multiple system atrophy (MSA) and pure autonomic failure (PAF). Pathological α-syn has been identified in the peripheral nervous system tissue of subjects with synucleinopathies and it is hypothesised that this develops prior to the clinical manifestation of disease. This systematic review aimed to investigate the temporal relationship between detection of peripheral α-syn and clinical or neuropathological diagnosis of synucleinopathies.

Methods:

A systematic search of Embase, MEDLINE, APA PsycINFO and Web of Science databases was conducted on 11/11/2023. Search terms were combinations of various synucleinopathies, peripheral organs and α-syn detection methods. All languages and timeframes were considered.

Results:

Thirteen studies of 6740 retrieved fulfilled inclusion criteria. Study designs included case reports (15%), prospective cohort studies (31%), retrospective case series (15%), retrospective cohort studies (31%) and a retrospective neuropathological cohort study (8%). These described 366 patients (n=185 Parkinson's disease (PD), n=1 PD dementia (PDD), n=12 dementia with Lewy bodies (DLB), n=43 unspecified LBD, n=124 idiopathic REM Sleep Behaviour Disorder (iRBD) and n=1 PAF) who had undergone peripheral tissue biopsy preceding diagnosis of a synucleinopathy. Tissues investigated included the gastrointestinal tract, salivary glands, skin, sural nerve and the gallbladder. Immunohistochemical (IHC) methods were utilised in all studies but significant methodological variation was observed between studies. The mean interval between α-syn detection and synucleinopathy diagnosis was 3.7 (SD± 2.4) years.

Conclusion:

There has been little investigation into the temporal relationship between peripheral α-syn pathology and diagnosis of synucleinopathies, particularly DLB. Heterogeneity in the methods by which α-syn positivity is determined precludes comparison of these studies. Large, retrospective cohort studies might present opportunities to investigate this temporal relationship, particularly since synuclein seeding amplification technology, has recently emerged as a sensitive alternative to IHC.

Hippocampal α-Synuclein Oligomers and Cognitive Trajectory in Dementia with Lewy Bodies

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Background:

Increasing evidence indicates that α-synuclein oligomers are toxic. We aimed to determine whether α-synuclein oligomers are associated with a rate of cognitive decline in prospectively assessed patients with dementia with Lewy bodies (DLB).

Methods:

Participants included 8 patients with autopsy-confirmed clinically probable DLB with 3+ years of longitudinal follow-up, a baseline Mini-Mental State Examination (MMSE) ≥ 24, and the final MMSE score obtained within 3 years of death. Examination of annualized rate of change in MMSE scores revealed 4 patients with a drop of 4 or more points (rapid decline group) and 4 patients with a drop of 2 or fewer points (slow decline group). Immunohistochemistry and digital pathology were conducted and examiners were blinded to clinical status. α-synuclein oligomers and Lewy-related pathology were detected by α-synuclein proximity ligation assay staining and immunohistochemistry with phosphorylated α-synuclein antibody and assessed semi-quantitatively (0-4) in the hippocampal subfields CA1, CA2, CA3, and CA4. Percentage of stained area of amyloid-β and tau immunohistochemistry was determined for each hippocampal subfield.

Results:

Groups classified by rapid and slow decline did not differ in death age (74±8 vs. 77±4, p=0.51) or disease duration from estimated cognitive onset (7±2 vs. 10±4, p=0.44). The rapid decline group had a higher α-synuclein oligomer score in the CA1 compared to the slow decline group (2.5±1.3 vs. 0.5±0.6, p=0.03). The rapid decline group also exhibited a greater burden of tau pathology in the CA1 (28.8±20.8 vs. 1.6±1.7, p=0.04), CA3 (3.2±2.1 vs. 0.2±0.2, p=0.03), and CA4 (3.4±2.1 vs. 0.1±0.1, p=0.02) compared to the slow decline group. The rapid and slow decliners did not differ in α-synuclein or amyloid-β pathologic burden in the hippocampal subfields.

Conclusion:

Given the toxicity of α-synuclein oligomers, their accumulation in the CA1 subfield of the hippocampus may accelerate cognitive decline in cooperation with tau pathology.

Comparison of DNA damage in post-mortem Dementia with Lewy Bodies and Alzheimer's disease cases

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Background:

DNA damage and its disruption to intact gene expression is an emerging pathological mechanism for driving neurodegeneration. Our prior work has demonstrated robust double strand DNA breaks (DSB) and correlative novel nuclear alpha-synuclein (aSyn) pathology in a cohort of Dementia with Lewy bodies (DLB) cases. However, neuropathological hallmark Lewy bodies (LB) are often present alongside comorbid Alzheimer's disease (AD) pathology; amyloid Beta (Aβ) plaques and tau Neurofibrillary tangles (NFT), which are also associated with DNA damage. Despite overlapping pathology, comparisons of the DNA damage subtypes present within DLB and AD brain tissue has not been conducted, nor a spatial characterisation of DNA damage in relation to hallmark neurodegenerative pathology (aSyn, Aβ and tau). As new therapeutics to treat DNA damage continue to emerge, understanding the role of hallmark pathology and DNA damage in dementia is essential.

Methods:

Slide mounted human post-mortem brain tissue, frontal and temporal cortex, and multi-regional tissue microarray slides from control, AD and DLB groups, will be quantified for single strand breaks (SSB) and DSBs and correlated with the relative burden of Aβ plaques, NFTs and aSyn Lewy bodies.

Results:

Preliminary data correlating SSBs and DSBs in DLB tissue, reports a correlation relationship between DSBs and nuclear pS129- aSyn pathology, but not Aβ plaque, NFT nor Lewy body burden, within the temporal cortex. Additional data, from frontal and temporal cortex tissue and tissue microarrays, comparing DNA damage between DLB and AD cohorts will be presented as well as in the context of neurons burdened with NFT and LB pathology and proximal to Aβ plaques.

Conclusion:

This work will identify the relationship between DNA damage and hallmark neurodegenerative pathology and will aid in future work to determine cause and effect relationships between cell damage and neurodegenerative associated pathology.

Investigating the role of cellular senescence in Lewy body dementia

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Background:

Ageing is the biggest risk factor for the development of neurodegenerative disorders that cause dementia, however there are aspects of the ageing process, and how they relate to age related neurodegenerative diseases, which are largely unknown.

Cellular senescence, the irreversible arrest of the cell cycle, is a common occurrence in ageing and can be triggered by several events including telomere dysfunction, DNA damage, and oxidative stress.

Astrocytes have been shown to express a senescent phenotype, which is increased in ageing, Alzheimer's disease (AD) and in a model of Parkinson's disease (PD). Recently a causal link was established between senescent astrocytes and tau pathology in the *MAPT*^{P301S}*PS19* mouse model of tauopathy, where treatment with a senolytic agent removed senescent astrocytes prevented tau aggregation and preserved cognitive function.

In addition to α-synuclein (α-syn), AD related pathology is a frequent finding in dementia with Lewy bodies (DLB) and therefore the aim of this study was to investigate putative associations between senescent astrocytes and neurodegenerative pathology in DLB.

Methods:

Using frontal and temporal tissue sections from DLB and control cases we performed double immunofluorescence staining for GFAP (and astrocyte marker) and p16INK4a (a marker of cellular senescence) and determined the proportion of astrocytes that displayed a senescent phenotype. We then investigated associations between senescent positive astrocytes and pathological protein aggregates tau, β amyloid (Aβ), and α-syn.

Results:

In the frontal cortex there was a significant positive correlation between the senescent positive astrocytes with tau ($p=0.02$) and Aβ ($p=0.046$), however no association was observed with α-syn ($p=0.407$). No relationships were observed in the temporal cortex.

Conclusion:

Initial results suggest a potential role for senescent astrocytes in the mediation of tau and Aβ in DLB and suggest targeting senescent cells may be a viable therapeutic option. Further studies are required to elucidate the mechanisms underlying this relationship.

Characterizing GBA1 Mutations and Alpha-Synuclein Aggregation in Dementia with Lewy Bodies Using Blood Cell Models

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Background:

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative disorder after Alzheimer's, yet it remains frequently underdiagnosed. The pathology involves the abnormal aggregation of alpha-synuclein (α-syn) in the nervous system, though the mechanisms driving this aggregation are poorly understood. GBA1 gene encodes for lysosomal enzyme glucocerebrosidase (GCerase) which is responsible for glycosphingolipid (GSL) catabolism. Carrying a mutant GBA1 gene is significant genetic risk factors for DLB, associated with more severe symptoms and earlier onset. Despite the strong link between GBA1 mutations and DLB, their contribution to the disease's pathophysiology remains unclear.

Methods:

This study investigates the cellular mechanisms underlying DLB, particularly focusing on the role of GBA1 mutations, using patient-derived blood cells. We will quantify and characterize both normal and pathological forms of α-syn in red blood cells (RBCs) from DLB patients, assessing soluble, insoluble, and membrane-bound fractions. By correlating these findings with GBA mutation profiles, we aim to evaluate the functional impact of GBA1 mutations. An erythrocyte cell line overexpressing mutant GBA1 will be used to further examine the mutation's effects on α-syn. Additionally, inflammatory and autophagy markers in monocytes/macrophages overexpressing mutant GBA1 will be assessed, with subsequent potential studies on primary macrophages from DLB patients.

Results:

The outcomes of this study will include detailed characterization of α-syn in RBCs, assessment of GBA1 mutation effects on cellular function, and insights into the state of DLB patient-derived blood cells. These results will provide a clearer understanding of the pathophysiological mechanisms at play in DLB.

Conclusion:

The study aims to offer new insights into the role of GBA1 mutations in DLB, potentially identifying novel model of the disease and informing future therapeutic strategies.

Endothelial dysfunction in dementia with Lewy bodies

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Background:

About half of patients with dementia with Lewy bodies (DLB) have cerebrovascular changes usually associated with small vessel disease. The role of vascular pathology in DLB needs further clarification. The vascular machinery may be controversial which doesn't let to clarify contribution of vascular pathology and makes it impossible to find target therapy. There are several studies investigating the endothelial dysfunction (ED) in neurodegenerative dementias. We aimed to assess some aspects of the peripheral ED in DLB.

Methods:

Thirty patients that fulfilled clinical criteria of McKeith I et al 2017 for probable DLB were examined. Patients underwent ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the right brachial artery. Laboratory examination included lipid profile, von Willebrand factor, urine creatinine/microalbumine ratio. Cerebrovascular changes were revealed with 1,5 T brain MRI in 15 participants.

Results:

Twenty-five patients had peripheral ED. Paradoxical vasoconstriction in hyperemia test was found in 14 patients (47%). Twenty patients from 30 had orthostatic hypotension. We found association between orthostatic hypotension and paradoxical vasoconstriction (p=0,011). There was no association between ED and vascular risk factors with WMH severity. Twenty-eight patients (93%) had normal level of von Willebrand factor.

Conclusion:

In our study 47% of the patients showed paradoxical vasoconstriction not associated with von Willbrand factor and vascular risk factors. It can be assumed that this variant of ED is associated with alpha-synuclein pathology in endothelial cells. Normal von Willebrand factor levels support this hypothesis. Further investigation of endotheliopathy associated with alpha-synuclein accumulation is needed.

Clinical evolution of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies in a post-mortem cohort.

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Background:

Almost all patients with neurodegenerative dementias experience neuropsychiatric symptoms (NPS) but the timing and clinical course is highly variable.

Methods:

In a prospective cohort study in Western Norway, patients with a new diagnosis of mild dementia were assessed annually the neuropsychiatric inventory for up to 9 years until death. Individual NPS were rated as clinically significant with scores >4. Patients with post-mortem neuropathological diagnoses of Alzheimer's disease (AD) (n=37), Lewy body disease (LBD) (n=14) or co-morbid AD+LBD (n=11) were included in this study. Neuropathological assessment was performed according to standardised protocols and blind to clinical information.

Results:

The odds of having clinically significant hallucinations were higher in LBD than AD or AD+LBD ($\beta = -5.33$, 95% CI −8.89 to −1.76, $p = 0.003$; AD+DLB ($\beta = -4.04$, 95% CI −8.02 to −0.05, $p = 0.047$) but there was a greater increase in the odds of hallucinations over time in AD and AD+LBD than LBD. Hallucinations in the first two years after diagnosis were associated with higher LBD Braak stages and neocortical LBD, in addition to lower Braak stages of tau and sparser amyloid distribution. The presence of vascular pathology, TDP-43 and increased numbers of co-pathologies were associated with increased odds of hallucinations late in disease and cerebrovascular disease and increasing additional co-pathologies were associated with greater odds of hallucinations over time.

Conclusion:

LBD, without comorbid AD pathology is associated with hallucinations early in the course of disease while multiple other pathologies may be implicated in aetiology of late-onset hallucinations. Hallucinations increase in AD+LBD as disease progresses, a trajectory more closely aligned with AD than LBD.

Mixed pathology and the clinical under-recognition of Lewy body disease

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Background:

The reported prevalence of Lewy body disease (LBD) is frequently lower in clinical studies than in neuropathological studies. Accurate clinical diagnosis of Lewy body disease remains a complex challenge. Identifying factors associated with lower diagnostic accuracy is essential for advancing clinical practice, improving patient outcome, and ensuring that more heterogenous LBD populations are represented in future clinical studies.

Methods:

Clinical and neuropathological assessments for 467 donors with dementia from the Brains for Dementia Research programme were examined as predictors of misdiagnosis and missed diagnosis of LBD. Demographic, neuropathological, and neuropsychiatric features were also assessed as predictors of accuracy of clinical diagnosis.

Results:

In this cohort, only 21.2% of cases with autopsy-confirmed neocortical Lewy body disease had a reported study clinical diagnosis of Lewy body dementia. Furthermore, specificity for neocortical Lewy body disease in males (25.8%) was almost twice as high as in females (13.3%). Mixed neuropathology was associated with lower specificity (10.1%) than pure LBD cases (42.9%). Specificity for LBD decreased with increasing levels of Alzheimer's disease neuropathological changes: 54.5% for low, 28.6% for intermediate, and 11.3% for high level ADNC. Neocortical LBD cases with concomitant high ADNC were 20 times more likely to be missed clinically. The presence of concomitant limbic TDP-43 pathology was also associated with a significant reduction in specificity (12.2% vs 29.0%).

Conclusion:

Clinical Lewy body disease is significantly under-recognised in this cohort, particularly in the presence of mixed neuropathologies and among females. Low diagnostic accuracy in females may be due to differences in symptom presentation or diagnostic biases. The presence of concomitant pathologies is common and can significantly complicate clinical presentation, reducing diagnostic accuracy. Addressing these issues could improve the clinical identification of LBD and optimise treatment strategies. These high rates of clinical under-recognition, potentially driven by mixed pathology, may also contribute to the efficacy of anti-amyloid therapies.

Neocortical tau pathology is associated with baseline memory and naming, but not visual performance, in autopsy-confirmed dementia with Lewy bodies

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Background:

The primary pathology of dementia with Lewy bodies is α-synuclein, but co-existing Alzheimer-related pathology can also occur. In autopsy-confirmed DLB, we examined whether the neocortical distribution of α-synuclein and tau pathology was associated with baseline performance on memory, naming and visual tasks.

Methods:

Participants included 137 autopsy-confirmed clinically probable DLB followed in the Mayo Clinic Alzheimer's Disease Research Center. Baseline cognitive assessment included the Dementia Rating Scale (DRS), Mini-Mental State Examination (MMSE), Boston Naming Test (BNT) including error types, Logical Memory (LM), Auditory Verbal Learning Test (AVLT), Block Design, and Rey Complex Figure copy (RCF). Linear regression models examined whether the distribution of α-synuclein (transitional vs. diffuse Lewy body disease: TLBD, DLBD) and tau pathology (Braak neurofibrillary tangle (NFT) stage 0 to VI) accounted for age-education-sex normed cognitive performance over and above the contribution of dementia severity.

Results:

The autopsy sample of clinically probable DLB included: 80% men, mean death age (77.3±7.5 years), education (15.4±2.8 years), years of follow-up (5.1±2.5 years), baseline mean DRS (122±12) and baseline MMSE (24.3±3.3) scores. Distribution of pathology included 30%TLBD, 70%DLBD, 52% Braak NFT stage 0 to III, 18% NFT stage IV, 18% NFT stage V, and 12% NFT stage VI. Separate multivariable models of each cognitive task showed that when age, education, sex, and dementia severity were taken into account, higher Braak NFT stages were associated with worse memory and naming performance on LM ($p<0.001$), AVLT ($p=0.003$), and BNT ($p=0.017$), but not with visual tasks of Block Design and RCF. Higher rates of circumlocutory BNT errors occurred in the DLB group with neocortical tangles compared to those without them ($p=0.003$).

Conclusion:

In autopsy-confirmed DLB, neocortical tau pathology was associated with worse baseline memory and naming performance and higher rates of circumulocutory naming errors, but was unrelated to baseline visual task performance.

Associations between neuropsychiatric symptom burden, change in cognitive status and survival in autopsy-confirmed cohorts of Lewy body disease and Alzheimer's disease

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Background:

Presence of pathological Lewy body disease (LBD) is typically associated with higher neuropsychiatric symptom (NPS) burden and poorer survival. Predictors of mortality at dementia diagnosis include age, more depression and worse cognitive status. Predictors of survival during early cognitive changes are unclear and presumably related to final pathological burden. We investigated the impact of NPS burden and cognitive status on survival in pathological cohorts of LBD and Alzheimer's disease (AD).

Methods:

We included 313 initially non-demented cases from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) with longitudinal Neuropsychiatric Inventory-Questionnaire (NPI-Q) scores who came to autopsy (mean follow-up duration 6±4 years). Participants were categorized by final Unified Staging System for Lewy Body Disorders (USSLB) (stage-I [n=9], IIA-B [n=32, 16], III [n=59], IV [n=70]); 127 cases had USSLB stage-0, including AD without LB (n=66). We performed Cox regression analyses, adjusting for cognitive status change, age, sex, motor subscale of Unified Parkinson's Disease Rating Scale (UPDRS-III), and Functional Assessment Scale (FAS) from the National Alzheimer's Coordinating Center.

Results:

Individuals with USSLB stages III-IV were younger at first NPI-Q (mean 79±7 years) and at death (mean 85±8 years) ($p<0.05$). UPDRS-III (mean 23±15) and frequency of mild cognitive impairment (MCI) status (37%) at first NPI-Q were highest for USSLB stage-IV ($p<0.05$). Total initial NPI-Q score was highest for USSLB stage-IIB (mean 3.6±3.4), followed by stage-IV (3.3±3.4) and III (2.9±3.7) ($p<0.05$). While nighttime behaviors were most frequent/severe in stage-IIB, hallucinations were most prominent in stage-IV ($p<0.05$). When analyzing survival across all cases irrespective of underlying pathology, higher first available total NPI-Q, progression to dementia, age and UPDRS-III at first NPI-Q were predictive of worse survival ($p<0.05$).

Conclusion:

Cognitive progression to dementia (not MCI), higher initial NPI-Q scores, older age, and poorer baseline motor function, were associated with worse survival across pathological cases of LBD and AD.

Mitophagy in Lewy Body Dementia

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Background:

Lewy bodies (LBs) are the pathological hallmark of Lewy body dementia (LBD), yet, how and why these intraneuronal inclusions form and their contribution to the disease process remains unclear. Recent studies have highlighted that LBs contain numerous organelles, including apparently damaged mitochondria, which could indicate that LB formation is a mechanism to encapsulate cellular waste in the context of deficient autophagy. The present study sought to determine whether there is evidence of mitochondrial dysfunction and the accumulation of autophagic mitochondria in LBD, as would be expected in the context of deficient mitochondria-specific autophagy (mitophagy).

Methods:

Post-mortem tissue was obtained from the cingulate gyrus of LBD (N=20) and control (N=20) cases. To characterise changes to mitochondria in LBD, mitochondria were isolated using density-based fractionation combined with immunoprecipitation, and the mitochondrial proteome determined with discovery proteomics using LC-MS/MS. Immunofluorescent staining was performed to assess the distribution of autophagic mitochondria within neurons.

Results:

Discovery proteomics of isolated mitochondria revealed alterations to mitochondrial homeostasis in LBD, particularly implicating proteins associated with the size and shape of mitochondria. Immunofluorescent studies identified the peri-LB accumulation of organelles labelled by the mitophagy marker, ubiquitin pS65, that were preferentially labelled with markers of the mitochondrial inner membrane, rather than the outer membrane. The accumulation of such organelles is consistent with deficient mitophagy.

Conclusion:

These findings suggest changes to mitochondrial homeostasis and deficient mitophagy in LBD. Mitochondrial homeostasis is closely coupled to mitophagy, which acts as a quality control mechanism to regulate the health of the mitochondrial network. These findings suggest mitophagy is deficient in LBD and this could underlie perturbed mitochondrial homeostasis. We are currently evaluating how these findings intersect with α-synuclein aggregation by determining whether pathologically modified α-synuclein is localised to mitochondria in LBD.

Analysis of CTSB, CTSD, and CTSL in Lewy Body Dementia

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Background:

The accumulation of misfolded alpha-synuclein in Lewy Body Dementia (LBD) has been linked with defective autophagy. Cathepsins B, D, and L are the most abundant lysosomal hydrolases; as such, the coding genes (CTSB, CTSD, and CTSL) have been postulated to mediate disease risk in synucleinopathies and other neurodegenerative diseases. Here, we investigated whether rare mutations in these genes are associated with LBD risk.

Methods:

We previously generated whole-genome sequencing data of 6,618 individuals of European ancestry (n = 2,591 LBD cases and 4,027 neurologically healthy controls). We conducted gene burden analysis of annotated rare (MAF <0.01) missense and loss-of-function variants in CTSB, CTSD, and CTSL. Further, we identified individuals with ClinVar-designated pathogenic variants or variants of uncertain significance in the European dataset and an additional cohort of 55 LBD cases and 149 controls of African and admixed ancestries.

Results:

Gene burden test found no significant enrichment of missense (p-values: 0.33, 0.42 and 0.77) or loss-of-function (p-values: 0.28, 0.22, and 0.35) variants in CTSB, CTSD, or CTSL, respectively. In the European cohort, 1 missense CTSB variant (chr8:11845763:T:A) was found in 4 LBD cases; 7 missense CTSD variants were found in 19 cases and 16 controls. In the non-European cohort, 2 CTSD missense variants (chr11:1759030:G:A, chr11:1761437:G:A) were found in 2 healthy controls.

Conclusion:

Analysis of the largest LBD WGS cohort to date finds no significant burden of rare, damaging mutations in CTSB, CTSD, and CTSL. However, this does not rule out the involvement of Cathepsins in LBD pathology, as an association could have been missed due to allelic heterogeneity. Increasing our sample size and conducting further complementary 'omics' studies will help shed light on the potential role of Cathepsins in LBD.

Exploration Shared Pathological Mechanisms in Dementia with Lewy Bodies and Alzheimer's Disease Based on Serum microRNA Expression Profiling

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Background:

Dementia with Lewy Bodies (DLB) and Alzheimer's Disease (AD) are two prominent neurodegenerative disorders that exhibit overlapping clinical and pathological features. This study was amid to investigate the shared pathological mechanisms associated with both DLB and AD through the analysis of serum microRNA (miRNA) expression profiles.

Methods:

We utilized the GSE120584 dataset from the GEO database to identify differentially expressed miRNAs in serum samples from patients with DLB and AD, compared to normal controls (NC), using the*limma* package in R. Then, differentially expressed miRNAs were used to predict target genes with the *multimiR* package. The *Cytoscape* software was used to identified the key hub genes. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted on these target genes respectively.

Results:

The study included 1,021 AD patients, 169 DLB patients, and 288 NC. Differential expression analysis revealed 6 miRNAs in both DLB *versus* NC and AD *versus* NC: a total of 5 downregulated miRNAs (hsa-miR-6875-3p, hsa-miR-6716-3p, hsa-miR-4747-3p, hsa-miR-3646, hsa-miR-208a-5p) and one upregulated miRNA (hsa-miR-24-3p). Key hub gene analysis identified MYC, BRCA1, CDKN2A, and CDK4 as common critical target genes for both DLB and AD. Then, GO and KEGG pathway analysis suggested that these miRNAs may contribute to the overlap pathological mechanisms of DLB and AD by regulating common biological processes and signaling pathways, including cellular senescence, p53 signaling pathway, FoxO signaling pathway, and HIF-1 signaling pathway.

Conclusion:

This study identified six differential expressed serum miRNAs in patients both with DLB and AD which may target at downstream genes and regulate potential signaling pathways, contributing to the overlapping clinical and pathological features between DLB and AD.

Multi-trait analysis of GWAS improves prediction of Lewy body dementia using polygenic risk scores.

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Background:

Compared to genome-wide association studies (GWAS) in Alzheimer's (AD), sample sizes in GWAS of Lewy body dementia (LBD) are small and underpowered. Multi-trait analysis of GWAS (MTAG) is a method which leverages the shared heritability between related traits to increase statistical power and can improve the accuracy of polygenic risk scores (PRS). We tested whether this improves prediction of LBD.

Methods:

Using the largest available case-control GWAS for LBD and AD ($GWAS_{LBD}$ and $GWAS_{AD}$), we performed a multi-trait analysis to produce updated genetic risk estimates for LBD ($MTAG_{LBD}$). In an independent sample of individuals with LBD (n=83) and healthy controls (n=57), we then derived PRS from GWAS ($PRS_{GWAS\text{-}LBD}$ and $PRS_{GWAS\text{-}AD}$) and using results of the multi-trait analysis ($PRS_{MTAG\text{-}LBD}$). We identified the optimal PRS to discriminate between LBD cases and controls in this sample (while controlling for age and sex) and measured predictive power using incremental R^2 (the increase in R^2 from addition of the PRS to a regression including only age and sex).

Results:

In keeping with previous studies, there was significant genetic correlation between LBD and AD (r_g=0.559, p=1.67x10^{-7}). The multi-trait analysis increased the effective sample size of the LBD GWAS from 6,306 to 14,938. $PRS_{MTAG\text{-}LBD}$ was significantly higher in LBD cases than controls (OR 1.68, 95% CI 1.15 – 2.53, p=0.009, incremental R^2 =5.91%), while we did not detect a significant difference in $PRS_{GWAS\text{-}LBD}$ (OR 0.73, 95% CI 0.49 – 1.05, p=0.096, incremental R^2 =2.35%), or $PRS_{GWAS\text{-}AD}$ (OR 1.38, 95% CI 0.95-2.05, p=0.097, incremental R^2=2.39%).

Conclusion:

This study showed that there is potential to leverage genetic correlation between LBD and AD to more than double the effective size of existing GWAS and improve polygenic risk estimates in LBD, however multi-trait approaches may bias results towards the higher-powered trait.

ABCA1 missense variants associated with Lewy body dementia: Insights from genome sequence data

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Background:

Lewy body dementia (LBD) is the second most common dementia in the United States. The complex genetic architecture of LBD partially overlaps with Alzheimer's disease (AD), sharing genetic variants and substantial co-pathology. Given the recent association of rare *ABCA1* and *ATP8B4* variants with AD, we assessed their association with LBD risk using whole-genome sequence data from a European-ancestry LBD case-control cohort.

Methods:

We examined the association of common (minor allele frequency; MAF > 0.01) and rare variants (MAF < 0.01) in *ABCA1* and *ATP8B4* in the whole-genome sequence data from 2,591 LBD cases and 4,027 controls. Common variants were extracted from the LBD genome-wide association study (GWAS). Rare coding variants were annotated using Ensembl Variant Effect Predictor. We evaluated the association of these rare missense and loss-of-function (LOF) variants with LBD risk using an optimized sequence kernel association test (SKAT-O), followed by single-variant analysis with Fisher's exact test adjusting for multiple testing corrections.

Results:

While the evaluation of common variants (MAF > 0.01) did not reveal any significant association between *ABCA1* and *ATP8B4* with LBD, we identified a significant enrichment of rare *ABCA1* missense variants with LBD risk (SKAT-O *p-value* = 2.68E-02). No significant associations were found between LBD and *ABCA1* LOF variants or *ATP8B4* LOF or missense variants. Single-variant analysis highlighted two *ABCA1* missense variants, c.5398A>C (p.N1800H; Fisher's test *p-value* = 1.16E-04) and c.3544G>A (p.A1182T; *p-value* = 4.29E-02). The p.N1800H variant remained significant after Bonferroni correction, found in twelve LBD patients and one control (odds ratio = 18.48, 95% CI = 2.4–142.8), and is known pathogenic, and previously associated with AD. Notably, six of these carriers also carried the *APOE ε4* risk allele.

Conclusion:

Our findings reveal rare *ABCA1* missense variants significantly increase Lewy body dementia risk, further identifying a specific pathogenic variant that warrants further investigation.

Genetic determinants of the progression of Lewy body pathology

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Background:

Parkinson's Disease (PD), PD dementia (PDD) and Dementia with Lewy bodies (DLB), collectively named as Lewy body diseases (LBD), are characterized pathologically by alpha-synuclein aggregates forming Lewy bodies and Lewy neurites. Cognitive and neuropsychiatric complications observed in LBDs correlate with the development of cortical Lewy body pathology. LB pathology can be divided into subcortical, limbic and neocortical stages. We aim to identify genetic risk factors associated with the distribution of Lewy body and Alzheimer's disease (AD) co-pathology in the LBD brain.

Methods:

We studied a large series (total n = 2429) of Brain Bank LBD cases to define the genetic drivers of regional LB pathology. We included 1308 pathologically defined LBD cases with summary pathological scores together with genotyping using the Illumina Neurobooster array (NBA) generated in the Global Parkinson's Genetic Program (gp2.org). We ran a genome-wide association study (GWAS) using LB Braak stage as the quantitative trait, with and without AD as a covariate. We further meta-analyzed with the Mayo clinic brain bank (n = 809) and Netherlands brain bank cohort (n = 312).

Results:

We found rs769449 tagging APOE e4 to be the most significant genetic risk associated with cortical LB (OR = 1.27, 95% CI = 1.21 - 1.33, P-value = 5.75e-21). A second signal, rs112119142, on chromosome 15 was also significant (OR = 1.49, 95% CI =

1.29-1.72, P-value = 4.27e-8). The APOE e4 and rs112119142 signals disappear when we control for AD co-pathology in the model.

Conclusion:

Our results suggest APOE e4 drives both Lewy body and Alzheimer's co-pathology in the LBD brain. Further analysis of variant rs112119142 as well as rare risk variants is underway to provide new insights into the pathogenesis of these diseases.

Fluid biomarkers

Oral Abstracts

DOPA Decarboxylase: High discriminative power in CSF, but confounded by treatment in blood

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Background:

DOPA Decarboxylase (DDC) has been proposed by several proteomics-based studies as a new biomarker for dopaminergic dysfunction in different Lewy body diseases (LBDs), such as dementia with Lewy bodies and Parkinson's disease. However, orthogonal measurement techniques are still lacking and the clinical value of DDC in different matrices still needs to be evaluated further.

Methods:

We measured DDC in cerebrospinal fluid (CSF) with two in-house developed immunoassays (Ella and Simoa) in four cross-sectional LBD cohorts (total n=828), including post-mortem confirmed patients. Plasma DDC levels measured with proximity extension assay (PEA) were analyzed in three LBD cohorts (total n=1635), including longitudinal samples and post-mortem confirmed patients. Group differences at baseline were analyzed by generalized linear models corrected for age and sex and receiver operating characteristics analysis was performed to assess diagnostic value of DDC. In longitudinal plasma samples, change of DDC over time and association of plasma DDC with dopaminergic treatment was assessed by linear mixed-effects models.

Results:

DDC in CSF as measured by Ella and Simoa was significantly increased in LBDs compared with controls and other neurodegenerative diseases, and could differentiate the LBD groups from the other groups with high discriminative power reaching AUCs of up to 0.90. Plasma DDC as measured by PEA did not differ between diagnostic groups at baseline, but increased longitudinally in the LBD group compared with controls ($p<0.0001$). However, this increase was not significant when no dopaminergic treatment was used ($p=0.061$), showing a strong association between plasma DDC and dopaminergic treatment.

Conclusion:

We show that CSF DDC has great potential to support clinical LBD diagnosis and present two novel immunoassays that can be implemented in clinical practice and research. Diagnostic utility of plasma DDC is limited due to the tight relation with dopaminergic treatment. However, plasma DDC could hold potential as a treatment response biomarker in clinical trials.

Predicting Dementia in Parkinson's Disease: Insights from α-Synuclein SAA, NfL, Aβ, and GCase Biomarkers

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Background:

Identifying reliable biomarkers to predict the risk and time to dementia in Parkinson disease (PD) is critical for early intervention. This study uniquely evaluates four key protein biomarkers—neurofilament light chain (NfL), alpha-synuclein seeding activity (α-syn SAA), amyloid-beta ($A\beta_{42}$), and glucocerebrosidase (GCase) activity—in a single cohort followed for over ten years, providing a comprehensive understanding of their predictive value for dementia.

Methods:

We collected samples at diagnosis from up to 172 non-demented PD patients in the Norwegian ParkWest cohort, a longitudinal population-based study initiated in 2004. We analyzed serum samples for NfL and cerebrospinal fluid samples for α-syn SAA, GCase activity, and $A\beta_{42}$. Dementia was diagnosed according to the MDS criteria. Parametric accelerated failure time models were applied and HR calculated to analyze the association of biomarkers with dementia-free survival.

Results:

Our results reveal that low CSF $A\beta_{42}$ levels (HR 3.2, 95% CI 1.2 to 5.1; p = 0.001) and reduced GCase activity (HR 2.3, 95% CI 0.3 to 4.4, P = 0.027) are significantly associated with the development of dementia within ten years of PD diagnosis. Elevated serum NfL levels and positive α-syn SAA status were not significantly linked to increased PDD risk. Furthermore, $A\beta_{42}$ and GCase activity demonstrated an additive effect, with individuals with both positive $A\beta_{42}$ and GCase biomarker status at substantially increased risk (HR 5.3, 95% CI 2.2 to 8.4, p < 0.001). Importantly, only 10% of patients with both negative $A\beta_{42}$ and GCase status at PD diagnosis developed PDD over ten years.

Conclusion:

This study highlights the strength of a multi-biomarker approach in predicting dementia. The additive effect observed between CSF $A\beta_{42}$ and GCase activity sheds light on different pathological mechanisms driving dementia in PD and provides tools to identify patients at both high and low risk at the time of PD diagnosis.

Diagnostic accuracy of plasma biomarkers for detecting amyloidosis in alpha-synucleinopathies

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Background:

Neurodegenerative diseases often involve multiple coexisting proteinopathies that influence clinical presentation and disease progression. Currently, three cerebral proteinopathies—amyloidosis (Aβ), tauopathy, and alpha-synucleinopathy (αsyn)—can be detected in vivo. While plasma biomarkers have shown high accuracy in detecting Aβ, their application in αsyn-positive individuals remains underexplored. Interpreting plasma biomarkers in the context of αsyn positivity is critical for their use in clinical trial screening. This study evaluated the diagnostic accuracy of plasma pTau181, pTau217, Aβ42/40, GFAP, and NfL in detecting Aβ among αsyn+ and αsyn- participants.

Methods:

We included 180 participants: 69 Aβ-/αsyn-, 44 Aβ+/αsyn-, 39 Aβ-/αsyn+, and 28 Aβ+/αsyn+. Plasma pTau181 and Aβ42/40 were measured using the Lumipulse G platform, pTau217 with the ALZpath pTau217 assay, and GFAP and NfL with the Neurology 2-plex E kit (Quanterix). CSF αsyn positivity was determined using SAAmplify. The diagnostic accuracy of plasma biomarkers for detecting Aβ (determined by CSF Aβ42/Aβ40 measured with the Lumipulse G platform) was evaluated using ROC curve analyses and compared with the DeLong test.

Results:

Plasma biomarker levels were abnormal in Aβ+ groups, irrespective of αsyn status. NfL levels were higher in Aβ+/αsyn+ compared to Aβ+/αsyn-. pTau217 and Aβ42/Aβ40 separately, showed the highest diagnostic accuracy (AUC up to 0.91) in detecting Aβ in αsyn+ and αsyn- participants. In αsyn+ participants, pTau217 and Aβ42/Aβ40 outperformed NfL. Adding age, sex, and APOE ε4 did not improve Aβ prediction. There was no difference in diagnostic accuracy between pTau217 and Aβ42/Aβ40, either individually or combined.

Conclusion:

Plasma pTau217 and Aβ42/40 accurately detected Aβ in αsyn+ individuals. Double positivity Aβ and αsyn was associated with increased neurodegeneration. Our results indicate that plasma pTau217 and Aβ42/40 could be used in clinical trials for Aβ screening and stratification to assess treatment response differences in α-synucleinopathies such as dementia with Lewy bodies and Parkinson’s disease.

Differential Associations of plasma NfL and Cognitive Performance in Lewy Bodies Disease Patients with and without Alzheimer's Disease Co-Pathology

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Background:

Alzheimer's Disease (AD) pathology (amyloid-β plaques and tau tangles) is found in 50–80% of Lewy Body Disease (LBD) patients, contributing to the heterogeneity of cognitive performance and complicating clinical diagnosis. Plasma Neurofilament Light Chain (NfL), a biomarker of neurodegeneration, has proven useful in predicting early LBD diagnosis and is associated with cognitive performance in patients at high risk for both LBD and AD. This study aims to assess whether the presence of AD co-pathology affects the association between plasma NfL concentration and cognitive performance in LBD patients.

Methods:

Cross-sectional study. We included 50 cognitively normal volunteers and 139 diagnosed patients (either prodromal or dementia): 52 with probable LBD clinical diagnosis ("pure" LBD), 50 "pure" AD and 37 mixed probable LBD/AD. AD co-pathology was defined by abnormal CSF Aβ42/40 ratio (A+:<0.062) and abnormal pTau181 levels (T+:>63pg/mL). A composite score was calculated for each cognitive domain using scores adjusted for age, sex, and education. We performed age- and sex-adjusted linear regression models to assess the association between plasma NfL levels and performance in cognitive domains in all groups.

Results:

Plasma NfL concentrations were higher in the LBD/AD ($\bar{x}$=3.08±0.57) and "pure" AD ($\bar{x}$=2.97±0.43) groups compared to "pure" LBD ($\bar{x}$=2.71±0.46), with significant differences (LBD/AD vs "pure" LBD p=0.002; "pure" AD vs "pure" LBD p=0.023). In LBD/AD group, higher concentrations of plasma NfL were associated with worse performance in visual memory (β=-0.82;p=0.036), language (β=-6.60;p<0.001) and visuoperception (β=-5.82;p=0.003). By contrast, higher plasma NfL concentration was only associated with worse performance in executive functions (β=-0.62;p=0.023) in the "pure" LBD group, and no significant associations were found with cognitive performances in pure AD.

Conclusion:

Plasma NfL levels were associated with differences in cognitive performance in LBD patients, depending on the presence of AD co-pathology. Our results suggest that mixed LBD/AD patients have more neurodegeneration and a worse cognitive profile

The US Dementia with Lewy Bodies Consortium: Description and Insights on the Performance of CSF Synuclein Aggregation Assay

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Background:

The US Dementia with Lewy Bodies Consortium (DLBC, U01NS100610) is a collaborative grant with the National Insitute of Neurologic Disorders and Stroke (NINDS) Parkinson's Disease Biomarker Program (PDBP). The study was established to develop a cohort of well characterized participants with Lewy body dementia (LBD) and collect and characterize linked imaging (structural and dopamine transporter) and biofluids (blood, CSF). With renewal fo the study, in addition to continued participant recruitment, there has been an increased focus on discovery and validation of biomarkers of aggregated alpha-synuclein, Alzheimer's diseae, inflammation, and neurodegeneration.

Methods:

DLBC participants undergo annual evaluation including characterization of cognition, motor, and behavior with matched blood and CSF collection. At baseline, and at 2-year follow up, participants undergo a volumetric MRI and dopamine transporter imaging. Data generated from the program is available through the PDBP Data Management Resource (PDBP-DMR) and biosamples are stored and can be formally requested through the linked BioSEND program.

Results:

Recently published results on CSF SAA in this cohort suggest approximately 70% are SAA positive. Neuropathologic assessment in DLBC autopsy cases suggest a high positive predictive value for SAA positive cases having limbic or neocortical Lewy body disease, irrespective of co-pathology. Amygdala-predominant and brainstem Lewy body disease cases are inconsistently SAA positive, and neuropathologically negative cases have all been SAA negative. Clinically, hyposmia, REM Sleep Disorder, and lower dopamine transporter binding were associated with CSF SAA positivity.

Conclusion:

These results reinforce the value of CSF SAA in diagnosing limbic or neocortical Lewy body disease and associated cognitive, motor and behavioral changes. Negative CSF SAA implies either the absence of Lewy body pathology or a limited anatomic distribution.

Protein panels for accurate diagnosis and monitoring of treatment responses in DLB

Charlotte Teunissen

Background:

There is a lack of specific biomarkers to diagnose DLB, and distinguish it from AD or PD. The aim of our studies is to develop such biomarkers.

Methods:

We applied different technologies, including mass spectrometry, Olink Proximity Extension Assays, and NULISA, in both CSF and plasma of different cohorts.

Results:

Consistent findings were observed across several mass spectrometry studies in CSF of DLB patients compared to AD patients or controls, such as a reduction in VGF concentrations and other proteins related to synaptic function. Moreover, using antibody based methods, such as Olink, panels of proteins, including the protein marker DDC have been identified. These panels have been validated in independent cohorts. Lastly, protein profile analyses of CSF samples of DLB patients treated with a phosphodiesterase inhibitor showed target engagement. Large scale plasma proteomics similarly lead to the identification of DLB-specific panels.

Conclusion:

Novel proteomics methods enabled the identification and successful validation of novel candidate biomarkers for DLB. Such panels are highly feasible for application in routine clinical settings and for drug development.

Poster Abstracts

Plasma phosphorylated tau and neuropsychiatric symptoms in dementia with Lewy bodies.

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Background:

Neuropsychiatric symptoms (NPS) are common in dementia with Lewy bodies (DLB) but their neurobiological mechanisms are poorly understood.

Methods:

Participants were recruited from centres in the European DLB Consortium longitudinal cohort study. NPS were assessed annually in standardised instruments (Neuropsychiatric Inventory (NPI), Fénelon scale and Mini-International Neuropsychiatric Interview) and the persistence of NPS was determined across the first 3 assessments (not present, single episode, persistent). Cognition was assessed annually in the Mini Mental State Examination (MMSE) for up to five years. Plasma ptau181 and ptau231 concentrations were measured with in-house Single molecule array assays at baseline. Associations between plasma biomarkers and cross-sectional and longitudinal NPS were explored in logistic regression. Linear mixed effects models were used to examine longitudinal changes in cognition associated with the presence of hallucinations at baseline and interactions with ptau.

Results:

In a cohort of patients with DLB (n=222) and Alzheimer's disease (AD) (n=125), hallucinations, delusions and depression were more common in DLB than AD. In a subgroup with longitudinal follow up (DLB n=172; AD n=83), persistent hallucinations and NPS were associated with lower ptau181 (hallucinations: RRR 0.55 95% CI [0.34-0.90], p=0.017; any NPS: RRR 0.38 95% CI [0.21-0.67], p=0.001) and ptau231 (hallucinations RRR 0.45 95% CI [0.29-0.72], p=0.001; any NPS RRR 0.31 95% CI [0.17-0.59], p<0.001). In adjusted linear mixed effect models, hallucinations at baseline were associated with greater longitudinal cognitive impairment in DLB (EST=0.11, 95% CI [0.06–0.16], p<.001) with a significant interaction with ptau231.

Conclusion:

In the early stages of DLB, higher ptau181 and ptau231 levels were associated with lower longitudinal risk of NPS and hallucinations. The association between hallucinations and cognitive impairment in DLB was moderated by ptau231, suggesting that when AD co-pathology and hallucinations co-exist in DLB, they may interact synergistically to exacerbate cognitive decline.

Maximizing sensitivity of cerebrospinal fluid (CSF) biomarkers to detect Alzheimer's co-pathology in autopsy-confirmed Lewy Body Disease (LBD)

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Background:

In α-synuclein (αSyn) Lewy body disease (LBD), concomitant Alzheimer's disease (AD) pathology is associated with worse clinical outcomes. Yet AD co-pathology can be challenging to detect since cerebrospinal fluid (CSF) AD-biomarkers may be less sensitive in primary LBD. Indeed, our autopsy study previously found that CSF phosphorylated tau 181 (p-tau$_{181}$) is inversely associated with postmortem α-synuclein. Still, this prior work used early-generation immunoassays, and the latest, ultra-sensitive immunoassays are not yet validated in LBD.

In autopsy-confirmed LBD, we used the Fujirebio Lumipulse G1200 platform to measure CSF β-amyloid (Aβ) 1-42 (Aβ$_{42}$), Aβ$_{40}$, p-tau$_{181}$, and t-tau. Linear models tested if αSyn pathology alters CSF AD-biomarkers. Receiver operating characteristic (ROC) determined performance and cutpoints in LBD to discriminate αSyn with AD (αSyn/AD+) from αSyn without AD (αSyn/AD-); we compared LBD-derived cutpoints to published AD-cutpoints (Gobom *et al.*, 2022).

Methods:

LBD were autopsy-confirmed αSyn/AD+ (n=23) and αSyn/AD- (n=27) with a clinical diagnosis of Parkinson's disease (PD), PD with dementia, or dementia with Lewy bodies; clinically amnestic, autopsy-confirmed AD were the reference group (n=54). AD pathology was defined as intermediate/high AD neuropathologic change (ADNC). Postmortem accumulations of brain Aβ, tau, and αSyn were scored from none(0) to high(3) and averaged over brain regions. Lumipulse measured CSF AD-biomarkers.

Results:

In ADNC cases (αSyn/AD+, AD), higher postmortem αSyn significantly associated with lower CSF p-tau$_{181}$ (β=-0.18, 95%CI=-0.32 – -0.04, p=0.012) and t-tau (β=-0.2, 95%CI=-0.32 – -0.071, p=0.0025), even after covarying for postmortem Aβ and tau, age, CSF-to-death interval, and sex. In αSyn cases, ROC analyses to detect αSyn/AD+ showed that cutpoints for CSF p-tau$_{181}$ (34.2 pg/mL, 95%CI=28.4 – 41.8) and t-tau (241.7 pg/mL, 95%CI=208 – 303.9) were significantly lower than published AD-cutpoints (p-tau$_{181}$=50.2; t-tau=409; Gobom *et al.,* 2022). The p-tau$_{181}$/Aβ$_{42}$ ratio demonstrated excellent performance to detect αSyn/AD+ (area under the curve=0.91)

Conclusion:

LBD-specific biomarker strategies improve detection of concomitant AD.

Plasma biomarkers and disease prognosis in mild cognitive impairment with Lewy bodies

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Background:

Plasma biomarkers have the potential to improve the accuracy of disease prognosis in mild cognitive impairment with Lewy bodies (MCI-LB), which would have a positive impact on clinical care and treatment trials.

The objective of this study was to investigate the association of four plasma biomarkers (glial fibrillary acidic protein (GFAP), neurofilament light (NfL), phosphorylated tau (pTau)181 and amyloid beta (Aβ) 42/40 ratio) with disease progression in MCI-LB, measured by conversion to dementia/death and longitudinal cognitive change.

Methods:

Participants with probable MCI-LB, possible MCI-LB and MCI due to Alzheimer's disease (MCI-AD) were recruited. Clinical assessment was carried out at baseline and annually, including the Addenbrooke's Cognitive Examination Revised (ACE-R). At each annual review, diagnosis, including conversion to dementia, was assessed by a three person panel. Plasma samples were analysed using Single molecule array (Simoa). Cox proportional hazards models and linear regression were used to assess the association of each plasma biomarker with conversion to dementia/death and cognitive decline respectively, with correction for age, sex and baseline cognition.

Results:

In probable MCI-LB (n=62), NfL (HR=1.74, 95% CI 1.22-2.48), GFAP (HR=1.74, 95% CI 1.21-2.50) and pTau181 (HR=1.50, 95% CI 1.11-2.02) were associated with an increased hazard of conversion to dementia/death. The same three biomarkers were also significantly associated with the rate of cognitive decline in MCI-LB (NfL: β=-.41, p=.01; GFAP: β=-.34, p=.02; pTau181: β=-.30, p=.05).

No plasma marker was significantly associated with hazard of conversion to dementia/death, or rate of cognitive decline in MCI-AD (n=43).

Conclusion:

Higher plasma pTau181, GFAP and NfL levels are associated with more rapid disease progression in MCI-LB. With further validation, these biomarkers could be used to support prognosis and stratification in clinical practice and treatment trials in MCI-LB.

Characterization of DLB plasma proteome

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Background:

Biomarker discovery can be confounded by comorbid neuropathology and therefore may be best used in combination with other markers. Comprehensive proteomics of biofluids, including plasma, identified biomarkers in different neurodegenerative disorders have been studied but less is known about the Dementia with Lewy Bodies (DLB) plasma proteome especially in carefully characterized cohorts. The aim of this project is to delineate the relationship between the plasma proteome and established biomarkers generated under existing biobanks including cerebrospinal fluid $A\beta_{42}/A\beta_{40}$ (A), p-tau_{181} (T), NfL (N), and Alpha-Synuclein (S) (ATNS). We hypothesize that the plasma proteome is different in DLB compared to cognitively normal individuals (CN) and individuals diagnosed with Alzheimer's Disease (AD) or Parkinson's Disease (PD).

Methods:

The cohort will be recruited from existing biobanking resources (Cleveland Clinic Lou Ruvo Center for Brain Health Aging and Neurodegeneration Biobank, Cleveland Alzheimer's Disease Research Center and the Dementia with Lewy Bodies Consortium). It will consist of CN, DLB, AD, and PD. The SomaLogic SomaScan 11K Assay v5.0 will be used to evaluate the DLB plasma proteome to quantify 11,000 protein measurements simultaneously.

Results:

Our preliminary data from a small sub cohort suggests that there are changes in the plasma proteome in DLB and PD, compared to CN and AD. When the plasma proteome of CN was compared to DLB, multiple proteins were significantly different between groups suggesting that a plasma biomarker signature can differentiate AD/ADRD.

Conclusion:

These preliminary findings warrant further study of the plasma proteome in DLB and is a first step in defining a blood-based biomarker tool for detection of underlying pathobiological features that are AD/ADRD pathology specific. This will help guide precision medicine therapeutic strategies in AD/ADRD.

Plasma Biomarkers of Alzheimer's Pathology, neuroinflammation and neurodegeneration Identify Prodromal Dementia with Lewy bodies

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Background:

Plasma biomarkers for Alzheimer's disease (AD) pathology, neuronal damage and neuroinflammation have been intensively investigated in AD-related neurodegeneration. Comorbid AD pathology is common in dementia with Lewy bodies (DLB) and neuroinflammation might contribute to neurodegeneration. Plasma biomarkers of AD pathology, neuronal loss or neuroinflammation might be useful to identify prodromal DLB in idiopathic/isolated REM sleep behavior disorder (iRBD), an incipient synucleinopathy. This study investigated whether plasma biomarkers of AD pathology, neuroinflammation or neurodegeneration can predict phenoconversion from iRBD to DLB.

Methods:

Participants with polysomnography-confirmed iRBD were recruited at Hôpital du Sacré-Coeur de Montréal between 2004 and 2022, each providing plasma for assessment markers for AD-related pathology (Aβ40,Aβ42,pTau181), neurodegeneration (NfL) and neuroinflammation (GFAP). Participants were prospectively followed to determine phenoconversion ('phenoconvertors') to a defined neurodegenerative disorder based upon meeting diagnostic criteria for DLB, Parkinson's disease (PD) or Multiple System Atrophy (MSA). People not meeting any criteria at censoring date were considered 'non-phenoconvertors'. Association analysis between plasma AD biomarkers at baseline and eventual development of DLB was performed, adjusted for age and sex.

Results:

144 iRBD patients (110M, 67.2±8.0y) were analyzed, of whom 32 individuals phenoconverted to DLB (n=18), PD (n=13) or MSA (n=1) during prospective follow-up. In phenoconvertors, plasma Aβ42/40 was lower compared to non-phenoconvertors (0.103±0.010 vs. 0.114±0.012, $p<0.001$), whereas pTau181 (0.997±0.355 vs. 0.786±0.268pg/ml, $p=0.004$) and GFAP (0.092±0.071 vs. 0.071±0.033ng/ml, $p=0.006$) were higher than in non-phenoconvertors. Differences were selectively seen in prodromal DLB compared to non-phenoconvertors for Aβ42/40 (-0.011, $p<0.001$), pTau181 (+0.282pg/ml, $p<0.001$), as well as GFAP (+0.044ng/ml, $p=0.010$) and NfL (+1.17pg/ml, $p=0.032$).

Conclusion:

Our results show that plasma Aβ42/40, pTau181, GFAP and NfL can identify prodromal DLB in an iRBD cohort. Moreover, this suggests AD pathology and neuroinflammation might be key factors in determining whether a patient with iRBD develops primary dementia or parkinsonism.

Plasma small extracellular vesicles enriched for microglial origin as potential blood-based diagnostic biomarkers for Dementia with Lewy bodies

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Background:

Accurate distinction between DLB and Alzheimer's disease (AD) is important because they differ in their prognosis, risk profiles, and treatment. Current radioisotopes-based imaging biomarkers for DLB are not feasible in many clinical settings. There is an urgent clinical need for identifying blood-based biomarkers that can be used routinely for distinguishing DLB from AD.

Microglia and neurons release small (30-100nm) extracellular vesicles (SEV) that transport RNA between brain and blood. Chronic microglial activation contributes towards AD pathology. Immunohistochemical, transcriptomic and proteomic studies revealed absence of chronic neuroinflammation in moderate to severe DLB. We have already demonstrated statistically significant downregulation of several pro-inflammatory RNA, including *IL1B*, *CXCL8*, *MIR320C2*, in post-mortem DLB brains and in blood-based SEV from people living with DLB.

Methods:

Neuroinflammation-focused plasma SEV RNA are hypothesised to aid distinguishing DLB from AD accurately. We have collected plasma samples from people with, (i)DLB; (ii)AD; and (iii)people without cognitive impairment or Parkinson's disease, for our Blood-based biomarkers for DLB (BBDLB) study. We separated SEV from platelet-free plasma samples using *Izon qEV* size exclusion chromatography. We enriched plasma SEV for microglial origin by TMEM119 immunoprecipitation. We confirmed separation and enrichment of SEV using cryo-transmission electron microscopy, *ZetaView* nanoparticle tracking analysis and *Exoview* interferometric reflectance imaging. We extracted total RNA from the enriched plasma SEV. We are investigating DLB-specific differentially expressed RNA using next-generation RNA-sequencing (RNA-Seq) now.

Results:

Our RNA-Seq data analysis pipeline will identify differentially expressed RNA. We have developed a scalable hybrid multi-objective evolutionary search and optimisation algorithm for developing multiplex diagnostic biomarker assays from omics data. We will identify the most accurate and most parsimonious differentially expressed RNA combination for differentiating DLB from AD using the algorithm.

Conclusion:

We will develop a bespoke prototype multiplex plasma SEV RNA assay using the identified RNA combination and will evaluate its diagnostic accuracy in an independent cohort.

Plasma Dopa-decarboxylase (DDC) is elevated in Lewy Body Dementia and is associated with cognitive impairment at baseline and longitudinal decline.

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Background:

Dopa-decarboxylase (DDC) in plasma and cerebrospinal fluid has been identified as a potential marker of parkinsonian disorders including Lewy body dementia (LBD).

Methods:

Twenty participants with LBD, fifteen with mild cognitive impairment with positive amyloid positron emission tomography or early Alzheimer's dementia (MCI+AD), and fifteen control participants from the Neuroinflammation in Memory and Related Disorders (NIMROD) study underwent plasma sampling. Levels of DDC were measured using the Olink Metabolism target96 assay. Baseline cognition and longitudinal decline (up to three years) were assessed with the Addenbrookes cognitive examination revised (ACE-R). Plasma phosphorylated tau-217 (ptau217) using the ALZpath assay and polygenic risk scores (PRS) from Illumina OmniExpress arrays were analysed. An analysis of variance compared levels of DDC across groups adjusting for age and sex. Areas under the curve (AUC) were calculated using logistic regression.

Results:

DDC was elevated in LBD compared to controls ($F=6.528$, $p=0.003$) but no significant differences were observed between LBD and MCI+AD or between MCI+AD and controls. Higher DDC levels were associated with lower baseline ACE-R scores ($F=5.9$, $p=0.001$) and greater longitudinal decline in ACE-R ($F=3.8$, $p=0.01$). DDC was not able to accurately discriminate between LBD and MCI+AD (AUC=0.55).

We then tested whether a combination of markers could improve the differentiation between LBD and MCI+AD. A model combining ptau217, Apolipoprotein E genotype (APOE) and a LBD PRS performed better than the individual markers and achieved AUC=0.85. The addition of DDC improved the LBD vs MCI+AD discrimination and achieved AUC=0.92.

Conclusion:

DDC is elevated in LBD and is associated with cognitive decline. A model combining DDC with ptau217 and genetic markers showed promise in accurately discriminating between LBD and AD. These findings will need replication in larger cohorts.

Diagnostic Performance of the RT-QuIC α-synuclein in Dementia with Lewy Bodies from the AlphaLewyMA Cohort

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Background:

There are currently no biomarkers used in routine clinical practice for diagnosing dementia with Lewy Bodies (DLB). In this study, we evaluate the diagnostic performance of the synuclein RT-QuIC protocol that we have set up in Strasbourg on a well-characterised cohort of patients (AlphaLewyMA's cohort). Our aim is also to determine the best parameters/cut-offs to use to facilitate the differential diagnosis between DLB and AD.

Methods:

149 CSF were subjected to RT-QuIC, including 88 DLB, 19 AD, 33 DLB+AD and 9 patients considered to be neurological controls. RT-QuIC were performed in 96-well plates, 40mM NaPO4, 170mM NaCL, 10µM Thiflavin T, 0.0005% SDS, ten zirconia/silica beads (0.5mm diameter), 0.07mg/mL recombinant alpha-synuclein and 15µL CSF, for 100µL per well. Plates were read on a FLUOstar Omega spectrophotometer (BMGlabtech) with regular agitation for 225h. Each patient was run in quadruplicate.

Results:

By comparing pure DLB and pure AD and using the cut-off of a minimum of 2 positive wells, we obtained a specificity of 89.5% and a sensitivity of 55.7%. However, by also including patients with a single positive well but exceeding the threshold of 28% fluo max, we improved the differential diagnosis with a final specificity and sensitivity of 95.2% and 68.2% respectively. We also noted that patients with DLB+AD had a lower sensitivity with a sensitivity of 45.5% improved to 54.5% with our parameters. Interestingly, 5 out of 9 controls patients had a positive RT-QuIC.

Conclusion:

We note that our RT-QuIC protocol provides excellent specificity, but lacks sensitivity. Surprisingly, comorbidities appear to be even less well detected. In addition, more than half of the patients for whom a diagnosis other than DLB or AD had been retained had a positive RT-QuIC. RT-QuIC therefore appears to be an interesting way of identifying DLB patients who do not respond to McKeith's criteria.

Plasma Phosphorylated-tau 217 and 231 are elevated in Lewy Body Dementia and have limited accuracy in differentiating Lewy Body dementia from Alzheimer's disease.

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Background:

Plasma phosphorylated tau 217(ptau217) and ptau231 show high accuracy in detecting Alzheimer's disease pathology. Their performance in differentiating AD from Lewy Body Dementia (LBD) may be limited, likely due to AD co-pathology in LBD.

Methods:

Fifty-two participants with LBD, 97 with mild cognitive impairment with positive amyloid positron emission tomography (PET) or early Alzheimer's dementia (MCI+AD) and 66 controls underwent plasma sampling. Ptau217 was measured using the ALZpath Simoa assay and ptau231 using the University of Gothenburg Simoa assay. Pittsburgh compound B amyloid PET was available for a subset of LBD (n=29, 15 positive). An analysis of variance compared the levels of ptau217 or ptau231 across controls, MCI+AD and LBD adjusting for age and sex. A logistic regression was used for comparing LBD based on amyloid PET status. Areas under the curve (AUC) were calculated using DeLong statistics.

Results:

Ptau217 was elevated in MCI+AD compared to controls (est=9.15, p=1.43e-16) and compared to LBD (est=2.65, p=0.02). Ptau217 was elevated in LBD compared to controls (est=5.42, p=4.87e-7). Ptau217 could not accurately differentiate MCI+AD from LBD (AUC=0.66, sensitivity=0.68, specificity=0.73). Ptau231 was elevated in MCI+AD compared to controls (est=0.17, p=0.001) and in LBD compared to controls (est=0.22, p=0.0001) but not in MCI+AD compared to LBD (p=0.46).

In LBD stratified by amyloid PET status, there were no significant differences in the levels of ptau217 (p=0.53, AUC=0.63) or ptau231(p=0.59, AUC=0.54) between amyloid PET positive and negative LBD. Ptau217 was more accurate in differentiating MCI+AD from amyloid PET negative LBD (AUC=0.74, sensitivity=0.72, specificity=0.90) while ptau231 showed lower sensitivity and comparable specificity (AUC 0.56, sensitivity=0.37, specificity=0.90).

Conclusion:

The elevations of ptau217 and ptau231 in LBD compared to controls suggest the presence of AD co-pathology in LBD may not be fully captured by amyloid PET positivity. Further research is needed to identify biomarkers that can accurately discriminate between AD and LBD.

The CSF profile of pathological Tau and P-Tau and normal Aβ42 corresponds mainly to patients with comorbid AD and DLB

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Background:

Some CSF Alzheimer's biomarker profiles are difficult to interpret due to a lack of information about them in the literature. This is the case for the profile with normal Aβ42 and pathologically increased levels of Tau and P-Tau. We decided to analyse patients from Strasbourg with this type of profile.

Methods:

We first extracted 184 patients with a normal Ab42 and pathological Tau and P-Tau profile who had been followed up in the neurology or geriatrics departments of Strasbourg. All these patients' files were reviewed by specialists and each patient was given a diagnosis. Secondly, we recovered Alzheimer biomarker results and clinical diagnoses from a cohort of patients who underwent lumbar puncture between February 2010 and August 2014. 1201 patients were classified according to the diagnoses made at the time, we then selected AD and DLB patients and determined their biomarker results.

Results:

57% of patients with a normal Aβ42 and pathological Tau and P-Tau profile are patients with AD and DLB co-morbidity, followed by patients with pure AD in 22% of cases. In our second cohort of patients, 59 patients were diagnosed with a co-morbidity of AD and DLB. We analysed the profile of these patients and found that the majority (64%) had a normal Aβ42 and pathological Tau and P-Tau profile, and only 22% had all 3 pathological biomarkers.

Conclusion:

These results suggest that AD+DLB comorbidities mainly have this biochemical profile of pathological Tau and P-Tau and normal Aβ42. This result is rather counter-intuitive, since Aβ42 levels are reduced in AD and DLB when they are ‘pure’ and the combination of the two does not seem to have a direct impact on Aβ42 levels in the CSF, suggesting a different action of the reduction in Aβ42 between the 2 diseases which ‘cancels out’ during a co-pathology.

Testing the alpha-synuclein seed amplification assay in dementia with Lewy bodies across European countries

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Background:

The diagnosis of Dementia with Lewy Bodies (DLB) relies on clinical features and cognitive tests and is supported by imaging biomarkers. Although the new diagnostic criteria have improved diagnostic rates, DLB is still underdiagnosed. Therefore, there is a need for laboratory tests to enable a more accurate diagnosis of DLB. The alpha-synuclein seed amplification assay (SAA) has recently shown promising results for diagnosing DLB using various types of samples, including cerebrospinal fluid (CSF). One of the current barriers to scaling up and implementing SAA clinically is the use of different protocols across laboratories. It is currently unknown how these different protocols perform head-to-head, which will be relevant for multi-center studies and the clinical implementation of SAA. Our goal was to test the performance of SAA across five different labs using different SAA protocols.

Methods:

The study included 20 DLB patients (all DAT scan positive, 10 Ab positive, 10 Ab negative, 67.6 years old, 60 % male, with mild to moderate dementia) and 10 age- and sex-matched cognitively unimpaired controls, analyzed at all labs.

Results:

Our interim result for 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. Formal statistical analyses showed a significantly lower specificity for Lab C compared to Lab A ($p=0.042$). The SAA result was statistically comparable in Ab positive and Ab negative DLB groups.

Conclusion:

On average, the three labs achieved 88% sensitivity and 83% specificity, highlighting 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.

A longitudinal study of blood biomarkers of inflammation and neurodegeneration in dementia with Lewy bodies

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Background:

Longitudinal studies of dementia with Lewy bodies (DLB) are needed to understand disease course and the relevance of emerging blood biomarkers. We aimed to describe associations between longitudinal clinical outcomes and blood biomarkers of neurodegeneration, inflammation and Alzheimer's disease (AD) in DLB.

Methods:

Twenty-eight participants with DLB underwent annual clinical evaluation (including mini-mental state examination [MMSE]) and blood collection up to three years. Plasma samples were analysed for neurofilament light (NfL), phosphorylated tau-181 (p-tau181), glial fibrillary acidic protein (GFAP), YKL-40 and inflammatory cytokines (IFN-γ, IL-1β, IL-4, IL-6, IL-10 and TNF-α). Change in MMSE and blood biomarkers was estimated from baseline to the final visit and compared between those who completed the study and those who did not using quantile regression.

Results:

Of 28 participants (median age 74 [IQR 70-78] years, 24 male), 20 completed the 3-year study. Non-completion was due to death (n=7) or clinical progression (n=1).

Compared to participants who completed the study, at baseline, non-completers were older (age 76 [68.-77.3] years, vs 71 [68.3, 77.3] years, p=0.049) and had worse MMSE scores (24 [22.5, 25.5], vs 26 [25.75. 28.25], p=0.015). Median baseline blood biomarker levels were not different between groups, although in the non-completion group IL-6 levels were higher and IL-10 levels were lower at the upper quartile.

Over 3 years we detected an increase for most participants in NfL, p-tau-181, GFAP, IL-6, IL-8 and IL-10, although GFAP was the only significant change on median regression (+63.89 pg/mL, 95% confidence interval 7.25-130.53, p=0.028).

Conclusion:

GFAP was the only blood biomarker observed to increase significantly over 3 years in our DLB cohort, although a trend towards increased NfL, p-tau181, IL-6, IL-8 and IL-10 was also detected. Study non-completion was related to death or disease progression and we did not detect differences in median biomarker levels at baseline.

Blood biomarkers of inflammation and neurodegeneration in dementia with Lewy bodies

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Background:

Whether blood biomarkers of neuroinflammation and Alzheimer's disease (AD) co-pathology are of utility in patients with dementia with Lewy bodies (DLB) remains to be established. We aimed to compare blood biomarkers of neurodegeneration, inflammation and AD between patients with DLB and healthy controls.

Methods:

Participants with DLB and cognitively normal healthy controls (age and sex-matched) provided fasting blood samples. Plasma was analysed for neurofilament light (NfL), phosphorylated tau-181 (p-tau181) and glial fibrillary acidic protein (GFAP) using single molecule array. The astrocyte marker YKL-40 was measured by enzyme-linked immunosorbent assay and inflammatory cytokines (TNF-α, IL-1β, IL-4, IL-6, IL-10, IFN-γ) were measured by mesoscale discovery immunoassay. Differences between groups were assessed with quantile regression and receiver-operating characteristic analysis for area under the curve (AUC) was performed to assess each biomarker's utility in discriminating DLB participants from healthy controls.

Results:

Fifty DLB participants (median age 74 [IQR 70-78] years, 41 male) and 20 controls (median age 75 [IQR 71.8-77.3] years, 16 male) were included. NfL levels were higher in the DLB group compared to controls (DLB median 18.1 [IQR 14.2-24.7] pg/mL vs 12.6 [10.7-16.4] pg/mL, p=0.033) and NfL was the most useful individual marker to discriminate between groups (AUC 0.704, 95% confidence interval 0.57-0.84). GFAP levels were significantly higher in the DLB group only at the upper quartile. No significant difference was observed between groups with other biomarkers, although there was a trend towards increased p-tau181 and IL-10 in the DLB group.

Conclusion:

Plasma NfL was higher in participants with DLB, compared to age and sex-matched healthy controls. In addition, there was a trend towards higher levels of biomarkers related to AD (p-tau181), astrocyte activation (GFAP) and the anti-inflammatory cytokine IL-10. The utility of these non-disease specific blood biomarkers in DLB remains uncertain.

Plasma brain-derived tau and phosphorylated tau 217 are associated with alzheimer's co-pathology in dementia with lewy bodies

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Background:

Concomitant Alzheimer's disease (AD) pathology affects clinical presentation and contributes to faster disease progression in Lewy body dementia (LBD). Recently, blood-based biomarkers have become promising tools for early and accurate AD diagnosis, however, their performance compared to the established cerebrospinal fluid (CSF) biomarkers in LBD is poorly investigated. We aimed to evaluate whether plasma phosphorylated tau 217 (p-tau217) and brain-derived tau (BD tau) can identify AD co-pathology in LBD.

Methods:

We included 130 memory clinic patients with probable LBD (n=52), AD dementia (n=53) and mild cognitive impairment (MCI) due to AD (n=25). Plasma p-tau217 and BD tau were quantified with in-house Single-molecule array assays. Neurofilament light (NFL) and glial fibrillary acidic protein (GFAP) in plasma were measured with Quanterix multiplex assay. The presence of AD pathology was determined by core CSF biomarkers (Innotest amyloid-beta 42 and 40, total-tau, and p-tau181).

Results:

Decreased CSF amyloid-beta 42/40 ratio was found in 49% of LBD patients and was associated with poorer performance on mini-mental state examination (18±4 versus 23±4; p=0.0001), higher plasma p-tau217 (3.80 versus 1.66 pg/ml; p=0.0001), BD tau (8.15 versus 5.50 pg/ml; p=0.0075) and GFAP concentrations (294 versus 176 pg/ml; p=0.0005) compared to LBD with normal CSF profile. BD tau and p-tau217 correlated with CSF amyloid-beta ratio (rho=-0.499 and -0.691; p<0.001), t-tau (rho=0.436 and 0.544; p<0.001) and p-tau181 (rho=0.380 and 0.494; p<0.01) and detected amyloid co-pathology in LBD with 73% and 83% accuracy, respectively. Plasma p-tau217 was higher in AD dementia than in LBD (3.71 versus 2.55 pg/ml; p=0.0032), while BD tau was similar across the patient groups. Nevertheless, the p-tau217/BD tau ratio differentiated LBD from AD (MCI and dementia) slightly better (AUC=70%; p<0.0001) than p-tau217 alone (AUC=63%; p=0.01).

Conclusion:

Plasma p-tau217 and BD tau are associated with underlying AD co-pathology in LBD and may prove useful for patient stratification in future clinical trials.

Changed in levels of plasmin-related proteins and brain-derived neurotrophic factor are associated with regional brain atrophy in alpha-synucleinopathies

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Background:

Plasmin is a serine protease acting in tissue/synaptic remodeling, inflammation regulation, NMDA-mediated signalling and modulation of neurotrophic factors. Brain plasmin is regulated by activating tissue plasminogen activator (tPA) and by inhibiting plasminogen activator inhibitor-1 (PAI-1). Brain-derived neurotrophic factor (BDNF) is an abundant neurotrophin. Levels of these factors and their associations with regional brain atrophy in alpha-synucleinopathies (PD, DLB and MSA) are unclear.

Methods:

Serum levels of tPA, PAI-1, BDNF and their ratios and MRI-derived brain atrophy were investigated in 34 DLB, 11 MSA and 11 PD patients vs 10 cognitively unimpaired controls. tPA, PAI-1 and BDNF serum concentrations were quantified using ELISA. Regional brain atrophy was measured using automated algorithm FreeSurfer v7.0 and autopsy-derived probabilistic mask of basal forebrain. Associations of regional atrophy measures with protein levels were assessed using multivariate linear regression models and false discovery rate-corrected.

Results:

We showed dysregulated plasmin synthesis by age-adjusted differences in PAI-1 among groups (p<.001): PD (p=.027) and especially MSA (p<.001) patients showed higher PAI-1 vs controls. PAI-1 differed in DLB vs MSA (p=.008). BDNF levels were higher in DLB (p<.001), PD (p<.001) and MSA (p=.012) vs controls. PAI-1/BDNF ratio differed in MSA vs DLB (p=.008). PAI-1 and PAI-1/BDNF ratio levels were inversely associated with regional atrophy in several regions including volumes of cholinergic basal forebrain nuclei, nucleus accumbens, hippocampus, basal ganglia and brainstem, and posterior cingulate, retrosplenial, parahippocampal cortical thickness (p<.05) in synucleinopathies.

Conclusion:

Plasmin system proteins and BDNF levels are altered in alpha-synucleinopathies and are associated with regional brain atrophy, notably in basal forebrain and several cortical regions receiving its cholinergic outputs. Increased BDNF levels may suggest a compensatory mechanism. Plasmin system and BDNF may be explored as therapeutic targets in alpha-synucleinopathies, however further research on these proteins and their role in brain atrophy is warranted.

Alzheimer biomarkers in spinal fluid as a measurement of progression and severity of Dementia of Lewy bodies

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Background:

Dementia with Lewy Bodies (DLB) is a neurodegenerative disease, pathologically characterized by the accumulation of alpha-synuclein in intraneuronal Lewy bodies. The disease is often seen with concomitant AD pathology with low levels of Aβ42, high levels of t-tau, and p-tau in CSF. This study aims to elucidate whether Aβ42, t-tau, and p-tau are related to the progression and severity of DLB.

Methods:

46 patients fulfilling the clinical criteria for probable dementia with Lewy bodies, followed in the movement disorder clinic at Copenhagen University Hospital from 2017 to 2023 with accessible results from lumbar puncture were included in this study. The values of Aβ42, t-tau, and p-tau were correlated to the patients' MoCA scores, the time from the onset of symptoms to diagnosis, the time from diagnosis to initiation of antipsychotics (n=28), and the time from diagnosis to nursing home admittance (n=22), and the time from diagnosis to death (n=18).

Results:

The mean value of Aβ42 in CSF was 702,2±248,8 pg/ml, 30% had an abnormally low value. Only 5 patients had abnormal high p-tau. Abnormally elevated t-tau was found in 20% of patients.

No significant correlation between Aβ42, t-tau, and p-tau and MoCA, the onset of symptoms to diagnosis, the time from diagnosis to initiation of antipsychotics (n=28), and the time from diagnosis to nursing home admittance (n=22), and the time from diagnosis to death (n=18). A trend was found between MoCA and lower levels of Aβ42 (p=0.08).

Conclusion:

These findings indicate that although AD pathology is frequent in patients with DLB, it does not play a major role in the progression and severity of DLB. More studies are needed to confirm this hypothesis.

Longitudinal Measurements of Cerebrospinal Fluid Biomarkers of Alzheimer's Disease and Neuronal Damage in Dementia with Lewy Bodies

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Background:

Pathology studies report up to 80% Alzheimer's disease(AD)-copathology in Dementia with Lewy Bodies (DLB). *In vivo* cerebrospinal fluid(CSF)-studies report a lower percentage: ±50%. Little is known about the development of CSF biomarkers in DLB. We aimed to investigate longitudinal changes in biomarkers of AD and neuronal damage in DLB versus healthy controls (HC).

Methods:

We included 38 DLB-individuals (68.0±5.6y, 89.5%male, MMSE 25.9±2.3) and 48 age-matched HC (68.0±6.2y, 47.9%male, MMSE 29.1±1.1) with 2 longitudinal measures of CSF (follow-up time 2.0±0.9y). In repeated CSF-samples (n=172), $A\beta_{1-42}$, t-tau and p-tau_{181} were measured with Lumipulse (n=162), Innotest (n=7) and Elecsys (n=3). Additionally, in repeated CSF-samples (n=56) of the DLB-group only, neurofilament-light chain (NfL) and glial fibrillary acidic protein (GFAP) were measured with SIMOA. Paired t-tests for SIMOA-results and repeated measures ANOVAs for Lumipulse-results were performed to investigate (group/)time-differences. For all AD-biomarker results, the change in proportion with abnormal $A\beta_{1-42}$ and p-tau_{181}/$A\beta_{1-42}$-ratio was described.

Results:

CSF-$A\beta_{1-42}$ and -t-tau were significantly lower in DLB (n=28) versus HC (p<.001 and p=.027). Also, CSF-$A\beta_{1-42}$ significantly declined over time in both groups (p<.001). The p-tau_{181}/$A\beta_{1-42}$-ratio was significantly higher in DLB versus HC (p<.001). Furthermore, CSF-NfL was significantly higher in DLB at follow-up (p=.008). For p-tau_{181} and GFAP no significant group/times-differences were found. The proportion of DLB-individuals (n=38) with abnormal $A\beta_{1-42}$(<714pg/mL) slightly increased over time from 50% to 55% (n=19 to 21). The proportion with an abnormal p-tau_{181}/$A\beta_{1-42}$-ratio(>0.072pg/mL) remained stable: 37% (n=14). In healthy controls these changes were respectively 15% to 17% (n=7 to 8) and 15% to 20% (n=*7* to 9).

Conclusion:

Our data suggest that only CSF-$A\beta_{1-42}$, -p-tau_{181}/$A\beta_{1-42}$-ratio and -NfL significantly change over time in DLB-individuals, but the proportion of patients with abnormal AD-biomarker levels is relatively stable. Further investigation of the development of AD-copathology in DLB over long time-frames becomes increasingly important in light of disease modifying treatments for AD-pathology.

Assessment of the Novel Neuronal Synuclein Disease Staging System in Stratifying Dementia with Lewy Bodies Patients

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Background:

This study explores the applicability of the integrated Neuronal Synuclein Disease (NSD) staging system, initially developed for Parkinson's disease (PD), in patients diagnosed with Dementia with Lewy Bodies (DLB). While both conditions are characterized by alpha-synuclein (αSyn) pathology, DLB exhibits unique clinical features. The NSD system anchors the diseases primarily on the presence of pathological αSyn (S), dopaminergic neurodegeneration shown by dopamine transporter (DAT) SPECT (D), and the degree of clinical signs and functional impairment.

Methods:

We hypothesize that most DLB patients will conform to the NSD staging system (S+/D+), although a significant subset (10-20%) may be S+/D-. the presence of Alzheimer's disease (AD) co-pathology will be assessed.

Results:

From the European DLB Consortium, we have selected 600 subjects with probable DLB, CSF and DAT-SPECT scans. CSF will be analyzed with αSyn Seed Amplification Assay (SAA) and robust AD biomarkers assays. DAT SPECT scans will be processed with DaTQuant software, incorporating additional metrics to improve the quantification of dopaminergic neurodegeneration. The study will compare DAT scan results with the Parkinson's Progression Markers Initiative dataset to establish z-scores and correlate these with clinical data and CSF markers. To test our hypothesis, we will conduct a quantitative analysis to determine the proportion of DLB patients aligning with the NSD staging system and identify any deviations. Additionally, we will evaluate the correlation between AD pathology biomarkers and deviations from the NSD stages using statistical methods, such as regression analysis, to explore this inverse relationship. Furthermore, we will expand on the clinical considerations by not only assessing functional impairment but also addressing the key DLB core symptoms.

Conclusion:

We anticipate that a sample size of approximately 600 patients will yield robust results, with an estimated margin of error of ±1.82%. Preliminary results will be presented at the meeting.

Platelet-derived miRNAs as biomarkers for dementia with Lewy bodies

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Background:

There is a need of peripheral biomarkers for clinical diagnosis of dementia with Lewy bodies (DLB) for its differential diagnosis versus Alzheimer's disease (AD). Different blood fractions represent accessible biomarker sources and since platelets were recently described to contain a functional miRNA pathway and mRNA processing machinery, we studied the platelet *miRNome* to identify a DLB biomarker signature.

Methods:

Platelet RNA was purified, the *miRNome* was profiled by NGS, and 22 differentially expressed miRNAs were identified. Two independent validation studies, Validation-1 (2017-2019) and Validation-2 (2021-2023), enrolled 124 and 130 individuals, respectively including 107 DLB, 70 AD patients, and 79 healthy controls. A prospective study with 157 participants including DLB patients from several EDLB partners is ongoing. miRNA expression levels were determined with Qiagen Custom miRCURY PCR panels. Statistical analysis comprised calculation of the optimal cut-off point based on the threshold best classifying DLB vs AD, or DLB vs control subjects. A random forest model was used to trained with the data of validation study (2) and obtain classification decision trees. The model is being tested with the data from the ongoing validation study.

Results:

NGS profiling revealed the deregulation of 22 miRNAs in DLB platelets. Validation-1 showed that seven miRNAs were drastically down-regulated comparing DLB and AD, and four DLB and controls. Validation-2 was analysed applying classification trees. High discrimination capacity of the algorithm to distinguish DLB from AD with sensitivity of 0.9 and specificity of 0.81 was achieved by stepwise interrogation of four miRNAs. To classify DLB and controls, stepwise interrogation of four different miRNAs resulted in discrimination capacity with sensitivity of 0.85 and specificity of 0.88.

Conclusion:

Platelet miRNAs might be useful biomarkers for DLB diagnosis. Whereas four miRNAs distinguish DLB from AD, other four differentiate DLB from healthy controls. These findings are being validated in a prospective study.

Novel plasma biomarkers to differentiate dementia with Lewy bodies from Alzheimer's disease

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Background:

Identifying dementia with Lewy bodies (DLB) at the earliest stages and differentiating from early Alzheimer's disease (AD) allows for appropriate clinical care, as well as access to research and trials of novel therapeutics.

Methods:

Plasma samples were collected from people living with either mild cognitive impairment (MCI)-DLB or early (CDR <1) DLB and MCI-AD or early AD. These were analyzed with novel single molecule array (SiMoA) alpha-synuclein aggregate assay, in addition to microtubule associated protein tau (MAPT) and amyloid-beta 1-40 enzyme-linked immunosorbent assays (ELISA).

Results:

Plasma ELISA levels of MAPT (p=0.01) and amyloid-beta 1-40 (p=0.04) were significantly elevated in MCI-AD/AD (n=19) compared to MCI-LB/DLB (n=9). As a diagnostic test, these assays had receiver operator characteristic curves with an area under the curve (AUC) of 0.865 and 0.796 respectively. Higher levels of plasma SiMoA alpha-synuclein aggregate levels were more frequent without significance in MCI-LB/DLB (n=10) than MCI-AD/AD (n=21) yielding an AUC of 0.714. The p value was 0.114, which could reflect a possible overlap in alpha-synuclein pathology and the need for a larger sample size.

Conclusion:

Plasma MAPT and amyloid-beta 1-40 ELISA levels are a promising diagnostic differentiator between early stage dementia with Lewy bodies and Alzheimer's disease. The novel plasma SiMoA alpha-synuclein aggregate assay was able to detect an increase in frequency of high signal in MCI-LB/DLB compared to MCI-AD/AD. This may be a useful tool to complement alpha-synuclein targeting therapeutics. Both assays should be investigated further with larger cohorts.

Evaluating multiplex proximity extension assays in plasma to identify patterns of inflammation associated with diagnosis and prognosis in DLB

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Background:

It is well recognised that inflammation is an important pathophysiological process in Alzheimer's disease (AD), and now a target in clinical trials. Less is known about the clinical significance of inflammation in Dementia with Lewy bodies (DLB). Multiplex proximity extension assays (PEAs) allow the measurement of numerous inflammatory markers simultaneously, which could identify novel immune biomarkers.

Methods:

Twenty participants with DLB, fifteen with AD or mild cognitive impairment (MCI) with positive amyloid PET scans (MCI+AD), and fifteen controls from the Neuroimaging of Inflammation in Memory and Related Other Disorders (NIMROD) study had inflammatory markers in plasma measured with the OLINK Target-96 Inflammation immunoassay. Cognition was assessed with the Addenbrookes cognitive examination revised (ACE-R) at baseline and follow-up periods up to three years. Inflammatory markers were compared between groups by Mann-Whitney U test. Principal components analysis (PCA) was used to identify patterns of inflammation, which were then used in logistic regression to predict diagnosis and in linear mixed-effects models to assess prognosis.

Results:

Several markers were differentially expressed in DLB compared to controls (with greater EN-RAGE, CCL20, TNFRSF9, IL-17C and lower DNER) but did not survive correction for multiple comparisons. PCA identified four components, with principal component 3 (PC3) distinguished DLB from controls ($p=0.044$, AUC=0.83), MCI+AD from controls ($p=0.03$, AUC=0.74) but not from DLB from MCI+AD ($p=0.45$, AUC=0.66). PC3 was associated with greater rate of cognitive decline in both DLB (estimate -3.35, $p=0.004$) and MCI+AD (estimate -3.3, $p = 0.002$).

Conclusion:

Compared to controls, our study identified distinct patterns of peripheral inflammatory markers in DLB using multiplex PEA. These changes were similar in MCI+AD, predicting cognitive decline in both, suggesting potential common mechanisms driving cognitive decline and that targeting inflammation may also be a putative therapeutic target in DLB. Further prospective and longitudinal studies are needed to validate these results.

Interest of α-synuclein seed amplification assay (SAA) in patients with dementia with Lewy bodies difficult to diagnose

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Background:

Lewy bodies in dementia with Lewy bodies (DLB) patients are composed of misfolded α-synuclein. The α-synuclein RT-QuIC technique has been shown to enable the diagnosis of DLB with excellent sensitivity and specificity. However, it has not been tested in the context of difficult or uncertain diagnoses in prodromal or demented DLB patients.

The main aim of our study is to assess whether α-synuclein RT-QuIC can differentiate DLB from other diseases in a context of diagnostic difficulties.

Methods:

We included 150 patients, including 3 groups : the « difficult » DLB group composed of 50 DLB patients with a difficult diagnosis, the probable DLB group with 50 probable DLB patients and the AD group including 50 patients with Alzheimer's disease.

Technic of the SAA : CSF is mixed with the reaction mix, the recombinant protein used for amplification, the thioflavin T (ThT), which enables detection of a fluorescent signal during fibril formation. The mixture is heated at 42°C, in a context of quaking, for at least 120 hours. This operation is performed simultaneously in 4 wells for each patient.

Results:

Our partial results, without analysis of the AD group and therefore of specificity for the moment, show a sensitivity of 62% with at least 2 positive wells out of 4, and a sensitivity of 83.1% if we consider the positivity of at least one well out of 4.

RT-QuIC analyses are still in progress and will be finalized for the congress in January 2025.

Conclusion:

It would seem that in difficult-to-diagnose DLB patients, we can increase the sensitivity of RT-QuiC by reducing the cut-off number of positive wells to 1. We will expand on our discussion at the conference when we have all the results.

Early blood-based identification of Lewy body disease and Alzheimer's disease

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Background:

Lewy body and Alzheimer's disease-related pathologies can be detected through blood biomarkers. Since 2010, the Danish Blood Donor Study has been collecting plasma samples from Danish blood donors. This study aims to determine how many years before a clinical diagnosis of dementia these pathological proteins can be detected in blood samples.

Methods:

We will link the Danish Blood Donor Register with the National Patient Register to identify blood donors who have received a diagnosis of Dementia with Lewy bodies or Alzheimer's dementia. Their previously collected blood samples will be analyzed for pathological proteins using seed-amplification assays or single-molecule array techniques. In the second phase of the study, we will prospectively invite newly diagnosed donors to join a cohort for comprehensive clinical evaluations.

Results:

We have identified 89 blood samples from 7 Danish blood donors diagnosed with Dementia with Lewy bodies between 2010 and 2022. Additionally, we have identified 1664 samples from 106 donors diagnosed with Alzheimer's dementia. We have obtained permission to analyze these samples for Lewy body and Alzheimer's pathology. Our in-house validation of the P-tau217 analysis demonstrated high precision, comparable to other assays routinely conducted in our laboratory. We are seeking a collaborator with expertise in seed-amplification assays. Based on data from the Danish Database for Dementia, we expect an increase in new diagnoses and an expansion in the number and age range of available plasma samples. Over the next five years, we anticipate enrolling 200 cases into our cohort.

Conclusion:

We expect that pathological changes in blood can be detected at least 15 years prior to a clinical diagnosis, paralleling the changes observed in cerebrospinal fluid. If early, presymptomatic detection of Lewy body and Alzheimer's disease is feasible, the next steps could involve screening individuals in mid-life to identify candidates for trials aimed at slowing or curing the disease.

Influence of α-synuclein on glucose metabolism in the Alzheimer's disease continuum: analyses of α-synuclein Seed Amplification Assay and FDG-PET

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Background:

Alpha-synuclein (α-syn) pathology is increasingly recognized as a frequent pathology alongside classical AD hallmarks in up to 50% of people with AD. The interaction between amyloid-β, tau, and α-syn may form a pathological triumvirate exacerbating neurodegeneration and disease progression. We investigated the association between α-syn pathology and brain glucose metabolism across the cognitive spectrum in the context of AD co-pathologies and examined how these associations may drive clinical disease severity in AD.

Methods:

FDG-PET data from 829 ADNI participants (648 cognitively impaired (CI), 181 unimpaired) were compared between α-syn seed amplification assay (SAA) positive and negative groups. Interactions with CSF AD biomarkers were examined. Mediation analyses assessed whether regional hypometabolism mediated the effect of α-syn pathology on disease severity, measured by Clinical Dementia Rating - Sum of Boxes (CDR-SB), controlling for CSF Aβ42 and ptau181. Statistical significance was set at $p < 0.05$, corrected for multiple comparisons using False Discovery Rate (FDR).

Results:

SAA positivity was associated with widespread hypometabolism among CI individuals, particularly in posterior cortical regions. This association persisted in occipital lobes after controlling for CSF Aβ42 and ptau181 levels, suggesting an independent effect of α-syn pathology on occipital hypometabolism. Mediation analyses revealed that regional hypometabolism, particularly in multi-modal association cortices, significantly mediated the effect of α-syn pathology on worse CDR-SB scores in CI individuals, independent of CSF Aβ42 and ptau181 levels (FDR $p < 0.05$).

Conclusion:

Our results support a model where α-syn aggregation plays a crucial role in metabolic dysfunction and disease progression in the AD spectrum, independent of AD pathology. SAA positivity could optimize participant selection and outcome measures for clinical trials in the AD spectrum, potentially leading to more targeted therapeutic interventions.

The Association between Plasma Biomarkers and Survival in Lewy Body Dementias

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Background:

Lewy body dementia (LBD) has been shown to have higher mortality than Alzheimer's disease (AD), but predictors of this and underpinning mechanisms are unclear. We studied the association between amyloid PET status, plasma phosphorylated tau (p-tau181), b-amyloid 1-42/1-40 ratio (Ab42/40), glial fibrillary acid protein (GFAP) and neurofilament light (NfL) and survival in LBD compared to AD.

Methods:

Baseline p-tau181, Ab42/40, GFAP and NfL were measured with highly sensitive single molecule immunoassays in 64 LBD and 28 AD spectrum participants (AD or PET amyloid positive mild cognitive impairment). Survival from biomarker collection to death was extracted from health records. Censure date was defined as last contact with health services for patients still alive. Survival analyses used Kaplan Meier or Cox proportional hazard models stratified by sex.

Results:

Groups were similar in age (mean age=74.7(0.82) vs 72.2(1.7), $p=0.20$). The LBD group was more cognitively impaired (mean ACER=70.0(1.8) vs 78.3(1.9), $p<0.01$), had more males (79.7% vs 57%, $p=0.048$) and a greater proportion of deaths (76.6% vs 46.4%, $p<0.01$) compared to the AD group. LBD participants had greater hazards of death compared to AD (HR=2.90(0.38), $p<0.01$) when controlling for age and baseline ACER. GFAP was a significant predictor of mortality in LBD, but not AD, when adjusted for age (HR=1.31(0.12) per 100pg/mL, $p=0.03$). This was no longer significant when the model adjusted for both baseline severity (as ACER) and age. P-tau181, Ab42/40 and NfL did not predict survival in LBD nor AD when adjusted for age. Survival in LBD did not differ by Amyloid PET status $(p=0.87)$.

Conclusion:

Survival with LBD remains poorer than with AD despite recent improvements in recognition and management. GFAP is a predictor of mortality when adjusted for age and stratified by sex in LBD but not AD. This may reflect an underlying neuroinflammatory process specific to LBD that drives disease progression.

Imaging/neurophysiology Biomarkers

Oral Abstracts

Imaging biomarkers of neurodegeneration in the DLB spectrum

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Background:

Imaging biomarkers will play a crucial role in detecting the topographically dynamic neurodegenerative changes in DLB starting from the prodromal stage and determining the various neurodegenerative phenotypes of neuronal synuclein disease. We investigated the imaging biomarkers of neurodegeneration in prodromal and overt DLB.

Methods:

Patients with prodromal DLB (MCI-LB) and probable DLB (pDLB) from the DLB Spectrum Study were investigated. Age and gender matched clinically unimpaired (CU) participants were included as the control group. Participants underwent annual MRI, DaTScan, FDG PET, amyloid-β and tau PET imaging along with clinical examinations. Cross-sectional and when available, longitudinal analyses were performed.

Results:

MCI-LB patients had greater atrophy in the basal forebrain which includes nucleus basalis and longitudinally, they showed greater rates of atrophy in cortical regions that receive cholinergic input from nucleus basalis compared to CU, particularly when they converted to pDLB during follow-up. These longitudinal atrophy rates were in-part influenced by tau deposition on PET. FDG PET showed reduced metabolism in the substantia nigra and greater cingulate island sign ratio in MCI-LB and pDLB. Longitudinally, the rate of decline in glucose metabolism was greatest in the occipital, parietal and temporal cortical regions compared to CU, and correlated with clinical decline across the DLB spectrum starting from the prodromal stages.

Conclusion:

Longitudinal imaging biomarkers have the potential to reveal the temporal and hierarchical spread of neuronal injury within the DLB spectrum. Imaging biomarkers of neurodegeneration can be utilized for the biological staging of neuronal synuclein disease, for determining the contribution of multiple dementia etiologies to the clinical phenotype, and as quantitative outcome measures in clinical trials in DLB.

Prediction of phenoconversion in isolated REM sleep behavior disorder using free water imaging: a longitudinal, multicentre, prospective cohort study

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Background:

Isolated REM sleep behavior disorder (iRBD) is the early manifestation most strongly associated with the development of synucleinopathies, as over 90% of patients eventually develop dementia with Lewy bodies (DLB) or Parkinson's disease (PD). iRBD offers a valuable time window for early intervention and the testing of new neuroprotective therapies. However, there is currently a lack of validated objective and quantitative biomarkers to predict disease progression in iRBD, particularly the progression to DLB compared to PD. Free water (FW) is a diffusion MRI-based approach that has been applied in neurodegenerative diseases. It is used to detect increases in extracellular FW of the brain as a proxy of neuroinflammation.

Methods:

A total of 438 participants (261 iRBD patients and 177 controls), underwent diffusion-weighted imaging scans. Of these, 230 patients had longitudinal follow-up data, with 64 (28%) having converted to a neurodegenerative disease and 166 (72%) remaining disease-free. FW fractions were calculated using the FreeWater Flow pipeline and extracted from the left and right basal forebrain (BF), and posterior substantia nigra (pSN). Binary logistic regressions assessed phenoconversion, while multinomial regressions examined phenoconversion subtypes, adjusting for age and sex.

Results:

When iRBD patients were stratified based on phenoconversion status, significant differences emerged, contrary to when comparing iRBD patients to controls. The iRBD patients who converted to a disease exhibited increased FW values in the left and right BF and the left pSN compared to those who did not develop a disease. Increased FW values in the BF were significantly associated with an increased likelihood of developing dementia with Lewy bodies.

Conclusion:

FW measurement in the substantia nigra and the basal forebrain has the potential of predicting the development of a synucleinopathy. Notably, it was associated with the differential development of dementia with Lewy bodies versus Parkinson’s disease, demonstrating the potential of this marker for early prognosis.

Increased functional coupling of EEG pre-alpha rhythms in patients with Dementia with Lewy Bodies

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Background:

In the present study we investigated if the specific EEG pre-alpha activity present in DLB patients could be associated to abnormal cortical functional connectivity. We hypothesized an increased pre-alpha connectivity in DLB patients compared to individuals with Alzheimer's Disease (AD) and healthy controls (HC).

Methods:

EEG recordings were obtained from 80 DLB, 80 AD, and 55 HC from four European DLB Consortium Centers. We used eLORETA to calculate lagged linear connectivity (LLC),

among specific cortical regions of interest across various frequency bands (delta, theta, pre-alpha, alpha, beta, gamma).

Results:

Statistical analyses unveiled enhanced fronto-occipital connectivity in the theta and pre-alpha bands in DLB patients compared to both the AD and HC groups, suggesting enhanced fronto-occipital connectivity. Both DLB and AD groups displayed reduced connectivity in the alpha band compared to HC.

Conclusion:

The results suggest that resting-state EEG pre-alpha activity specific of DLB patients, potentially generated in the cerebral cortex due to dysfunctional thalamocortical connectivity, is linked to increased fronto-occipital connectivity.

The dementia with Lewy bodies related metabolic brain pattern expression in patients with dementia with Lewy bodies, Alzheimer dementia and Parkinson disease dementia: a multicentric study

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Background:

DLB-related metabolic brain pattern (DLBRP) has been identified from the FDG-PET brain imaging of DLB patients and normal controls (NC). The pattern can discriminate between DLB and NC and DLB and Alzheimer dementia (AD). The DLBRP expression has not been studied in multicentric setting neither in Parkinson disease dementia (PDD).

Methods:

We analysed 935 FDG-PET scans from patients with DLB (n=317), AD (n=213), PDD (n=75) and NC (n=330) from UMC Ljubljana, Slovenia (LJU), FIMR, NY, USA, Asan Medical Center, Seoul, South Korea**,** European DLB Consortium, ADNI and AIMN database. After pre-processing we used topographic profile rating to calculate the expression of DLBRP and metabolic brain patterns characteristic for AD (ADRP and default mode network (DMN)) and PD (PDRP and PDCP). Scores were compared between groups and correlated to clinical parameters. LJU dataset (79 DLB, 63 AD, 20 PDD, 41 NC) was used to define the cut-offs.

Results:

DLBRP scores (cut-off Z=1.43) could accurately distinguish between DLB and NCs (all AUCs>0.94). Based on DLBRP, but not ADRP or DMN, we could discriminate between DLB and AD (Z=3.9, AUC=0.85 in validation cohort). Based on DLBRP, PDRP, PDCP or DMN we could only modestly differentiate between DLB and PDD (AUC=0.67 for single network and AUC=0.77 for composite). We observed metabolic differences in frontal, parietal and occipital cortices between groups (p<0.05, bonf-adjust). DLBRP expression correlated with MMSE in DLB (r=−0.30, p<0.001) and multiple linear regression showed that MMSE scores were related to DLBRP gain and DMN loss but not to ADRP or PDCP.

Conclusion:

DLBRP can accurately distinguish between DLB and NC and between DLB and AD from multiple centres and different scanners, proving the robustness of the pattern. The network differences between DLB and PDD warrant further exploration, especially due to observed regional metabolic differences and different network mechanism of cognitive impairment in DLB.

Glymphatic dysfunction contributes to development of cognitive impairment in Parkinson's independently from white matter degeneration

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Background:

Impaired clearance due to glymphatic system dysfunction may contribute to misfolded alpha-synuclein accumulation, and amyloid and tau co-pathology in Lewy body disease. Glymphatic dysfunction is seen in Parkinson's (PD) but how it contributes to cognitive impairment remains unclear.

Methods:

Here we use diffusion tensor image analysis along the perivascular space (DTI-ALPS) to assess glymphatic system efficiency in-vivo in 98 PD patients (31 PD-poor cognition who developed dementia or mild cognitive impairment during follow-up; 67 PD-normal cognition) and 28 age-matched controls at baseline, and after 18- and 36-months. We assess the relationship of DTI-ALPS index to cognition, white matter integrity (fibre cross-section of contralateral hemisphere), and plasma levels of neurofilament light chain (NFL) and phosphorylated tau 181 (p-tau) at baseline and longitudinally, adjusting for age and sex.

Results:

Baseline DTI-ALPS index was lower in PD-poor cognition (mean± standard deviation: 1.08±0.162) compared to PD-normal cognition (1.20±0.16) and controls (1.18±0.20)($p=0.005$). DTI-ALPS index showed additional longitudinal reductions in PD-poor cognition, but remained stable in PD with stable cognition and controls (group*time interaction: $\beta=-0.013$, $p=0.021$). DTI-ALPS index was correlated with overall disease severity at baseline (UPDRS total, $p=0.036$) but not longitudinally ($p=0.083$).

Lower DTI-ALPS index was associated with lower fibre cross-section within right posterior thalamic radiation and left anterior corona radiata at baseline and left corona radiata and superior longitudinal fasciculus at follow-up (whole-brain, age- and sex-corrected, FWE $p<0.05$); this was spatially distinct from white matter changes seen in PD-poor outcomes. There was no correlation between DTI-ALPS at baseline and subsequent plasma ptau-181 ($p=0.642$) or NFL ($p=0.448$).

Conclusion:

PD patients who develop cognitive impairment over 3-years show glymphatic dysfunction at baseline and worsening longitudinally. DTI-ALPS was correlated with white matter integrity but in a different spatial distribution and not with NFL; this suggests that glymphatic dysfunction contributes to the development of dementia independently from white matter degeneration.

Pathways for the progression of neurodegeneration in dementia with Lewy bodies

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Background:

The determinants of regional neurodegeneration in dementia with Lewy bodies (DLB) remain largely unexplored. The underlying alpha-synuclein pathology is hypothesized to spread along structural connections with affected brain regions undergoing neurodegeneration. We aimed to determine whether brain regions that are more closely connected to amygdala and brainstem, i.e. two suggested origins of the alpha-synuclein pathology, exhibit greater volume reductions compared to more distantly connected regions. Additionally, we investigated whether regions that are more integrated in the brain network overall exhibit greater volume reductions compared to less integrated regions.

Methods:

We included 80 DLB patients and 65 cognitively healthy controls (HCs) from the Newcastle cohort of the European DLB consortium. Volumetric differences between DLB patients and HCs were quantified in 122 brain regions from T1-weighted MRI, using averaged w-scores. Tractography of white matter pathways between brain regions was performed on diffusion-weighted images from DLB patients to build an average structural network. The distance of brain regions to amygdala and brain stem, and the regions' integration in the network was calculated using graph theoretical network measures. Lastly, we correlated network measures with regional volumetric w-scores.

Results:

Most brain regions showed lower volumes in DLB patients compared with HCs, with neurodegeneration being most pronounced in temporal and parietal lobes. Regions more closely connected to the amygdala showed more volume reductions. In contrast, distance to the brainstem did not significantly correlate with regional w-scores. Likewise, the integration of brain regions within the structural network did not significantly correlate with regional w-scores.

Conclusion:

Our results emphasize that structural connections with the amygdala predict regional neurodegeneration, suggesting that the amygdala is an important relay region for the spread of the alpha-synuclein pathology. Moreover, our findings support the use of imaging biomarkers to track disease progression in the absence of a topographic biomarker for the alpha-synuclein pathology.

Poster Abstracts

Distinct brain atrophy progression subtypes underlie phenoconversion in isolated REM sleep behaviour disorder

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Background:

Synucleinopathies encompass a spectrum of disorders with varying features and severity, including isolated REM sleep behavior disorder (iRBD) and dementia with Lewy bodies

(DLB). Brain atrophy patterns in iRBD already resemble those of advanced stages of the disease and are linked to cognitive impairment, particularly in the progression to DLB. However, the progression of brain atrophy remains poorly understood.

Methods:

A multicentric cohort of 1134 participants, namely 451 with polysomnography-confirmed iRBD, 87 with DLB and 596 healthy controls, was recruited from 11 centers. All participants underwent T1-weighted MRI imaging and longitudinal clinical assessments. Scans were processed using vertex-based cortical surface reconstruction and volumetric segmentation to quantify brain atrophy, followed by parcellation, scan harmonization, and z-scoring for age and sex. The unsupervised machine learning algorithm SuStaIn was employed to map spatiotemporal patterns of brain atrophy progression and to correlate distinct subtypes with clinical markers of disease progression.

Results:

SuStaIn identified two subtypes of brain atrophy progression: 1) a "cortical-first" subtype, where atrophy begins in the frontal lobes and extends to the temporal and parietal areas, with subcortical structures affected later; and 2) a "subcortical-first" subtype, where atrophy starts in the limbic areas, progresses to the basal ganglia, and affects cortical structures at later stages. Patients classified into either subtype exhibited higher motor and cognitive disease burdens and were more likely to phenoconvert to overt disease compared to those who were not classifiable. The iRBD patients with a subcortical-first atrophy pattern were more likely to phenoconvert at earlier SuStaIn stages, particularly to a parkinsonism phenotype. Conversely, later disease stages in both subtypes were associated with more imminent phenoconversion to a dementia phenotype.

Conclusion:

Synucleinopathy patients can be categorized into distinct atrophy patterns that correlate with disease burden, highlighting the potential value of patient categorization in clinical trials.

Influence of alpha-synuclein pathology on brain FDG-PET pattern in amnestic MCI

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Background:

The diagnostic assessment of patients with amnestic mild cognitive impairment (aMCI) remains challenging due to the possible co-occurrence of Alzheimer's disease (AD) and alpha-synuclein (alpha-Syn) pathology. Misfolded alpha-Syn aggregates in cerebrospinal fluid (CSF) measured by seed amplification assays (alpha-Syn SAA) are highly accurate biomarkers of alpha-Syn pathology. Here, we investigated whether alpha-Syn pathology, detected by CSF alpha-Syn SAA, could influence the brain [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) pattern in subjects with aMCI.

Methods:

The cohort comprised 562 aMCI participants and 204 cognitively unimpaired controls (CN) with available CSF alpha-Syn-SAA data and FDG-PET measurements of regional cerebral metabolic rate for glucose utilisation (rCMRgl). CSF Beta-Amyloid 1-42 (A) and p-tau 181 (T) levels were also available for 735 participants.

Results:

CSF alpha-Syn-SAA positivity (alpha-Syn+) was detected in 136 aMCI cases (24%). rCMRgl was reduced in typical AD regions in both alpha-Syn+ and negative (-) aMCI participants compared to alpha-Syn- CN. Compared to alpha-Syn - aMCI, alpha-Syn + aMCI showed lower rCMRgl in brain areas typically affected in AD and Lewy body dementia, such as the bilateral precuneus, dorsal portions of the lateral temporal cortex, and parietal and occipital regions. These results remained almost identical when comparing alpha-Syn + A+ aMCI vs. alpha-Syn - A+ aMCI and alpha-Syn + A+T+ aMCI vs. alpha-Syn - A+T+ aMCI.

Conclusion:

Alpha-Syn pathology contributes to a distinct brain FDG-PET hypometabolism in aMCI patients. The *in vivo* identification of AD and alpha-Syn mixed pathology may improve clinical management and stratification of aMCI patients in clinical trials.

BEHOLD (BioEnergetic Hallmarks of Lewy Body Dementia (LBD)): Background and design of multimodal neuroimaging study to elucidate mitochondrial/bioenergetic dysfunction as LBD develops

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Background:

Mitochondrial dysfunction is central to pathogenesis of Lewy Body Dementia (LBD). Specific dysfunction of mitochondrial respiratory Complex-1 (mito-C1) may be involved, but it is difficult to distinguish mitochondrial respiratory dysfunction from other specific mechanisms, such as failure of glycolysis or energy reserves. Elucidating different pathways of metabolic dysfunction, and determining their temporal sequence, are critical to elucidating LBD pathogenesis and developing targeted therapies.

Methods:

Differentiating specific mechanisms and patterns of these changes in vivo has been difficult, until development of ^{18}F-BCPP-EF, a PET radioligand targeting mito-C1, coupled with glycolysis (FDG-PET), brain lactate (7T ^{1}H-MRS), ATP and high-energy phosphate metabolites (7T ^{31}P-MRS). Our study is enrolling participants across the spectra of at-risk (isolated REM behavioral sleep disorder), prodromal (MCI-LB) and clinically established LBD, controls, and Alzheimer's disease, undergoing ^{18}F-BCPP-EF, PiB and FDG-PET, 7T MRI and MRS, neurocognitive and motor testing, systemic mitochondrial-bioenergetics, olfaction, and skin a-Synuclein testing, at baseline and year 2, allowing characterization of specific mitochondrial respiratory chain and other bioenergetic dysfunction across the LBD spectrum, and analyzing relationships between brain mitochondrial and bioenergetic dysfunction with cognition and peripheral bioenergetics.

Results:

Pilot analysis of ^{18}F-BCPP-EF binding in Control (n=9), LBD/Parkinson's disease dementia (n=8), and cognitively unimpaired PD (n=15) revealed a negative correlation between disease duration and ^{18}F-BCPP-EF binding in anterior putamen (R=-0.619, p=0.0008) and posterior putamen (R=-0.517, p=0.0058). In some cases, early in disease course, high ^{18}F-BCPP-EF binding was observed in these regions, suggesting an early upregulation of mito-C1. In LBD, there was reduced ^{18}F-BCPP-EF binding in occipital lobe compared to controls (p= 0.042), which was not observed in cognitively intact PD. We have now begun enrolling in the multimodal study.

Conclusion:

Initial results suggest that occipital mito-C1 loss may represent distinct localized mitochondrial impairment. Our ongoing study utilizes a multimodal approach to dissect the specific bioenergetic changes from at-risk individuals through LBD.

Neuropathological correlates of basal forebrain atrophy in Alzheimer's and Lewy body disease

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Background:

Degeneration of the basal forebrain cholinergic system is a hallmark feature shared by Alzheimer's disease (AD) and Lewy body disease (LBD). While previous studies have focused on studying basal forebrain volume in clinically defined AD and LBD cases, we aimed to investigate the relationship between basal forebrain atrophy, cognitive decline, and neuropathology in an autopsy sample of people with varying degrees of AD and LB pathology.

Methods:

Data were obtained from the National Alzheimer's Coordinating Center (NACC) database, including people with autopsy-confirmed pure AD (N=248), pure LBD (N=22), or mixed AD/LBD (N=185). Basal forebrain volumes were extracted using an established automated MRI volumetry approach based on a stereotactic atlas. We also estimated hippocampal volumes as a control analysis. Associations of basal forebrain and hippocampus volumes with pathological markers (Braak stage for tau, CERAD score for amyloid, and McKeith criteria for Lewy body pathology) and cognitive performance were assessed using Bayesian statistical methods.

Results:

Posterior basal forebrain atrophy was most severe in individuals with mixed AD/LBD pathology compared to those with pure AD or pure LBD. In contrast, hippocampal atrophy was primarily associated with AD pathology, independent of co-occurring LB pathology. Cognitive performance, particularly in memory and language domains, was more impaired in groups with AD pathology, with Braak stage emerging as the strongest predictor of cognitive decline. Mediation analyses indicated that hippocampal volume partially mediated this relationship between tau pathology and cognitive impairment, while posterior basal forebrain volume had a limited role in mediating the relationship between pathological burden and cognitive outcomes.

Conclusion:

In a heterogeneous autopsy sample, AD and LB pathology both contribute to cholinergic basal forebrain degeneration whereas hippocampus atrophy is more specifically related to AD pathology. Cognitive deficits are primarily associated with tau pathology which is partly mediated by hippocampus, but not basal forebrain atrophy.

Quantitative Susceptibility Mapping differences in Lewy body dementia

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Background:

Lewy body dementia (LBD) encompasses both Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

In Lewy body diseases, excessive iron interacts with *α*-synuclein to synergistically cause neurodegeneration. Therefore, Quantitative Susceptibility Mapping (QSM), an MRI technique which enables local differences in iron content to be quantified reliably, may have utility in LBD.

Here, we present, for the first-time, whole brain QSM analysis comparing LBD with Parkinson's and controls, as well as DLB with PDD.

Methods:

66 participants with LBD (45 DLB; 21 PDD), 55 with Parkinson's and 37 healthy controls were included.

All participants had susceptibility- and T1-weighted MRI scans. Following QSM pre-processing, voxel-wise, whole brain statistical analyses were performed using absolute QSM values. Permutation analyses (in *FSL randomise*), adjusting for age and sex, were used to compare group differences and test associations between magnetic susceptibility and relevant clinical measures (FWE-corrected $P < 0.05$).

Results:

We found significantly increased absolute QSM in the bilateral frontotemporal and right precentral regions, and the left cerebellum in LBD compared to controls and Parkinson's.

For PDD compared to DLB, there was significantly increased absolute QSM in the bilateral cerebella, left frontal lobe and left precuneus. Further, the findings remained after adjusting for atrophy (TBV) and a conventional VBM analysis did not find any volumetric differences.

In the LBD group, increases in absolute QSM in the right thalamus and left pallidum as well as the bilateral middle frontal and left temporal lobes, were associated with increased disease severity (Total UPDRS).

Conclusion:

We showed differences in magnetic susceptibility between PDD and DLB across several brain regions. This may imply that the underlying neurobiology of these conditions, whilst overlapping, may also be different. We demonstrated that magnetic susceptibility correlated with disease severity in LBD suggesting that this MRI measure is relevant in this spectrum of diseases.

Evaluating white matter microglial activation with [11C]-PK11195C PET in Lewy body dementia and its clinical and biomarker associations

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Background:

Whereas previous studies have investigated microglial activation within the grey matter, the extent and clinical associations of white matter microglial activation remain unknown. This study investigated the patterns of white matter neuroinflammation using [11C]-PK11195 PET in Lewy body dementia (LBD), compared to controls and people with Alzheimer's disease (AD). We then explored relationships between white matter hyperintensities (WMH), cognitive function, and plasma biomarkers.

Methods:

15 healthy controls, 30 people with AD/MCI+ (AD and amyloid positive MCI) and 24 people with LBD comprising dementia with Lewy bodies (n=19) and Parkinson's disease dementia (n=5), underwent [11C]-PK11195 PET with dynamic imaging to quantify microglial activation. A subset of LBD patients underwent [11C]-Pittsburgh Compound B PET for beta-amyloid quantification. Plasma biomarkers (neurofilament light chain, phosphorylated tau 181 (pTau181), glial fibrillary acidic protein, and Aβ 42/40 ratio) were assessed. Group differences and correlations were assessed using non-parametric permutation tests.

Results:

People with LBD ($T=1.9$, $p=0.04$) and AD/MCI ($T=3.6$, $p< 0.01$) showed higher global white matter [11C]-PK11195 uptake compared to healthy controls, adjusting for age. These effects were independent of plasma pTau181 and Aβ 42/40. Regionally, the LBD group showed more selective frontal and occipital white matter increases, while the AD/MCI+ group showed widespread increases compared to controls. In LBD, global white matter [11C]-PK11195 uptake correlated with greater WMH, lower ACER memory and visuospatial scores as well as lower RAVLT A30 scores.

Conclusion:

White matter neuroinflammation was increased in LBD and AD with distinct regional patterns. In LBD, this increase was independent of AD co-pathology. Our findings support the role of white matter neuroinflammation as a pathophysiological process in both dementias. The associations of [11C]-PK11195 PET imaging with both cognitive function and WMH may highlight white matter neuroinflammation as a therapeutic target in LBD.

Investigation of the Glymphatic System as a prognostic marker for Dementia with Lewy bodies

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Background:

Isolated REM sleep behavior disorder (iRBD), a parasomnia characterized by a loss of muscle atonia during REM sleep, is recognized as one of the earliest indicator for developing Dementia with Lewy Bodies (DLB). The glymphatic system is a waste clearance network whose dysfunction is suggested to be associated with numerous cognitive disorders. As a prodromal synucleinopathy, studying the glymphatic system in iRBD patients is crucial for understanding the progression to DLB.

Methods:

Diffusion MRI data from 535 participants from an international multicentric cohort (276 iRBD, 259 controls) were analyzed. Using the FA map from the ICBM_DTI-81 atlas, we created cubic binary masks (5mm) on bilateral associative and projection fibers at the level of the lateral ventricle. These masks were then aligned to the standard space of each participant using ANTs, followed by quality control. The masks were then multiplied by each directional diffusivity map (x,y,z) obtained from the Tractoflow (FA RGB) results in the subject space. Bilateral, left and right APLS indices were extracted from the diffusivity data of the x, y and z axes.

Results:

A significant difference in the right ALPS index was observed between controls and iRBD participants, with no significant difference in bilateral and left ALPS indices. A decreased left ALPS index was revealed between non converted and phenoconverted iRBD. Further analyses showed a correlation between MoCA scores and the ALPS index, but no correlation with MDS-UPDRS III scores. A logistic regression analysis identified the left ALPS index as a significant predictor of conversion, while a multinomial regression showed a significant result for the left ALPS index to predict DLB, but not PD.

Conclusion:

These findings confirm the presence of glymphatic dysfunction in the prodromal stages of DLB and could serve as a valuable early prognostic biomarker.

Brain Connectivity Alterations in Prodromal Synucleinopathy: Evidence from the Largest International Neuroimaging Study of Individuals with Idiopathic REM Sleep Behavior Disorder

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Background:

Isolated REM sleep behavior disorder (iRBD) is a parasomnia characterized by vivid dreams and abnormal movements during REM sleep. This prodromal symptom has the strongest association with the progression towards dementia with Lewy bodies (DLB). Brain connections are disrupted in DLB, but the presence and impact of connectivity disruptions in iRBD remains to be investigated. Here we investigated structural connectivity alterations in iRBD compared to healthy controls (HC) using the largest international neuroimaging dataset of polysomnography-confirmed iRBD patients.

Methods:

Diffusion-weighted MRI (DWI) data from eight cohorts were processed using advanced tractography and connectomics pipelines (Tractoflow-ABS, Connectoflow) to generate structural connectivity matrices for each HC and iRBD participant. Quality control was performed after each step of the tractography to remove DWI and T1w-MRI data with artifacts. Pairwise connectivity matrices of 448 cortical and 14 subcortical regions (Cammoun atlas) from 198 iRBD and 174 HC subjects were created for between-group analysis. Structural connectivity differences between iRBD and HC were assessed using the Network-Based Statistic toolbox, with age, sex, and center as covariates (FDR method, 10 000 permutations).

Results:

Reduced density was observed in iRBD in 14 connections between 27 regions, while increased density was found in 6 connections between 11 regions ($p\text{-value}_{FDR}<.05$). Density was predominantly reduced in the bilateral inferior parietal, superior temporal, lateral frontal, cingulate, and insular cortices, as well as in the right superior parietal, mediolateral occipital, and middle temporal cortices. Conversely, increased density was detected in a few regions part of the frontal, parietal, and temporal cortices, along with the cingulate cortex.

Conclusion:

IRBD is associated with connectivity alterations across specific cortical regions, many of which are also implicated in DLB. These findings suggest local network reorganization in this prodromal stage and could help better understand the mechanisms underlying neurodegeneration towards DLB.

Brain network connectivity underlying neuropsychiatric symptoms in prodromal Lewy body dementia.

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Background:

Neuropsychiatric symptoms (NPS) are common and occur early in Lewy body dementia (LBD). Such symptoms are highly distressing and associated with poorer outcomes for individuals. Research suggests NPS may reflect LBD related dysfunction in distributed neuronal networks. This study aimed to investigate this in prodromal LBD using resting-state functional MRI (rs-fMRI).

Methods:

Fifty-seven participants with mild cognitive impairment (MCI) indicative of prodromal LBD, including MCI with Lewy bodies (MCI-LB, n=28) and Parkinson's disease MCI (PD-MCI, n=29), underwent rs-fMRI. Twenty bilateral cortical seeds (6mm spheres) assessed connectivity in five resting-state networks: the default mode network (DMN), dorsal attention network (DAN), salience network (SN), limbic network (LN), and primary visual network (PVN). NPS were measured using the Neuropsychiatric Inventory. A principal component analysis identified three neuropsychiatric factors: affective disorder (apathy and depression), psychosis (delusions and hallucinations) and anxiety. Seed-to-voxel connectivity maps were analysed to determine significant associations between neuropsychiatric factors and functional connectivity of network seeds with the rest of the brain.

Results:

In PD-MCI, affective disorder and anxiety were associated with greater connectivity between both DMN and LN seeds and the subgenual cortex, and weaker connectivity between the LN and the brainstem (all $p<0.001$). Anxiety was additionally associated with weaker connectivity between subgenual cortex and the SN ($p=0.004$). Psychosis was related to greater connectivity in the DMN, LN, DAN and PVN (all $p<0.001$). In MCI-LB, no NPS was significantly related to connectivity of any resting-state network.

Conclusion:

NPS related functional connectivity in PD-MCI reflects both established neural mechanisms of mood disorders and theoretical models of Parkinson-related hallucinations. Lower brainstem-limbic connectivity associated with anxiety and affective disorder may further reflect the contribution of neurotransmitter denervation to NPS in LBD. It is unclear, however, whether mechanisms overlap across LBD sub-types. As such, further research, particularly in MCI-LB, is essential for the identification of symptomatic treatment targets.

The clinical use of indicative imaging biomarkers in DLB and MCI-LB: A Delphi consensus study

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Background:

Striatal dopaminergic imaging and cardiac meta-iodobenzylguanidine (MIBG) scintigraphy are indicative imaging biomarkers in International Consensus Criteria for the clinical diagnosis of dementia with Lewy bodies (DLB) and proposed biomarkers in the research criteria for mild cognitive impairment with Lewy bodies (MCI-LB). The aim of this Delphi process was to develop consensus guidelines to support the effective use of these biomarkers in clinical practice.

Methods:

Following a systematic review of the literature, the core study team developed draft statements on indications for the use of dopaminergic imaging and cardiac MIBG and clinical situations in which each biomarker should and should not be used.

A Delphi consensus panel of 37 international experts (clinicians, radiologists, medical physicists) independently indicated their agreement or disagreement with each statement via an online portal. Statements were accepted if they reached >80% agreement.

Results:

In round 1, 36/70 statements (51%) reached agreement. Round 2 is almost complete; 37 further statements were proposed and it is expected that approximately half of these will be accepted, leading to over 50 accepted statements.

The Delphi panel agreed that:

- when both biomarkers are available, dopaminergic imaging should be the first-choice investigation in most cases

- dopaminergic imaging and cardiac MIBG may be clinically useful in the investigation of MCI-LB

- dopaminergic imaging may be useful in the investigation of late onset psychiatric disorders and recurrent, prolonged or unexplained delirium.

Further guidance will be presented at the conference, including clinical situations in which each biomarker may be particularly useful, when they should not be used and which medications to consider withholding prior to imaging.

Conclusion:

The Delphi Consensus process has developed guidelines for the practical clinical use of dopaminergic imaging and cardiac MIBG for the diagnosis of DLB and MCI-LB. The Guidelines will be disseminated through international conferences and peer-reviewed publications.

Semiquantitative Analysis of the Longitudinal 123I-FP-CIT SPECT in Dementia with Lewy Bodies

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Background:

Reduced nigrostriatal binding on the ^{123}I-FP-CIT SPECT (DaT-SPECT) reflects loss of dopamine transporters (DaT), which is considered as the primary pathological mechanism behind parkinsonism. We sought to semiquantitatively assess how serial DaT-SPECT scans change over time in combination with parkinsonism in dementia with Lewy bodies (DLB).

Methods:

Participants with probable DLB from the Mayo Clinic ADRC who had longitudinal DaT-SPECT scans were included. Diagnosis of probable DLB was made using the 2017 consensus criteria. Nigrostriatal dopamine transporter binding was measured, and putamen z-scores were calculated using DaTQUANT 2.0 software (GE Healthcare). DaT-SPECT scan was determined as abnormal when at least one of the putamen had a DaTQUANT z-score <-1. Presence of parkinsonism was determined in participants with bradykinesia plus at least one of rigidity, rest tremor, or postural instability.

Results:

Forty-nine DLB participants completed 3.1±1.2 scans (male 86%, age at the initial scan 69.6±7.7, follow-up years 2.6±1.7). Seven participants (14%) had either neocortical or limbic Lewy body disease at autopsy. The baseline UPDRS-III, MMSE and CDR® sum-of-box scores were 20.1±14.0, 25.9±2.1, and 2.3±2.1, respectively. At the initial scan, 38 (78%) participants had an abnormal DaT-SPECT and parkinsonism (D+/P+); 3 (6%) participants had an abnormal DaT-SPECT without parkinsonism (D+/P-). Three (6%) participants had a normal DaT-SPECT with parkinsonism (D-/P+); 5 (10%) participants had a normal DaT-SPECT without parkinsonism (D-/P-). All autopsy confirmed participants were D+/P+ at baseline. At the most recent visit, 42 (86%) participants were D+/P+, 3 (6%) were D+/P-, 2 (4%) were D-/P+, and 2 (4%) were D-/P-; UPDRS-III score was 25.7±15.1. The annualized change of DaTQUANT putamen z-score was -0.22±0.55.

Conclusion:

Most DLB participants had abnormal DaT-SPECT at baseline. DaT binding continued to decline with serial scans. Half of participants with a normal DaT-SPECT at baseline eventually became abnormal.

Atrophy of individual thalamic nuclei in Lewy body dementias and Alzheimer's disease revealed in vivo with ultra-high resolution MRI

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Background:

Thalamic nuclei are implicated in a range of brain functions including regulation of arousal, attention, visual processing, sleep and movement. They are of particular interest in Lewy body dementia (LBD), as key features include fluctuating cognition, visual hallucinations, sleep and movement disorder. At lower MRI field strengths, it is challenging to segment individual thalamic nuclei. The increased signal and contrast to noise ratios of ultra-high-field (7T) MRI mean that this method is ideally placed to measure thalamic nuclei volumes in vivo.

Methods:

Participants: LBD (n=23), Alzheimer's disease (AD, n=25), controls (n=20). Imaging: 7T MP2RAGE, whole brain, 0.75x0.75x0.75mm^3 resolution, TE/TR=1.99/4300ms. Processing: including automated thalamus segmentation performed in FreeSurfer 7.4.1. Analysis: left and right volumes were combined and divided by individual total intracranial volume. Groups were compared using ANCOVA with age as covariate and Tukey post-hoc tests used for group contrasts. Significance is defined as p<=.05.

Results:

Whole thalamic volumes did not differ significantly between groups. Three nuclei were smaller in LBD than controls: anteroventral (AV), laterodorsal (LD), and mediodorsal lateral parvocellular (MDL). Several nuclei were significantly smaller in AD than controls: AV, LD, MDL, central medial, lateral geniculate, lateral posterior, medial ventral, pulvinar inferior, ventral anterior, and ventral posterolateral. Two were also smaller in AD than LBD: LD, MV. No nuclei were smaller in LBD than AD.

Conclusion:

7T MRI revealed volumetric differences in individual thalamic nuclei in LBD and AD. Of the three nuclei smaller in LBD than controls: AV plays a role in cognition receiving inputs from areas including the hippocampus and entorhinal cortex; MDL has strong connections with the prefrontal cortex and may be involved in task switching and attentional processes as well as cognition more generally; while LD's connections include the visual cortex. Consequently, atrophy in these areas may help explain key features of LBD.

Comparing patterns of microglial activation between dementia with Lewy bodies and Alzheimer's disease

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Background:

Neuroinflammation, characterized by microglial activation, is a prominent feature in neurodegenerative disorders such as Lewy body dementia (LBD) and Alzheimer's disease (AD). While previous research has examined regional patterns of microglial activation in LBD and AD, often comparing each to normal aging, a direct comparison of neuroinflammatory patterns between LBD and AD has not been undertaken.

Methods:

Participants with dementia with Lewy bodies and Parkinson's disease dementia (LBD, n = 24) and AD with amyloid positive mild cognitive impairment (AD-MCI+, n = 26) underwent dynamic PET imaging with [11C]PK11195. [11C]PK11195 binding potentials (BP_{ND}) were calculated for each region using the simplified reference tissue model (SRTM) with a cerebellar grey matter reference region. BP_{ND} values were then averaged across hemispheres for bilateral regions, resulting in 41 regions of interest (ROIs) per participant. Regional [11C]PK11195 BP_{ND} were compared between AD-MCI+ and LBD groups using age-adjusted linear regressions. To quantify the evidence for group differences, we computed Bayes Factors (BF10), interpreted as follows: 1-3 (weak evidence), 3-10 (moderate evidence), 10-30 (strong evidence), and >30 (very strong evidence) for the alternative hypothesis.

Results:

Significantly elevated [11C]PK11195 BP_{ND} values were observed in AD-MCI+ compared to the LBD groups across multiple brain regions. The most pronounced differences were in the amygdala and anterior temporal lobe ($p < 0.0002$, BF10 > 50). Notable differences were also found in frontal and parietal lobes ($p < 0.002$, BF10 > 7), with moderate but significant differences in hippocampus, posterior temporal, and occipital lobes ($p < 0.006$, BF10 > 3).

Conclusion:

Our findings reveal distinct, increased neuroinflammation patterns in AD-MCI+ and LBD, most notably in limbic and temporal regions. These differences likely reflect pathophysiological differences between Lewy body dementia and AD. Future research should investigate how these distinct neuroinflammatory profiles relate to clinical outcomes, cognitive decline, and protein aggregation in AD and LBD.

Cortical microstructural abnormalities in dementia with Lewy bodies and their associations with Alzheimer's disease copathologies

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Background:

Dementia with Lewy bodies (DLB) frequently co-occurs with Alzheimer's disease (AD) neuropathologic changes, exacerbating disease progression and neurodegeneration. However, the pattern of cortical microstructural injury in DLB and its relationship with amyloid, tau, and cerebrovascular pathologies remain unclear. This study aimed to assess cortical microstructural integrity in DLB and investigate its associations with AD pathology.

Methods:

Neurite Orientation Dispersion and Density Imaging (NODDI) was used to evaluate cortical microstructural integrity in 57 individuals within the DLB spectrum and 57 age- and sex-matched cognitively unimpaired controls. Mean Diffusivity (MD), tissue-weighted Neurite Density Index (tNDI), and Orientation Dispersion Index (ODI) were quantified. Amyloid and tau levels were measured using PiB and Flortaucipir PET imaging, respectively. Structural Equation Modeling was used to assess relationships between APOE genotype, amyloid, tau, and neurite injury.

Results:

Compared to controls, DLB participants exhibited increased MD and reduced tNDI, independent of macrostructural atrophy. Localized reductions in ODI were observed in the occipital cortex. Structural Equation Modeling revealed that APOE genotype influenced amyloid levels, which in turn elevated tau, leading to neurite injury.

Conclusion:

Oiur NODDI study revealed widespread regional gray matter microstructural abnormalities, including elevated MD, reduced NDI, and a distinctive pattern of reduced ODI in occipital regions in the DLB spectrum group. SEMs were used to elucidate the pathological pathways underpinning these changes, implicating tau as a critical nexus in the amyloid cascade by mediating the effects of APOE and amyloid-β accumulation on neurite injury. Future research efforts are warranted to evaluate the therapeutic potential of multipronged intervention strategies targeting diverse pathologies in DLB patients with concurrent AD pathologies.

Characterization of oscillatory and aperiodic resting-state EEG spectrum in Neurodegenerative Diseases: A multicentric study

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Background:

Abnormalities in resting-state electroencephalogram (rsEEG) dominant alpha rhythm are promising biomarkers of neurodegenerative diseases (NDDs), often assessed via spectral analysis, ignoring the signal's non-rhythmic (aperiodic) component. Evidence assessing both aperiodic and oscillatory rsEEG abnormalities in various NDDs is scarce and often underpowered. Multicenter studies can address these limitations, but data pooling might introduce site-related rsEEG differences (batch effects). This multicentric study aims to characterize rsEEG oscillatory and aperiodic patterns across NDDs, minimizing potential batch effects.

Methods:

RsEEG signals from 639 subjects across 11 sites were automatically preprocessed. The pooled sample comprised healthy controls (HC = 152), Lewy Body Dementias (LBD = 96), Parkinson's Disease (PD = 70), Alzheimer's Disease (AD = 187), Frontotemporal Dementia (FTD = 23), Mild Cognitive Impairment (MCI) in cases with positive Lewy Bodies pathology or PD (MCI-LBD = 35), and MCI in positive AD pathology (MCI-AD = 77). Batch effects on the rsEEG power spectrum were harmonized using reComBat (age, sex, and diagnosis-adjusted), and harmonization was evaluated with functional and mass-univariate permutation ANOVAs. Oscillatory and aperiodic parameters were extracted from the batch harmonized power spectrum using Fitting Oscillations and One-over-frequency (FOOOF). Differences across NDDs were estimated with ANCOVAs (age

and sex-adjusted), bootstrap pairwise comparisons, and mass-univariate permutation tests.

Results:

Qualitative visualizations and statistical testing with functional and mass-univariate ANOVA consistently showed a reduction of batch effects on the harmonized power spectrum. As consistent significant findings in the unharmonized and batch harmonized data, steeper aperiodic parameters and lower oscillatory center frequency were observed in LBD compared to all other NDDs. Besides, oscillatory extended alpha power was lower in AD vs. LBD.

Conclusion:

Batch effects in the rsEEG power spectrum can be mitigated with harmonization. Oscillatory alpha power reduction may better reflect AD abnormalities, whereas pronounced oscillatory frequency slowing and greater aperiodic activity characterize LBD.

Cortical inhibitory and facilitatory alterations in the continuum of alpha-synucleinopathies

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Background:

Alpha-synuclienopathies are neurodegenerative disorders characterized by a wide range of motor and non-motor symptoms. The clinical course of alpha-synuclienopathies is heterogeneous and different pathophysiological processes may be involved at different disease stages. Among these, the role of inhibitory and facilitatory neuronal circuits and their possible alterations early in the disease course is increasingly recognized as a potential key to understanding the onset and progression of this disease. Despite these insights, a comprehensive understanding of neurotransmitter circuit alterations in alpha-synuclienopathies, especially in its prodromal stages, remains elusive.To address this gap, we aimed to explore changes in GABAergic, glutamatergic, and cholinergic circuits in patients with PD, including drug-naive PD, patients with iRBD and patients with DLB using transcranial magnetic stimulation (TMS), a non invasive brain stimulation technique able to detect the impairment of specific neurotransmitter circuits in vivo.

Methods:

The study enrolled consecutive patients with PD, dementia with Lewy bodies (DLB)**,** polysomnography-confirmed idiopathic REM Sleep Behavioral Disorders (iRBD) and age-matched healthy controls (HC). Participants underwent a standardized comprehensive clinical assessment including motor and cognitive testing. TMS paired-pulse protocol evaluating $GABA_A$ergic circuits (short interval intracortical inhibition, SICI), glutamatergic circuits (intracortical facilitation, ICF) and cholinergic circuits (short latency afferent inhibition, SAI).

Results:

One-hundred and thirty participants entered the study, namely 75 PD (45 drug-naïve and 30 treated early-stage PD), 20 DLB, 15 iRBD, and 20 HC. Compared to HC, both drug-naïve and treated PD, as well as iRBD and DLB showed a reduction in SICI. SAI was reduced in both iRBD and DLB compared to HC and PD.

Conclusion:

Cortical inhibitory abnormalities were found to characterize alpha-synucleinopathies stages. In idiopathic RBD patients, cholinergic alterations were found, similar to that observed in DLB cases, in line with the known higher risk of cognitive dysfunction in these subgroups of patients.

An international neuroimaging consortium for lewy body disorders

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Background:

The ENIGMA consortium brings together scientists and clinicians from across the world to collaborate in well-powered analyses on imaging indices of brain disorders. Our ENIGMA-Parkinson's disease consortium has performed analyses on cortical, subcortical, cerebellar and white matter abnormalities over the last four years. Current endeavours center on staging of the disease, connectivity, brainstem and spinal cord markers. We envisage the inclusion of related alpha-synucleinopathies such as Dementia with Lewy bodies, Multiple system atrophy, and the premorbid diagnosis of REMsleep behaviour disorder.

Methods:

ENIGMA-PD currently has over 40 cohorts in more than 20 countries across six continents, that collaborate in the largest world-wide neuroimaging consortium. Analyses require local sites to perform standardized processing, rendering derived metrics that can then be shared with the coordinating site for the respective analyses. This procedure crucially ensures local ownership of the data and scans, while the derived anonimized data can be shared for group analyses.

Results:

We have shown incremental decrease of neural integrity at the level of cortical thickness, cortical surface area, subcortical shape, cerebellar lobar volume and white matter integrity across the PD disease stages. At the same time, analyses show that in the *de novo* state (Hoehn&Yahr stadium 1), interestingly larger local volumes and white matter connectivity occurs. It is at this point unknown whether this represents compensation, local inflammatory or degenerative processes, or premorbid markers for the disease process.

Conclusion:

Expanding the worldwide investigation of MRI markers of Parkinson's disease to other alpha-synucleinopathies will allow us to track the ongoing neurodegeneration in as yet un-parallelled ways, while offering clues for premorbid changes that may provide clues for diagnosis, prognosis and interventions.

Regional Gene Expression Patterns and Connectivity Underlie Cortical Thinning in Dementia with Lewy Bodies

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Background:

Previous studies showed diffuse cortical thinning in Dementia with Lewy bodies (DLB), but mechanistic underpinnings of cortical changes are not elucidated yet. This study aimed to assess cortical alterations and associated transcriptomics in DLB.

Methods:

A total of 83 patients with DLB and 86 age- and sex-matched healthy controls were included. T1-weighted MRI scans were processed using FreeSurfer to generate thickness, surface area, and volume cortical maps and parcellated into Desikan-Killiany atlas. Bilateral cortical measures were compared between DLB and controls, correcting for scan site, age & sex. Neighborhood analyses were used to assess whether DLB atrophy patterns were constrained within the structural and/or functional connectome. Regional gene expression data from Allen Human Brain Atlas were extracted from 6 healthy post-mortem brains. Partial least squares (PLS) regression was used to identify transcriptomic patterns predicting cortical thinning in DLB followed by gene set enrichment analysis (GSEA) to assess patterns of enrichment in terms of biological processes and cellular components. All comparisons were tested against null models with preserved spatial autocorrelation.

Results:

Region-based analysis showed significant bilateral parieto-temporo-occipital cortical thinning in DLB. Regional brain atrophy was restrained by structural (P_{spin}= 0.02), but not functional connectomics (P_{spin}= 0.07). PLS regression revealed two latent variables of gene expression that significantly predicted cortical thinning in DLB (respectively 35.6% and 22.3% of covariance explained). GSEA uncovered that atrophy in DLB occurred in regions with higher expression of genes related to synaptic transmission, as well as mitochondrial a metabolic factors.

Conclusion:

DLB was associated with widespread posterior-dominant cortical thinning, constrained by structural connectivity. Regions showing cortical thinning in DLB were enriched for genes involved in synaptic signaling and mitochondrial function.

Non-invasive imaging correlate of central cholinergic degeneration and its relation to clinical expression and conversion in prodromal and early Parkinson's disease

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Background:

Parkinson's disease (PD) patients are at high risk of developing dementia. However, there are still no robust predictors of conversion to dementia among PD patients that are well validated. In addition, given that cognitive impairment is already common in PD patients at diagnosis, there is a great need in identifying patients at greater risk for phenoconversion to manifest disease at prodromal stages. Isolated REM-sleep behaviour disorder (iRBD) is the strongest marker for prodromal PD, with high risk of developing manifest synucleinopathy. Cholinergic degeneration and dysfunction, especially of the Nucleus Basalis of Meynert (NbM), have been proposed as a mechanism for dementia in Lewy body disorders.

Methods:

Here, we used the data of 394 early PD patients, 133 iRBD, and 187 controls, from two longitudinal observational studies, the Oxford Parkinson's Discovery Cohort (OPDC) and the Parkinson's Progression Markers Initiative (PPMI), to examine the grey matter volume of the NbM in prodromal (iRBD) and early PD, and its relationship with future conversion to dementia in PD or manifest disease in iRBD, as well as with clinical manifestations.

Results:

We found lower NbM grey matter volume in PD and also iRBD compared to controls. Furthermore, lower NbM volume was associated with higher probability of future conversion to dementia and shorter time to diagnosis in PD, and future phenoconversion to PD in iRBD. Interestingly, lower NbM volume was associated with non-motor and motor symptoms in PD, but not in iRBD, attesting for the complex pathological nature of this early prodromal subtype of Lewy body disease.

Conclusion:

Our results suggest that central cholinergic degeneration is already present at early prodromal phases of Lewy body disease, and that NbM grey matter volume could be a potential non-invasive imaging marker for disease burden and future risk of dementia in early PD patients, and for phenoconversion to PD in iRBD.

Imaging brain class I histone deacetylase changes in the Lewy body dementias and Parkinson's disease

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Background:

Dysregulation of the epigenetic molecules histone deacetylases (HDACs) has been linked to neurodegenerative diseases. Here, we used the class I HDAC PET radioligand [^{11}C]Martinostat to quantify and map brain changes in class I HDACs in dementia with Lewy bodies (DLB) and Parkinson's disease (PD).

Methods:

In this cross-sectional study, we acquired detailed clinical examinations and brain PET imaging with [^{11}C]Martinostat in 14 DLB, 10 PD, including four with cognitive impairment (PD-impaired) and six without (PD-normal), and 17 healthy control (HC) participants. [^{11}C]Martinostat uptake was compared amongst groups using a whole brain voxel-wise analysis and a targeted region of interest (ROI) approach.

Results:

[^{11}C]Martinostat uptake in DLB was increased in precentral gyrus (primary motor cortex) and putamen, as well as in cognitive and limbic circuitry that included the anterior cingulate and entorhinal cortex. In contrast, [^{11}C]Martinostat uptake in DLB was decreased in inferior parietal cortex, consistent with prior observations in AD. In PD, [^{11}C]Martinostat uptake was also increased in precentral gyrus corelating with both disease duration and Hoehn and Yahr stage. In PD-impaired participants, [^{11}C]Martinostat uptake was additionally increased in anterior cingulate cortex in voxel-wise analysis and was reduced in inferior parietal cortex in both voxel-wise and ROI analyses, similar to DLB. In postmortem DLB tissue, class I HDAC expression was elevated in anterior cingulate and reduced in inferior parietal.

Conclusion:

These findings reveal overlapping, bidirectional changes in regional HDAC expression in DLB and PD that may contribute to or reflect their motor and cognitive features.

Alpha-synuclein radioligand development: Pipeline to human PET imaging

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Background:

PET radioligands are needed to detect aggregated alpha-synuclein, the core pathology of dementia with Lewy bodies. The low density and intracellular localization of alpha-synuclein fibrils and frequent presence of amyloid and tau in DLB have complicated this effort. Here, we describe a novel pipeline to identify selective alpha-synuclein radioligands and report on 11C-SY08, the first hit under evaluation in patients.

Methods:

We performed an affinity-based screen of a large DNA-encoded small molecule library (WuXi DEL) to identify selective binders to alpha-synuclein pre-formed fibrils (PFFs), amplified from LBD brain tissue and recombinant, over alpha-synuclein monomer, amyloid-beta, and tau. Following a secondary screen with biolayer interferometry, top candidates underwent evaluation in human brain tissue. Given promising properties, C11-SY08 was evaluated in cell and rodent models and primates. C11-SY08 PET is being acquired and compared (SUVR, corpus callosum reference) in DLB, PD, MSA, and healthy participants.

Results:

Sixteen unique scaffolds were identified as alpha-synuclein binders in the DEL screen. Of ten compounds that underwent chemical synthesis and secondary screening using biolayer interferometry, SY08 showed high binding to biotinylated alpha-synuclein PFFs. In human brain tissue homogenates, Kd was < 6 nM with Bmax 697 fmol/mg protein, with >70-fold selectivity over AD tissue. H3-SY08 showed competitive binding in LBD brain tissue. SY08 had no significant off target binding at 10 μm for 52 CNS targets. C11-SY08 brain uptake was increased in PFF-seeded iPSC models, the alpha-synucleinA53T mouse, and regionally in the AAV-alpha-synucleinA53T rat. In non-human primates, PET imaging showed rapid CNS entry across brain regions, and plasma radioactivity analysis showed rapid clearance from blood with limited brain uptake of radiometabolites. C11-SY08 PET imaging is underway in DLB, PD, MSA, and healthy participants (n=14 to date). Findings will be presented.

Conclusion:

This DEL-based pipeline holds promise for development of alpha-synuclein PET radioligands such as C11-SY08 for DLB.

Cortical dopaminergic vulnerability across Alzheimer's and Lewy Bodies spectrum: a 123I-FP-CIT study

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Background:

Dopaminergic alterations are core in Dementia with Lewy Bodies [1]. However, both post-mortem and in vivo data suggested dopamine dysfunction in patients with Alzheimer's Disease (AD) [2,3]. Describing disease-specific patterns of dopaminergic alterations might explain the wide heterogeneities of clinical presentation across Alzheimer and Lewy Spectrum. In this study, we aimed to evaluate cortical dopaminergic alterations across the two disease-spectra.

Methods:

We included n=65 AD patients (n=27 MCI-AD; n=38 AD-DEM), n=50 DLB patients (n=23 pDLB; n=27 DLB-DEM), and n=50 age-matched controls (CG). Only AD patients belonging to the AD continuum were included, accordingly to the NIA-AA research criteria. DLB patients who resulted amyloid-positive were excluded from the study. All subjects underwent ^{123}I-FP-CIT DaTSCAN imaging. Between-groups differences in ^{123}I-FP-CIT binding were assessed using ROI-based and voxel-wise analyses on brain regions belonging to ventral and dorsal dopaminergic systems.

Results:

In all AD patients, nigrostriatal imaging resulted negative according to a pre-defined ranking scale [2]. As expected, DLB patients were significantly more impaired than AD in striatal regions (i.e., pallidum, putamen, and caudate) both in prodromal and dementia phases. We found significant alterations in bilateral anterior cingulate cortex and parahippocampal gyrus in AD patients even in the MCI phase, when compared to controls and pDLB. In the dementia phase, dopaminergic alterations in AD extended to frontal regions (i.e., olfactory and rectus gyri, and middle frontal cortex). The direct comparison by means of voxel-wise analyses revealed that DLB showed more significant dopaminergic alterations in striatal regions, while AD resulted more impaired in fronto-temporal regions.

Conclusion:

This study indicates subtle dopaminergic alterations in AD patients in cortical regions belonging to the ventral dopaminergic system mostly involving fronto-temporal cortical regions, able to differentiate AD and DLB spectra.

A systematic review of diffusion tensor imaging and tractography in Dementia with Lewy Bodies and Parkinson's Disease Dementia.

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Background:

Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD) can be difficult to differentiate from other types of dementia, and the anatomical origin of common symptoms is poorly understood. Diffusion tensor imaging (DTI) and tractography are magnetic resonance imaging modalities which can sensitively detect microstructural white matter changes. We review DTI and tractography studies in DLB and PDD to assess whether there is evidence for white matter changes, and whether any changes are associated with common symptoms.

Methods:

We searched MEDLINE and EMBASE for studies using DTI or tractography in subjects with DLB or PDD, and assessed the evidence for white matter changes through a narrative synthesis. The quality of included studies was assessed using the Newcastle-Ottawa scale, and the manuscript was written in line with the PRISMA 2020 guidelines.

Results:

Data was extracted from 57 studies, of which the majority (56%) were considered 'good quality'. Subjects with DLB and PDD had widespread white matter changes compared to healthy controls and compared to subjects with Parkinson's disease without cognitive impairment, with a relative sparing of the hippocampus. Compared to subjects with Alzheimer's disease (AD), DLB had greater changes in thalamic connectivity and in the nigroputaminal tract, while AD had greater changes in the parahippocampal white matter and fornix. While cognitive performance was associated with white matter changes across the brain, there was no associations with cognitive fluctuations. Visual hallucinations were associated with thalamic and cholinergic connectivity, while parkinsonism was associated with changes in structures involved in motor control.

Conclusion:

There are extensive microstructural white matter changes in DLB and PDD. DTI and tractography is therefore well suited for studying the aetiology of common symptoms and may be useful to discriminate DLB and PDD from other types of dementia.

Macro-and microstructural white matter changes in Lewy Body Dementia

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Background:

Whether dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are separate conditions or one disease is not yet established. Brain imaging of white matter connections could shed light on this. Fixel-based analysis of diffusion imaging provides measures of fibre density (relating to small vessel disease); and fibre cross-section (relating to neurodegeneration).

Methods:

We performed clinical assessments, diffusion-weighted and susceptibility-weighted MRI in 30 PD, 21 PDD and 45 DLB patients.

After standard preprocessing of diffusion-weighted MRI images fibre orientation distributions were computed using spherical deconvolution. Groups were compared using fixel-based measures, corrected for age and gender, at whole brain and tract of interest analysis. Microbleed counts were derived from susceptibility-weighted images using blinded visual ratings.

Results:

PDD and DLB patients did not differ in age (mean age PDD=72.1, 67% male; mean age DLB=71.8, 91% male, p=.98). PD patients were younger than LBD (mean age PD=68.0, 30% male, p=.0009). LBD patients had higher proportion of men than PD (p <.0001).

MoCA scores were comparable between PDD (21.8) and DLB (21.2) and were reduced for LBD versus PD (mean=28.9, p<.0001).

Fibre cross-section did not differ between PDD and DLB, but fibre density was reduced for PDD relative to DLB in regions including corpus callosum, internal capsule and corona radiata (each p<0.05 FWE-corrected). When comparing LBD and PD, fibre cross-section was decreased within corpus callosum and medial lemniscus (p<0.05 FWE-corrected); but fibre density was increased compared with PD (p<0.05 FWE-corrected). In LBD, mean fibre density in all regions of interest was associated with higher microbleed count (r=-0.35 to -0.49, p<.05).

Conclusion:

Our findings of reduced fibre cross-section, but increased fibre density in LBD compared to PD suggest an important role for small vessel disease in understanding differences between subtypes of Lewy body dementia, which could have implications for targeted treatment interventions.

Novel application of high-density task-based EEG in DLB

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Background:

Posterior slowing on electroencephalography (EEG) during resting-states is a supportive biomarker in dementia with Lewy bodies (DLB). The utility of task-based EEG (tsEEG) paradigms to assess cortical activity in DLB is unclear.

Methods:

Resting-state (rsEEG) and tsEEG data were collected from 128 channels in 25 cognitively unimpaired adults (mean age 70.1±9.8 years; 40% male) and individuals with DLB or mild cognitive impairment with Lewy bodies (MCI-LB) (6=DLB, 6=MCI-LB; mean age 71.0±6.0 years; 75% male) from the 1Florida Alzheimer's Disease Research Center (ADRC) at the University of Florida. All participants completed demographic and clinical evaluations. During tsEEG, participants performed a visually guided grip force task with high or low visual gain. Error scores were calculated from the behavioral data, and EEG data were analyzed using a beamformer technique to localize cortical oscillations in time-frequency windows (alpha, beta, theta).

Results:

DLB/MCI-LB cohort had lower total Montreal Cognitive Assessment (MoCA) scores (20.8±2.6 versus 25.3±2.7; $p<0.01$). DLB/MCI-LB group had slower peak alpha frequency during rsEEG (7.4±1.1 Hz versus 9.4±1.0 Hz; $p<0.001$). Individuals with DLB/MCI-LB also exhibited higher offset and steeper slope for aperiodic components during rsEEG. During the grip force task, individuals with DLB/MCI-LB had greater force error, and did not show the expected reduction in error from low to high visual gain that was evident in controls. tsEEG showed a significant group difference where DLB/MCI-LB had an attenuated reduction in low beta power (14-22 Hz) in occipital regions ($p_{FDR}<0.05$) compared to the control group, across both visual gain conditions.

Conclusion:

The rsEEG dominant frequency was significantly slower in DLB/MCI-LB, consistent with prior studies. Individuals with DLB/MCI-LB performed worse during the motor task, possibly modulated by decreased neuronal activation in posterior occipital regions. This is a promising task-based paradigm to better understand changes in cortical neuronal activity in DLB.

A spatial covariance 123I-5IA-85380 SPECT study of α4β2 nicotinic receptors in dementia with Lewy bodies

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Background:

Cholinergic dysfunction is key in dementia with Lewy bodies (DLB), and likely to influence the cognitive and psychiatric symptoms of this condition. However, patterns of spatial covariance in DLB in terms of nicotinic acetylcholine receptors (nAChRs) is unknown. In this study we used ^{123}I-5-iodo-3-[2(S)-2-azetidinylmethoxy] pyridine (^{123}5IA-85380) SPECT (α4β2 nAChR assessment) to investigate the covariance patterns in DLB and their associations with cognition.

Methods:

Fifteen DLB and 16 healthy controls underwent ^{123}5IA-85380 and rCBF (^{99m}Tc-exametazime) SPECT scanning. We applied voxel principal components (PC) analysis, generating a series of PC images representing common intercorrelated voxels across subjects. Linear regression generated specific α4β2 nicotinic and rCBF covariance patterns that contrasted DLB from controls.

Results:

A α4β2 pattern that distinguished patients from controls ($F_{1,29}$ = 165.1, p<0.001), showed relative decreased uptake in bilateral temporal pole, inferior frontal, amygdala, olfactory cortex, insula, anterior/mid cingulate and putamen, as well as relative preserved/increased uptake in sensorimotor, fusiform and occipital lobe, implicating regions in a nicotinic receptor expression sense, within limbic, salience, default mode, olfactory, sensorimotor and visual networks. We then successfully derived from patients, α4β2 nicotinic receptor patterns that correlated with $CAMCOG_{total}$ (r = -0.52, p = 0.04), MMSE (r = -0.68, p = 0.01) and $CAMCOG_{memory}$ (r = -0.70, p = 0.01), demonstrating a common 'cognitive' topography of relative decreased binding in lateral/medial prefrontal, lateral temporal, inferior parietal and thalamus along with relative preserved/increased binding in cingulate, insula, occipital and medial temporal regions, structures representing a range of networks supporting executive, language, social cognition, attention and sensory functions.

Conclusion:

Disease and cognitive related patterns of cholinergic α4β2 nicotinic receptor binding were apparent in DLB and could inform future therapeutic targets of these receptors in this condition.

Cortical Thickness of Prodromal DLB and AD: A Retrospective ADNI Cohort

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Background:

While extensive research exists on prodromal AD, early-stage of DLB remains less understood, particularly at the mild cognitive impairment (MCI) stage. Distinguishing between MCI-AD and MCI-LB is challenging due to overlapping symptoms. This study aims to identify differential neuroimaging biomarkers in MCI-LB and MCI-AD using structural MRI data from the ADNI database. We hypothesize that MCI-LB will exhibit posterior atrophy, while MCI-AD will show more medial temporal and frontal lobe atrophy.

Methods:

Data from 887 participants (24 MCI-LB, 560 MCI-AD, and 303 cognitively normal subjects (CN)) were retrieved from the ADNI database, all with valid structural MRI T1-weighted data. Clinical classifications were performed by through consensus among a researcher, a neurologist, and a neuropsychologist, using McKeith et al.'s (2020) criteria for prodromal DLB. Core symptoms like visual hallucinations, REM sleep behaviour disorder (RBD), cognitive fluctuations, and Parkinsonism, along with supportive biomarkers were available. Cortical thickness analysis was performed using Freesurfer to quantify and compare cortical atrophy across the groups.

Results:

MCI-LB group had significant cortical atrophy in the right lingual gyrus and precuneus compared to CN ($p = 0.05$, FDR corrected). While MCI-AD group exhibited significant cortical atrophy in frontal, parietal, temporal and occipital lobes ($p = \leq 0.05$, FDR corrected) and in the entorhinal cortices along with parahippocampal gyrus ($p = <0.0001$, FDR corrected) compared to CN. However, we found no statistically significant differences in cortical atrophy between MCI-LB and MCI-AD in any regional area.

Conclusion:

Although not statistically significant in our preliminary analysis, the data suggested that there may be a different spatial distribution in cortical atrophy patterns between MCI-LB and MCI-AD. That is, MCI-LB exhibited localized atrophy consistent with DLB's characteristic symptoms such as visual hallucinations. Conversely, MCI-AD showed more widespread atrophy, aligning with AD's broader cognitive decline. Future evidence awaits studies with larger sample size.

Distribution of perivascular spaces in dementia with Lewy bodies: a cohort study

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Background:

Perivascular spaces (PVS) are postulated to be involved with the clearance of interstitial fluid and waste within the central nervous system. Emerging data suggest that an increased burden of enlarged PVS on magnetic resonance imaging (MRI) is associated with age, cerebral small vessel disease, and an increased incidence of all-cause dementia. We aimed to describe the prevalence and clinical association of enlarged PVS on MRI in people with dementia with Lewy bodies (DLB).

Methods:

Participants with DLB and age- and sex-matched healthy participants underwent clinical and cognitive assessments, including Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and standardised Mini-Mental State Examination (sMMSE). Participants also had brain imaging with 3T MRI. T2-weighted MRI scans were visually rated for PVS in three regions - midbrain, basal ganglia, and the centrum semiovale, according to the STRIVE-2 neuroimaging standard.

Results:

Imaging from 51 participants with DLB (11.8% female, mean age = 73.8 ± 5.6 [standard deviation] years, median sMMSE = 26 [IQR: 23 – 27], and median UPDRS-III = 19 [IQR: 15 – 27]) and 23 matched healthy participants (20.8% female, mean age = 75.5 ± 4.9 [standard deviation] years, median sMMSE = 30 [IQR: 29 – 30], and median UPDRS-III = 3 [IQR: 2 – 6]) were analysed. Prevalance and distribution of PVS within the midbrain, basal ganglia, and the centrum semiovale will be compared between participants with DLB and controls. Association with co-morbidities, cognitive function, and motor impairment will be assessed.

Conclusion:

This study will provide important data regarding the burden of enlarged PVS in DLB and help facilitate the comparison of PVS burden with other causes of dementia. The results will shed light on the potential utility of PVS as an imaging biomarker in DLB.

Functional connectivity changes associated with depression in Dementia with Lewy bodies

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Background:

Depression is frequent in the early stages of dementia with Lewy bodies (DLB), and have an impact on both disease progression and patients' quality of life. However, to our knowledge, no study has yet looked specifically at the depression-related functional connectivity changes in DLB. The aim of the present study was therefore to investigate the functional changes associated with depressive symptoms in prodromal to mild DLB patients compared with healthy volunteers.

Methods:

Resting-state functional MRI data were collected from 66 DLB patients and 18 healthy volunteers. Depression was evaluated with the Mini International Neuropsychiatric Interview 5.0.0. Resting-state functional connectivity (rsFC) was investigated with the CONN toolbox using a seed-based analysis, with region of interest corresponding to the main nodes of the default mode network (DMN), the salience network (SN), the visual network (VN), the dorsal attentional network (DAN), the fronto-parietal network (FPN), the language network (LN) and the cerebellar network (CN).

Results:

DLB patients with depressive symptoms (dDLB) showed decreased rsFC within the SN, increased rsFC between the DMN and the LN as well as decreased rsFC between the CN and the FPN compared to DLB patients without depressive symptoms (ndDLB) ($p < 0.05$, uncorrected). Moreover, higher depression scores in DLB patients were associated with reduced rsFC within the salience network ($p < 0.05$, uncorrected), and with altered rsFC between the inferior fronto-temporal regions and the calcarine cortex ($p < 0.05$, FDR corrected).

Conclusion:

The occurrence and the severity of depressive symptoms in DLB patients appear to be associated with functional connectivity changes. In particular, the SN, already known to be altered in both major depression and DLB, seems to play an important role. Additionally, we hypothesized that the increased rsFC between the DMN and LN in dDLB compared to ndDLB might indicate internal speech and/or ruminative thoughts.

Cerebrovascular disease in cholinergic white matter and associations with neurodegeneration and cognition along the Lewy body continuum

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Background:

Cerebrovascular disease (CVD) and cholinergic dysfunction are common in Dementia with Lewy bodies (DLB). CVD can be assessed in-vivo through white matter signal abnormalities (WMSA) on magnetic resonance imaging (MRI). However, the association between WMSA and cholinergic dysfunction is not fully understood. We aimed to investigate WMSA intercepting cholinergic white matter pathways and assess associations with neurodegeneration and cognitive performance.

Methods:

We included 35 participants along the Lewy Body (LB) continuum (mild cognitive impairment with Lewy bodies and DLB) and 36 controls from the Sant Pau Initiative on Neurodegeneration cohort. Using MRI, we modelled the cholinergic white matter pathways from Nucleus basalis of Meynert (NbM) through cingulum or external capsule and estimated NbM volume. We modelled global WMSA and lobar WMSA. We compared patients and controls on these measures and evaluated associations between WMSA, cholinergic measures, and cognition. All cholinergic WMSA measures were accounted for global WMSA to gain knowledge about specific vulnerability of cholinergic system. Analyses were adjusted for age, intercranial volume, and education.

Results:

The LB-group had more WMSA than controls in cholinergic pathways irrespectively of global WMSA. This finding was specially observed in frontal cholinergic areas. Higher WMSA in cholinergic pathways was associated with a lower integrity of cholinergic pathways. The volume of cholinergic NbM was associated with WMSA in frontal cholinergic areas as well as lower integrity in cholinergic pathways. Further, WMSA in frontal cholinergic areas were associated with cognitive performance in attention and WMSA in temporal cholinergic areas with performance in memory. LB and controls exhibited differing association patterns between WMSA, NbM and cognitive measures.

Conclusion:

WMSA in cholinergic system may be implicated in the neurodegeneration of cholinergic system in the LB continuum, with implications for cognitive perfomance in attention and memory. These findings may suggest a selective vulnerability of cholinergic neurons to cerebrovascular co-pathology in LB.

Connectivity-based classifier model as a promising biomarker for cognitive fluctuations in dementia with Lewy bodies

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Background:

Cognitive fluctuation (CF) is a core diagnostic feature of dementia with lewy bodies (DLB). Despite its clinical significance there are no objective or reliable biomarkers for tracking CF as clinical semi-structured questionnaires are often used. The lack of a gold standard for capturing CF frequency and severity has limited its utility as a clinical outcome. Imaging of brain connectivity using resting state functional MRI (rsfMRI) represents a promising approach to probe the underlying neural basis for CF. Previous rsfMRI studies of CF have examined global connectivity and predefined connections within intrinsic networks, but none have systematically explored all possible functional connections to model potentially novel features specific to CF.

Methods:

22 DLB subjects with CSF α-synuclein seeding amplification assay (SAA) biomarker positivity from US-DLBC were evaluated (11 CF+ and 11 CF-). CF status was determined by a Mayo Fluctuation Composite Score (MFCS) of 3 or greater. Structural and functional MRI was collected on a 3T scanner using the ADNI-3 protocol. A data-driven group cohesive parcellation was performed to optimize connectivity-based analyses. We trained a differential support vector machine (SVM) classifier using these functional connections to separate CF+ from CF- subjects.

Results:

285 significant candidate connections ($p < 0.001$) were identified for further training. An extremely efficient model utilizing only 17 total connections was synthesized for accurate classification of CF status. The model isolated connections related to the salience network that have been implicated in previous studies, including the anterior insula, inferior parietal cortex, and the lateral prefrontal cortex. Additional internetwork connections were also found, including a premotor/prefrontal connection that strongly correlates to CF status ($p<0.00001$).

Conclusion:

These results suggest rsfMRI connectivity can be used to capture neuroimaging biomarkers for CF status. Our connectivity-based model implicates specific inter- and intra-network changes that could contribute to CF and needs validation in more subjects.

Individual hippocampal subfield atrophy in Lewy body dementias revealed with ultra-high-resolution MRI

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Background:

With improved resolution ultra-high-field (7T) MRI is ideally placed to measure in vivo volumetric changes in small brain areas including hippocampal subfields. Limited 7T studies demonstrate subfield changes in Alzheimer's disease (AD) but no Lewy body dementia (LBD) studies are yet published. Though traditionally considered relatively preserved, hippocampal subfield atrophy may explain some cognitive deficits in LBD.

Methods:

Participants: LBD (n=23), AD (n=25), controls (n=20). Imaging: 7T MP2RAGE, whole brain, 0.75x0.75x0.75mm3 resolution, TE/TR=1.99/4300ms. Processing: including automated hippocampal subfield segmentation performed in FreeSurfer 7.4.1. Analysis: left and right volumes were combined and divided by individual total intracranial volume. Groups were compared using ANCOVA with age as a covariate and Tukey post-hoc tests used for group contrasts. Significance defined as p<=.05.

Results:

Whole hippocampal volumes were significantly smaller in both LBD and AD than controls. Cornu Ammonis (CA)1 head, CA3 body, CA4 head and body, presubiculum head and body, subiculum head and body, granule cell layers of the dentate gryus (GCMLDG) head and body, molecular layer (MLHP) head and body, hippocampus-amygdala transition area (HATA), and hippocampal tail were significantly smaller in both LBD and AD compared to controls with larger effect sizes for the AD group. CA1 body, CA3 head, and fimbria were significantly smaller in AD but not LBD compared to controls. CA3 head, and MLHP body were significantly smaller in AD than LBD. No subfields were smaller in LBD than AD. Across groups, subfield volumes correlated with Addenbrookes Cognitive Examination scores and sub scores (adjusted for age).

Conclusion:

These findings provide compelling evidence of whole hippocampus and hippocampal subfield atrophy in LBD which differ in degree and pattern from that seen in AD. Furthermore, atrophy is strongly associated with cognitive deficits in these patient groups. Thus, 7T MRI reveals group differences and key clinical correlations not readily evident at lower field strengths.

Heterogeneity of cholinergic dysfunction in early cognitive impairment due to Lewy body disease

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Background:

There is well-established evidence supporting the use of cholinesterase inhibitors in Lewy body diseases to ameliorate cholinergic function, however the response at the individual level is highly variable. The aim of this study is to investigate the degree of variability in cholinergic dysfunction in participants with early cognitive impairment due to Lewy body diseases with the view to inform personalised treatment.

Methods:

Participants with probable LB-MCI, PD-MCI, probable mild DLB and mild PDD were recruited. We assessed EEG alpha reactivity which has been shown to be associated with cholinergic system integrity, we also included Montreal cognitive assessment (MoCA) as a measure of cognitive function and MRI nucleus basalis of Meynert (NBM) volumes. Correlation between these markers in the patients was reviewed as well as comparing the range of results between controls and patients to assess heterogeneity.

Results:

Patient alpha reactivity (n=34) had a significant correlation with MoCA score ($r = .487$, $p = .003$). The strongest correlation in structural imaging was seen between alpha reactivity and right NBM volume, this did not reach statistical significance ($r = .404$, $p = .069$) but may be explained by the reduced sample of MRI results (n=22). The patient group had a lower median alpha reactivity .144 (IQR .022 - .281, range 1.077) compared to the control group (n=10) median .573 (IQR .521 – .601, range .541). The range was higher in the patient group with three having alpha reactivity within the control interquartile range.

Conclusion:

There is heterogeneity of cholinergic dysfunction which may explain differences in response to current treatments. The potential for cholinergic markers such as alpha reactivity to delineate responders and non-responders will be explored in future with change in MoCA score comparing donepezil and placebo at the individual level with further results from this clinical trial dataset.

The Frontoparietal and Salience Networks in Dementia with Lewy bodies: a Functional Connectivity Impairment Related to Disease Progression Towards Dementia

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Background:

Previous resting-state fMRI studies in dementia with Lewy bodies (DLB) have described functional connectivity impairments in key brain networks related to cognition, attention, psychiatric and motor functions. However, little is known about the evolution of these changes as the disease progresses towards dementia. Here we aim to compare the functional connectivity of DLB patients at different stages of the disease with healthy elderly subjects and Alzheimer's disease (AD) patients in key brain networks of neurodegenerative diseases.

Methods:

Seventy-seven DLB patients, including 55 DLB patients with mild cognitive impairment (MCI-DLB) and 22 DLB patients with dementia (DLB-d), along with 13 patients with Alzheimer’s disease (AD) and 34 healthy control subjects (HCS) underwent a detailed clinical and neuropsychological evaluation and resting-state functional MRI. Functional images were analyzed using group-level seed-based connectivity analyses within- and between-network using the CONN toolbox.

Results:

The global DLB patients group showed significantly lower functional connectivity within the salience network when compared with HCS group, but no significant difference was observed with the AD group. While we only found non-significant trends in MCI-DLB patients, DLB-d patients showed reduced functional connectivity within the salience and the frontoparietal networks when compared with HCS and AD. AD patients showed lower connectivity between the default mode network and the salience network when compared with DLB-d patients. The MCI-DLB group showed significantly lower functional connectivity when compared with DLB-d group.

Conclusion:

The salience and frontoparietal networks impairment was specific to DLB patients in our study. Even though we observed non-significant trends of impairment in these networks in the MCI-DLB patients, these networks were clearly affected in patients with dementia. These networks appeared to be key factors in progress towards dementia in DLB and may be related to core clinical features of the disease.

Visually Evoke MEG in Dementia with Lewy Bodies

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Background:

Dementia with Lewy bodies (DLB) as the second commonest neurodegenerative dementia and is challenging to diagnose clinically due to its symptoms overlap with other diseases such as Alzheimer's. Neuroimaging biomarkers may help to improve diagnostic accuracy and specificity. In this study, a visual object recognition experiment was conducted to test visual functions in DLB, and magnetoencephalography (MEG) was used to investigate differences between the evoked responses in DLB compared with cognitively health controls (HC).

Methods:

Thirty-six participants (14 DLB and 22 healthy controls) from the Multimodal Imaging in Lewy Body Disorder (MILOS) study completed the MEG scan. In the object recognition task, there were 12 animal stimuli and 12 non-animal stimuli represented in random order and repeated across six blocks. Participants responded by pressing one of the two buttons to indicate whether the image was an animal. After making the response, the image will disappear and the next trial will begin.

Results:

Behaviorally, DLB had a lower accuracy and slower reaction time than HC. MEG showed that DLB had smaller evoked responses in both animal (t=4.84, p<0.01) and non-animal (t=3.74, p<0.01) conditions after approximately 500ms post stimulus onset. Using power spectral density (PSD) analysis, DLB evoked a weaker activity in the central parietal regions and showed significant differences from HC in both animal (t=2.93, p<0.01) and non-animal (t=2.087, p=0.044) conditions mainly in the delta band (1-4 HZ). However, no other significant differences found in other frequency bands and brain regions.

Conclusion:

These findings were consistent with previous literature that patients with DLB have performed worse in this high-level visual tasks. The MEG data also confirmed previous studies that DLB is associated with visual processing deficits in low frequency range.

Neuropsychiatric symptoms and microglial activation in dementia with Lewy bodies and Alzheimer's disease: A Positron Emission Tomography study

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Background:

Microglial activation is a recognised feature of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Neuropsychiatric symptoms (NPS) are frequent and distressing symptoms of both dementias, yet their underlying biological mechanisms remain poorly understood. Some previous studies suggest a link between NPS and inflammation, but findings are inconsistent. We explored associations between NPS and [11C]PK11195, a positron emission tomography (PET) marker of microglial activation, in DLB and AD.

Methods:

12 participants with early AD, 14 with amyloid positive mild cognitive impairment (MCI) and 20 with DLB underwent [11C]PK11195 PET. NPS were assessed at baseline and annually for up to 3.6 years after using the Neuropsychiatric Inventory (NPI). Associations between temporo-parietal regions and identified principal components of [11C]PK11195 PET with baseline and longitudinal NPI scores were examined using correlations and linear mixed effect models respectively.

Results:

In a combined group, AD and MCI participants showed a positive correlation between total NPI score and [11C]PK11195 binding in the anterior lateral temporal lobe (rho = 0.466, p = <0.05), though this did not survive false discovery rate (FDR) correction. In DLB, increased [11C]PK11195 binding in principal component 2 (PC2) was positively associated with total NPI score (rho = 0.526, p = <0.05), with PC2 primarily loading onto the substantia nigra. Again, this did not survive correction.Longitudinal analysis showed no significant [11C]PK11195 x time interactions for PC1, PC2 or PC3 in any group

Conclusion:

While our results did not survive correction for multiple testing, they may provide preliminary evidence that regional microglial activation, particularly in the substantia nigra, is associated with total NPI score in DLB. Similar associations were observed within the anterior lateral temporal lobe of the AD/MCI group. Larger studies incorporating repeated measures across multiple stages of disease are required to confirm our findings.

Dopaminergic connectivity changes in prodromal and early alpha-synuclein spectrum

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Background:

The impairment of dopaminergic network is a core feature of alpha-synucleinopathies. Less is known about involvement and reconfiguration of nigrostriatal and mesolimbic dopaminergic circuitries in the alpha-synuclein spectrum. We aim to investigate in vivo the dynamic changes of local and long-distance dopaminergic connectivity in patients with isolated REM sleep behavior disorder (iRBD), Parkinson's Disease (PD), and Dementia with Lewy Bodies (DLB).

Methods:

Brain 123I-FP-CIT SPECT was acquired for patients with iRBD, PD, and DLB. Age and sex-matched controls were selected for each group of patients. Dopaminergic connectivity alterations were analyzed using correlation analysis. Briefly, a correlation matrix was computed for each group of patients and controls. Fisher's transformation was applied to each coefficient and a z-test was performed to assess significant changes between patients and controls.

Results:

iRBD subjects showed significant dopaminergic connectivity alterations both in nigrostriatal (13%) and mesolimbic (13%) networks, primarily involving subcortical nodes. Of note, statistically significant altered connectivity in mesolimbic network was mostly due to an involvement of hyper-connectivity, while alterations in nigrostriatal network were due to a prominent hypo-connectivity. In DLB patients there were significant connectivity alterations mostly in mesolimbic (27%) rather than nigrostriatal (10%) network. Indeed, we found a higher proportion of hypo-connectivity primarily affecting cortico-limbic nodes. In PD patients there was a higher percentage of connectivity alterations involving nigrostriatal (20%) rather than mesolimbic (10%) networks, due to an involvement of hypo-connectivity in basal ganglia and pre-frontal nodes.

Conclusion:

This study indicates that dopaminergic connectivity alterations are core features of alpha-synucleinopathies since prodromal stages, involving both nigrostriatal and mesolimbic projections. The shift from an increased to a decreased connectivity might be hallmark of transition from prodromal to more severe stages of the disease.

REM Without Atonia Index is Inversely Correlated with Caudate Asymmetry in Dementia with Lewy Bodies

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Background:

Alpha-synucleinopathies, such as Dementia with Lewy Bodies (DLB), exhibit clinical heterogeneity, potentially due to distinct pathways of Lewy body accumulation. REM sleep behavior disorder (RBD) has been often associated with early brainstem involvement (i.e. "body-first" phenotype), while asymmetric nigrostriatal denervation has been suggested as a marker of “brain-first” phenotype. This study explored the relationship between polysomnographic features and nigrostriatal denervation, as assessed by DaT-SPECT, in patients with DLB.

Methods:

We enrolled 13 DLB patients (69.71±8.39 years) diagnosed using McKeith 2017 criteria. All patients underwent clinical examination, polysomnography (PSG) to assess REM without atonia (RWA), and DaT-SPECT imaging. Quantitative DAT-SPECT analyses were performed using DaT-QUANT software, and Pearson's correlation was used to assess relationships between PSG findings and DAT-SPECT measures.

Results:

Of the 13 patients, 11 showed evidence of RWA on PSG and 11 had abnormal DAT-SPECT findings. We found a significant positive correlation between sleep efficiency and striatal asymmetry (r=0.866, p=0.001), and a negative correlation between sleep latency and putamen asymmetry (r=-0.608, p=0.036). Additionally, caudate asymmetry was inversely correlated with the RWA index (r=-0.690, p=0.019) and positively correlated with motor symptoms (UPDRS, r=-0.697, p=0.025).

Conclusion:

These findings suggest that patients with a higher RWA index (indicative of RBD) tend to have more symmetric nigrostriatal degeneration, aligning with the "body-first" phenotype. Conversely, those with lower RWA index and more pronounced motor symptoms show greater asymmetry in nigrostriatal denervation, consistent with a "brain-first" phenotype. Our results support the notion of two distinct pathological pathways in DLB, characterized by differing patterns of sleep disturbances and motor symptoms.

Personalized rTMS Targeting the Anterior Insular Cortex in Dementia with Lewy Bodies: Preliminary Evidence from Cognitive Evoked-Related Potential and Behavioral Sustained Attention to Response Task

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Background:

Cognitive fluctuations are a core symptom in DLB, manifesting early in the disease and persisting throughout its progression, often representing the most debilitating symptom. In DLB, they primarily involve variations in alertness and attention. Studies have reported early insular anomalies, notably hypoperfusion, in prodromal DLB. We hypothesize a connection between the insula and attentional processes in DLB, leading us to design an rTMS trial targeting the anterior insular cortex. We hypothesize that excitatory rTMS to the insula could improve cognitive fluctuations and attentional functions.

Methods:

We performed a preliminary analysis of electroencephalographic and behavioral data within an ongoing proof-of-concept trial (ID: NCT05138588). This randomized, double-blind, crossover study compares rTMS targeting the anterior insular cortex with the posterior (occipital) cortex, focusing on cognitive fluctuations as the primary outcome. Five participants (N=5) completed a 20-minute Go/NoGo task (Sustained Attention to Response Task – SART) with EEG recording at four time points, following a pre/post rTMS design. Recordings were taken one week before and after each rTMS session. A cluster of seven fronto-central electrodes was selected for ERP analysis. Data were filtered, baseline-corrected, and inspected for artifacts. N200 and P300a components underwent current source transformation and were analyzed pre/post rTMS, focusing on latencies, peak amplitudes, and mean amplitude. Behavioral analysis focused on reaction times, omissions, and commissions from the SART.

Results:

Preliminary results show significant effects following insular rTMS, with the most robust finding being an increased mean amplitude of the P300 component. Behavioral analysis also revealed improvements post-insular rTMS, including reduced reaction times, omissions, and commissions. In contrast, post-occipital rTMS showed no improvement and even some deterioration. These findings suggest enhanced attentional resource allocation, improved cognitive control, and better sustained attention following insular rTMS.

Conclusion:

While these promising results indicate potential stabilization of cognitive fluctuations post-insular rTMS, further data are needed to confirm these effects.

Systematic Review of Cardiovascular Autonomic Dysfunction in Alpha-Synucleinopathies

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Background:

Alpha-synucleinopathies encompass a range of neurodegenerative disorders defined by development of abnormal alpha-synuclein pathology throughout the nervous system, including Parkinson's Disease, Lewy Body Disease, Multiple Systems Atrophy and Primary Autonomic Failure. Autonomic dysfunction is a well-recognized feature of alpha-synucleinopathies and is incorporated as part of the diagnostic criteria in the majority of these conditions.

It is becoming increasingly well-defined that many of these conditions have a prodromal phase with early autonomic dysfunction. Not much is known about autonomic biomarkers as markers of disease prognosis.

There is evidence that these conditions can undergo conversion from one to another over time (phenoconversion), but the determinants of these longitudinal conversions are poorly understood.

Methods:

This review poses two questions:

Does the severity of cardiovascular autonomic dysfunction, primarily orthostatic hemodynamics, predict prognosis in alpha-synucleinopathies?

Is the severity of cardiovascular autonomic dysfunction, primarily orthostatic hemodynamics, associated with rate of phenoconversion between alpha-synucleinopathies?

This review considers all original cohort, observational, longitudinal and epidemiological studies. Studies have been searched for and selected independently based on title, keywords and abstract by two independent researchers. Potentially eligible studies will be read in full to determine their suitability. The EMBASE, Web of Science Core Collection and Google Scholar databases have been used. Any disagreements on study selection will be resolved by discussion, if no agreement can be reached, a third-party opinion may be sought.

Results:

Our initial search identified 503 articles for further review. Critical analysis of these articles in a systematic approach will be presented to answer the research questions.

Conclusion:

The exact relevance of cardiovascular autonomic dysfunction as a prognostic marker and predictor of phenoconversion in alpha-synucleinopathies is unclear. By completing our systematic review, we hope to add clarity to these important questions, particularly in the era of alpha-synuclein biomarkers and potential disease modifying therapies.

Outcome measures in LBD

Oral Abstracts

The utility of composite endpoints for tracking disease progression in Lewy body dementia

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Background:

Lewy body dementia (LBD) is associated with heterogenous expression and progression of symptoms across cognitive, motor and neuropsychiatric domains. Disease-specific endpoints for LBD remain a crucial challenge for the field, with most clinical trials to date relying on unimodal endpoints or general measures of global impression of change. Interindividual variability in symptom trajectories across different domains may render such measures insensitive to disease progression. We have previously shown that significant changes in individual symptom domains can be detected over the time frame of a clinical trial. In this study, we aimed to assess the feasibility of a composite clinical endpoint using validated scales across different LBD symptom domains for detecting disease progression.

Methods:

116 patients with LBD (DLB=72,PDD=44) underwent assessment at baseline, 3 and 6 months as part of a prospective multi-centre cluster randomized controlled trial (DIAMOND-Lewy) of an intervention involving the provision to clinicians of an evidence-based management toolkit to optimise symptomatic treatment of LBD. Linear mixed models were constructed for composite outcome measure using the Mini-Mental State Examination (MMSE), motor section of the Unified Parkinson's disease rating scale (UPDRS-III), Dementia Cognitive Fluctuations Scale (DCFS) and the Neuropsychiatric Inventory (NPI).

Results:

Over a 6-month period, a composite measure constructed using MMSE, UPDRS-III, DCFS and NPI was able to identify a statistically significant progression of symptom severity over time ($P<0.01$). Simulated power calculations showed favourability of the composite score over individual measures. The composite score correlated with clinician rating of change, measures of carer burden (Zarit,$P<0.001$) and function (Bristol-ADL,$P<0.001$) demonstrating criterion-related and concurrent validity. Exploratory analysis demonstrated a positive and significant effect of the intervention ($P=0.04$), not detected using standard measures.

Conclusion:

Composite endpoints using validated scales across different symptom domains may be feasible and appropriate for measuring progression in DLB. Such endpoints can help inform design of new disease-specific scales for DLB.

A standardised approach to outcome measurement in dementia with Lewy bodies: Core Outcome Set (COS) development

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Background:

The absence of a consensus on which outcome measures should be used in DLB presents several challenges to the field. Methodological heterogeneity is recognised to contribute to publication bias and preclude effective evidence synthesis, and there is an agreed need to standardise clinical data so that larger, more representative samples can provide novel insights into pathogenesis and treatment targets. This project aimed to develop a Core Outcome Set (COS) for DLB in alignment with COSMIN (Core Outcome Measures in Effectiveness Trials) guidelines to improve consistency and comparability in research outcomes.

Methods:

A comprehensive literature review was conducted to identify commonly reported outcomes and measurement instruments used in DLB research. Subsequently, a two-stage Delphi survey was administered to a panel of experts, including clinicians and researchers ("*professional respondents*"), and people with DLB and their care partners ("*lay respondents*"), to prioritize outcomes most relevant to DLB. Delphi results informed a consensus meeting, which was held online and attended by lay and professional respondents.

Results:

Literature review identified 49 outcomes reported in DLB studies. Following the Delphi process, to which 48 professional and 40 lay respondents contributed, a final COS for DLB, comprising eight symptoms, was established: cognitive function, delusions and paranoia, fluctuations in cognition, attention and arousal, functioning, hallucinations, quality of life; parkinsonism; and REM sleep behaviour disorder. These outcomes were selected based on their relevance, feasibility, and impact on patients and caregivers. A subsequent literature review identified a recommended measurement tools for each outcome.

Conclusion:

The COS for DLB developed through this project provides a standardized framework for outcome assessment and reporting in DLB research. By focusing on outcomes that are critical to patients, caregivers, and clinicians, this COS aims to enhance the comparability of research findings and facilitate standardisation and harmonisation.

LBD Caregiver Preferences for Peer-to-Peer Support in the Connect2Caregiver Research Study Cohort

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Background:

The Connect2Caregivers (C2C) study aims to evaluate if caregivers would find a technology-based peer-to-peer matching tool a useful method for finding support on their caregiving journey.

Methods:

Current and former caregivers are enrolled in the C2C study; they complete questionnaires about emotional well-being, isolation, and stress at Baseline, 3 month ("M"), 6M, and 15M (study completion). Once 3M surveys have been completed, participants then complete their C2C match profile, and answers to the profile questions are used to provide up to four matches for each caregiver. Caregivers are either matched randomly or are matched using the C2C algorithm.

Results:

Data from 235 caregivers (77.0% female; mean age 60.12 ±16.12 yrs) were analyzed; 80% are current caregivers, 14.5% are former caregivers, and 9.4% identify as both a current and former caregiver. Most are caring for a spouse/partner (69.4%) or a parent (14.0%). C2C participants are caring for those with different dementia diagnoses: Alzheimer's Disease (34.0%), FTLD (27.2%), Lewy Body Dementia (20.8%), Vascular Dementia (2.1%), MCI (3.0%), and other/mixed/not specified (12.8%). Participants are asked to rank how important 13 different characteristics would be for a potential match to have (not, a little, somewhat, very, or extremely important). When considering participants caring for someone with LBD having the same diagnosis was very important (40.8%), similar symptoms was somewhat important (42.9%), the same overall symptom severity was somewhat important (49.0%), the same life stage was somewhat important (42.9%), and having the same relationship was very important (32.7%). Characteristics like having similar religious beliefs, similar race/ethnicity, same gender, and living close to one another were not important to LBD caregivers.

Conclusion:

It's important to consider the unique experiences and challenges that LBD caregivers experience to help identify support, especially peer-to-peer support.

Comparing the diagnostic accuracy of different cognitive fluctuations scales for discriminating between Dementia with Lewy Bodies and Alzheimer's Disease

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Background:

Cognitive fluctuations are a core diagnostic feature in Dementia with Lewy Bodies (DLB). Despite their importance, they remain poorly understood and difficult to systematically assess in clinical practice. Several scales were developed to assess cognitive fluctuations but direct comparisons between them are scarce. Our aim was to assess the ability of different cognitive fluctuation assessment scales to discriminate between DLB and Alzheimer's Disease (AD).

Methods:

We included patients with DLB (n=60) or AD (n=60), diagnosed according to the most recent international criteria with CSF-AD biomarkers available in 67 patients (33 DLB/34 AD). We assessed the Clinician Assessment of Fluctuation scale (CAF), the One-Day Fluctuation Scale (OFS), the Mayo Fluctuation Composite Score (MFCS) and the Dementia cognitive fluctuation scale-research version (DCFS-R). Cognitive (MMSE), behavior (NPI), motor (UPDRS) and dysautonomia (SCOPA) scales were also performed.

Results:

DLB patients had higher CAF, OFS, DCFS-R, MFCS, NPI, UPDRS and SCOPA scores. MFCS, CAF and DCFS-R had similar accuracy to differentiate between DLB and AD, with area under curve (AUC) values of 0.744 (95%CI, 0.647-0.842), 0.742 (95%CI, 0.644-0.840) and 0.740 (95%CI, 0.644-0.836) respectively. The OFS had lower accuracy, with an AUC of 0.654 (95%CI, 0.547-0.761). Combining the four most discriminative questions from the different scales led to an AUC of 0.792 (95%CI, 0.705-0.880). Regarding clinical variables, there was a positive correlation with NPI scores and negative correlation with MMSE scores. There were no significant associations with CSF-AD biomarkers values or the presence of amyloid co-pathology in DLB.

Conclusion:

Cognitive fluctuations are an important clinical finding in DLB regardless of amyloid co-pathology. They correlate with behavior impairment but are inversely related to cognitive decline. Different scales had a similar and modest accuracy to discriminate between DLB and AD, except for the OFS. We prospect to improve diagnostic accuracy by combining different aspects of the scales.

An update on the Lewy Body Dementia Domain rating scale (LBD-DRS)

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Background:

LBD trials currently rely on scales and measurements created for other neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease. Industry and regulatory authority stakeholders and LBD triallists have recognised the absence of an LBD-specific scale as an unmet need in the drug development pipeline. Methodological heterogeneity in LBD trials, particularly concerning outcome measures, precludes effective evidence synthesis and data harmonisation. Here, we describe the preliminary development of the Lewy Body Dementia-Domain Rating Scale (LBD-DRS).

Methods:

Led by a core working group and steering committee, a three-round Delphi survey process was used to establish consensus around the conceptual framework and preliminary content of the LBD-DRS among invited LBD researchers and clinicians. "Consensus" was established when ≥75% of respondents concurred on any survey statement or questions

Results:

Consensus around the need for an LBD-DRS, specifically for use in early LBD, has been established among 41 respondents. After feedback was received for two early versions of LBD, a third draft of LBD-DRS has been adopted for further development. This third version, and the results of the second Delphi survey round will be presented. A pragmatic approach that favours an inclusive scoring approach for symptoms has been adopted, recognising that further iterations will be required once field data becomes available.

Conclusion:

After consensus on the conceptual framework and preliminary content is established, consultation with a broader range of stakeholders, including people with LBD and their care partners, will be required to further develop LBD-DRS. Engagement with regulatory bodies and the pharmaceutical industry will guide further development before validation studies are pursued.

Poster Abstracts

LUMEN: A Large Language Model for Dementia Assessment through Conversational AI

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Background:

Dementia diagnostic assessments are complex, time-consuming, and often distressing for patients and their relatives. The rising prevalence of dementia and potential disease-modifying therapies necessitate more efficient, accurate clinical care. LUMEN (Large Language Model for Understanding and Monitoring Elderly Neurocognition) is a prototype conversational AI that streamlines dementia assessments by gathering collateral information from relatives/carers before diagnostic appointments, aiming to reduce assessment time, improve diagnostic accuracy, and enhance patient/carer experience. LUMEN uses an open-source Large Language Model (Mistral 7B) to interact with carers, extracting critical diagnostic information through structured dialogues.

Methods:

Development: The initial design was informed by a Patient and Public Involvement (PPI) meeting. A clinician workshop followed by modified Delphi process, involving 130 clinicians, was used to script and annotate clinical conversations covering dementia subtypes and safety concerns. Prompt engineering ('chain-of-thought' prompting, 'flipped classroom' approach) enhanced contextual understanding and empathy. Embedded vectors translated text into high-dimensional space for accurate symptom/diagnosis categorisation.

Testing: LUMEN was tested with clinical case vignettes simulating patients with specific dementia diagnoses. Clinicians, acting as carers, interacted with LUMEN; the LLM's diagnoses were compared with vignette diagnoses to calculate AUROC. Clinicians also summarised/categorised conversations based on the LLM's instructions; these were compared to LLM outputs using Cohen's kappa.

Results:

LUMEN achieved a diagnostic accuracy of AUC 0.75, with substantial agreement between the LLM and clinician categorisations (Cohen's kappa 0.66). The Systems Usability Scale (SUS) indicated high clinician satisfaction and usability. Feedback from clinician and PPI workshops confirmed LUMEN's acceptability and clinical utility.

Conclusion:

LUMEN shows strong potential as an AI tool to improve dementia diagnostics by reducing clinician workload and enhancing accuracy and consistency through advanced prompt engineering and machine learning. Future work will focus on broader clinical validation and optimisation for healthcare settings.

The Lewy body dementia domain rating scale (LBD-DRS): a roadmap for validation and adoption

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Background:

LBD trials currently rely on outcomes designed and validated for other neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases. The development of an LBD-specific scale represents an unmet need, that if unaddressed would significantly limit the LBD drug development and approval pipeline. Here, we present the evaluation and validation processes planned for the Lewy Body Dementia-Domain Rating Scale (LBD-DRS).

Methods:

An ongoing Delphi study will establish the conceptual framework for the scale. Thereafter, a series of workshops with diverse panels of stakeholders will be held to solicit their perspectives on the framework, the content of the scale, and how it is administered. Stakeholders will include people with LBD, their care partners, clinicians, researchers, policymakers, and representatives from regulatory agencies (such as the US Food and Drug Administration (FDA)), voluntary organisations and the pharmaceutical industry.

Results:

The resulting version of the LBD-DRS will be published and embedded in both clinical trials and prospective natural history studies. This will permit evaluation of feasibility and acceptability as well as internal consistency, test-retest reliability, and criterion validity. Comparison with more established rating scales will support benchmarking of effectiveness and sensitivity to change, and inform further development of the LBD-DRS.

Conclusion:

Development of LBD-DRS requires an iterative approach, which adopts best practices in scale development and validation. Critical characteristics of this approach will be the involvement of a diverse group of stakeholders and real-world testing.

Exploring Knowledge, Awareness and Practice (KAP) of Lewy Body Dementia in Irish care home staff

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Background:

While Lewy body dementia (LBD) is a common form of dementia, there is a notable lack of understanding and training among healthcare professionals, particularly in nursing homes and long-term care (LTC) facilities. Residents with LBD often have complex care needs and a lack of knowledge and skills regarding LBD care can hamper best practice in LTC settings.

Objective:

To evaluate the current level of knowledge, awareness and practice (KAP of LBD among Irish care home staff regarding LBD.

Methods:

A mixed methods, online, anonymous, self-reported survey. Respondents answered demographic questions, rated their agreement on a five-level Likert scale, ranging from 'strongly disagree' to 'strongly agree'. Respondents also rated their level of knowledge on a 1-10 scale and are asked to name other forms of dementia besides Alzheimer's. A series of questions regarding awareness and practices were also asked.

Design: Survey.

Setting: Long-term care facilities in Ireland providing dementia care.

Participants: All grades of staff working in Irish nursing homes.

Results:

Over 8% of LTC staff surveyed reported no awareness of LBD. There was a higher level of knowledge in senior nursing staff, and activity coordinator positions, compared to non-clinical staff such as front-line care staff and administrative staff, although a full understanding of the range of symptom presentations was poor. 'Vascular dementia' was the most reported dementia type on direct questioning. Trained nursing staff were generally able to name more than one type of dementia. Activity coordinators and nurses report a higher level of knowledge, awareness and comfort in care practice regarding LBD compared to other staff grades.

Conclusion:

The level of KAP of LBD of Irish LTC staff is moderate, but low in comparison to KAP of Alzheimer's. Findings suggest the need for bespoke LBD training and education for LTC staff of all grades.

Differences in mental health hospitalisations between Lewy body dementia and Alzheimer's disease

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Background:

People with Lewy body dementia (LBD), which includes dementia with Lewy bodies and Parkinson's dementia are more likely than people with Alzheimer's (AD) to be admitted to an acute hospital, and once admitted, to stay longer. This may also occur with mental health (MH) hospital admissions due to LBD related neuropsychiatric symptoms such as hallucinations, depression, and anxiety.

Methods:

Pseudonymised electronic patient records from Cumbria, Northumberland, Tyne and Wear NHS Trust, UK were examined using a Clinical Records Information System (CRIS). Records of 309 AD patients and 314 with LBD were randomly selected using ICD-10 codes. As LBD is often under-diagnosed and uncoded, records with text searches indicative of LBD were also included following a confirmatory clinical notes review based on the consensus criteria. Outcomes were compared between AD and LBD cohorts.

Results:

The proportion of people with a LBD or AD diagnosis admitted to a MH hospital was LBD:78/314, 24.8%, and AD:16/309, 5.2%, $p < .01$, (OR= 4.80, 95% CI [2.74, 8.40]). There was no significant difference between LBD and AD in the proportion of admissions involving detention under the Mental Health Act (MHA); LBD 58/78, 74.4% and AD 14/16, 87.5%, $p = .069$ (OR= 0.85, 95% CI [0.38, 1.88]). Detained LBD patients reflected the gender split of the total LBD sample, 65.5% male from a 64.6% male cohort. For AD 50% of detained patients were male from a 43.8% male sample. Mean hospitalised days were greater for LBD (161.75 days admitted, 93.70 detained) versus AD (75.44 days admitted, 70.79 detained).

Conclusion:

People with LBD are more likely both to be admitted to a MH hospital and detained under the MHA than people with AD. Furthermore, people with LBD spend substantially longer in hospital. Further work is needed to understand these disparities and develop strategies to reduce LBD admission rates and duration.

Predictors of Death within 6 Months in Individuals with Dementia with Lewy Bodies

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Background:

Individuals with dementia with Lewy bodies (DLB) commonly die of disease-related complications. However, hospice is often initiated only in the final weeks. We investigated predictors of impending death in DLB.

Methods:

Individuals with moderate-advanced DLB and their primary informal caregivers enrolled as dyads. The study collected demographics, disease-related measures, and measures of patient and caregiver experiences every 6 months. Variables predicting end of life were assessed: (1) through a time-varying Cox model involving all participants, with backwards and forwards variable selection and (2) through paired t- and signed rank sum tests investigating which variables changed significantly between the last two study visits for participants who died after completing at least two visits.

Results:

Individuals with DLB (n=189) were commonly male (77.8%), with 95.2% identifying as White and 97.4% as non-Hispanic. Mean age was 75.0 (SD 8.0) and mean disease duration was 3.2 (SD 3.1) at baseline/enrollment. Ninety-seven participants died prior to the analysis (mean 3.9 ± 2.0 years post-diagnosis). In the final Cox model using baseline and time-dependent covariates, variables associated with shorter survival included age (HR 1.03, 95% CI 1.01-1.06), shorter disease duration (HR 1.19, 1.08-1.32), daily falls (4.30, 1.98-9.30), pressure ulcers (2.25, 1.27-4.00), dementia severity (as assessed by the Quick Dementia Rating Scale total score, 1.09, 1.03-1.15), and greater ADL dependence (1.06, 1.02-1.09). When comparing scores between the last visits in individuals who died after at least two visits (n=72), there were significant changes in cognition, sleepiness, fluctuations, ADL dependence, and Advanced Dementia Prognostic Tool scores with approaching death.

Conclusion:

Worsening of disease-related experiences (e.g. cognition, fluctuations, sleepiness, ADL dependence) and increased complications (e.g. falls, pressure ulcers) signal approaching end of life in DLB. These clues can alert clinicians to hospice needs and inform patient and family counseling regarding prognosis.

What's missing in LBD quality of life assessment? The case for a new preference-based PROM

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Background:

Lewy Body Dementia (LBD) significantly impacts the quality of life of people living with the condition, yet there is no LBD-specific patient-reported outcome measure (PROM) for assessing quality of life (QoL). This gap potentially undermines our understanding of the experiences of people with LBD and the evaluation of interventions. We risk misallocating healthcare resources and undervaluing interventions that could significantly improve QoL for people living with LBD. This study establishes the rationale for developing an LBD-specific, preference-based PROM for assessing QoL.

Methods:

A mixed-methods approach, including: 1) in-depth interviews with people diagnosed with LBD, focusing on their perceptions of a 'good life'; 2) a systematic review of qualitative literature on QoL themes in LBD; and 3) a critical analysis of existing measures used in LBD. Thematic analysis was used to synthesize data from interviews and literature, while mapping was performed to identify gaps and overlaps, determining whether existing measures accurately reflect the aspects most relevant to lived experience.

Results:

Our analysis revealed primary QoL domains in LBD. People with lived experience emphasised a wide symptom spectrum beyond cognition, not captured by existing measures. The review highlighted additional themes like fluctuating cognition and maintaining independence. Existing measures showed gaps in addressing LBD-specific concerns, particularly the unique combination of cognitive, psychiatric, and motor symptoms.

Conclusion:

This study provides evidence for the need to develop an LBD-specific, preference-based health-related QoL PROM. Current measures fail to capture the unique lived experiences of LBD, potentially leading to incomplete or inaccurate assessments. A tailored PROM would enhance patient-centered care, improve outcome measurement in clinical trials, and advance our understanding of quality of life with LBD. Our findings provide a foundation for the development of such a measure, ensuring it reflects what truly matters to people living with the condition.

Creating a virtual Community of Practice for Lewy body dementia

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Background:

Communities of Practice are 'groups of people who share a concern, a set of problems, or a passion about a topic, and deepen their knowledge and expertise by interacting on an ongoing basis.' Recognition of Lewy body dementia (LBD) as a complex and often poorly understood condition led to the development of a virtual Community of Practice (vCoP) for LBD. This aimed to support nurses, allied health professionals (AHPs) and social care staff.

Methods:

The LBD focussed vCoP was conceptualised by a multi-disciplinary group of clinical and academic nurses and AHPs. It was founded in July 2023 following a scoping exercise to gauge interest. The Lewy Body Society UK acted as host. An initial survey identified information gaps and informed a series of hour-long webinars, delivered at three to four monthly intervals with recordings available. The format comprised several brief presentations and an interactive case discussion. Topics included hallucinations and delusions, movements and motor symptoms and sleep disturbance.

Results:

The vCoP membership comprises predominantly of nurses (Parkinson's, dementia, community psychiatric) but includes a full range of AHPs and students. Their feedback regarding the webinar format and topics has been positive with significant discussions generated by the case studies. Total attendees number over 600 with a maximum of 213 people attending the hallucinations and delusions webinar. Following this over 88% of attendees reported a moderate or substantial improvement in their knowledge

Conclusion:

A vCoP is a low cost and globally accessible way to optimise the knowledge, and skills, of nurses and AHPs working with people affected by LBD. It can encourage the implementation of evidence-based practice and may reduce the risks of sub-optimal care resulting from the particular needs of people with LBD being overlooked. Future plans include a resource bank of downloadable material and a moderated discussion area.

Sex-Specific Reproductive Health Risk Factors in Lewy Body Dementia

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Background:

Females may have a lower cumulative risk for Lewy body dementia (LBD) than males, but prevalence rates by sex become more balanced after age 70-75. This differential baseline risk and age-related shift may be associated with reproductive factors. Although the findings are inconsistent, reproductive factors likely impact the risk for Alzheimer's disease (AD), with shorter reproductive life spans and higher number of pregnancies associated with lower risk, though a greater cumulative risk in females compared to males. Reproductive factors may have a differential effect on LBD risk compared to AD risk for females and males.

Methods:

Analysis included 130 people with LBD (39% females, 61% males) and 119 controls (55% females, 45% males) matched for age and years of education for each sex, from LBD-TOROS, a remote survey study. Sex-specific reproductive factors were compared between LBD and control groups; risk was assessed for statistically significant factors.

Results:

Mean age and years of education were 63.1 (11.2) and 16.8 (2.8) for females, 65.4 (9.3) and 16.6 (4.3) for males (p>0.05). The majority identified as non-Hispanic (88.8%) and White (81.5%). Compared to controls, females with LBD were older at menarche, had more pregnancies, were younger at first live birth and at oophorectomy/surgical menopause (if applicable)(p<.037 for all). Higher number of pregnancies (OR=1.45, 95% CI=1.02-2.07) and younger age at first live birth (OR=0.90, 95% CI=0.82-0.99) were associated with LBD risk. Compared to controls, males with LBD were more likely to report erectile dysfunction before cognitive decline onset and difficulty with conceiving (p<.030 for both), with both associated with LBD risk (OR=3.34, 95% CI=1.52-7.32; OR=2.75, 95% CI=1.08-6.98; respectively).

Conclusion:

Reproductive factors may play a role in LBD risk, with some similarities to their putative role in AD risk. Identifying the role of sex hormones can provide modifiable risk factors and treatment options for LBD.

Test-retest reliability of computerised attentional tasks in prodromal Lewy body dementia

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Background:

Computerised attentional tasks are increasingly used as outcome measures for clinical trials but their reliability in the prodromal stage is not well established. The aim of this study is to review the test-retest reliability of these measures.

Methods:

The patient group were recruited at the prodromal stage and early-stage Lewy Body Dementia and included probable LB-MCI, PD-MCI, probable mild DLB and mild PDD. Participants completed a baseline assessment which included simple reaction time (SRT), choice reaction time (CRT) and digit vigilance (DV) computerised tasks. These tests were repeated whilst taking a placebo tablet between 8 weeks and 20 weeks after the baseline assessment. Intraclass correlation coefficient (ICC) was calculated to assess test-retest reliability, Montreal Cognitive Assessment (MoCA) ICC results are reported as a comparison.

Results:

For n=23 participants, the average mean reaction time of all computerised tasks demonstrated good reliability (ICC > 0.75). DV mean reaction time had the highest reliability (ICC = 0.880), this was greater than the reliability measured from the MoCA (ICC = 0.836). These were followed by CRT mean reaction time (ICC = 0.832) and SRT mean reaction time (ICC = 0.797).

Conclusion:

These results indicate that computerised attentional tasks are an appropriate outcome measure for clinical trials in patients with early and prodromal DLB.

Models of Peer Support for Lewy-Body Dementia: A Systematic Scoping Review

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Background:

Despite Lewy Body Dementia (LBD) being prevalent and challenging for families to navigate, models of support for people living with LBD and/or their family caregivers are not always available, accessible or acceptable. Peer support is known to be effective, however models of peer support specific to LBD are not well understood. The aim of this study is to systematically scope the body of existing literature to better understand models of peer support for people living with LBD and their families.

Methods:

The search strategy was devised to identify peer-reviewed research papers relating to the above aim. This process was iterative, and the search strategy was refined as evidence emerged and was reviewed. All types of study designs and both quantitative and qualitative studies of peer support interventions were considered for inclusion.

Results:

The data synthesis process is ongoing, but the following trends are evident: Most peer support interventions in the published literature are targeted at people with dementia generally and acceptability and effectiveness of these in the context of LBD is unclear. The research that has been conducted on LBD primarily focuses on peer support for family members and caregivers, not directly on people living with LBD. In recent years, there has been a shift towards online models of peer support, which makes support more accessible, but also presents challenges.

Conclusion:

While many models of peer support exist for LBD, few robust empirical evaluations of specific models have been conducted. Many models appear to lack a theoretical basis and/or intervention protocol, which impedes identification of the 'active ingredients' and presents significant challenges for replication and development.

Optimizing Nursing Care for Patients with Lewy Body Dementia: A comprehensive Approach to Management and Support.

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Background:

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder characterized by motor, cognitive, neuropsychiatric and autonomic symptoms. The management of this complex clinical phenotype embodies a challenge for clinical and nursing practice and poses a significant burden care partners of people with DLB. This study aims to develop effective nursing strategies to manage DLB symptoms and ease the burden of care partners.

Methods:

A two-stage approach was implemented. Firstly, a review of the existing literature related to common symptoms of DLS and the nursing care of people with DLB was conducted. Then, ten members of the nursing staff of the acute psychiatric ward of the University General Hospital of Patras were asked to fill in a questionnaire consisting of open-ended questions about the adequate nursing care of common symptoms of people with DLB.

Results:

The literature review unveiled falls, obstipation, hypotension, urinary incontinence, parkinsonism, visual hallucinations, executive dysfunction, anxiety, illusions, delusions, apathy and depression as the most common DLB symptoms requiring nursing care. Symptoms associated with sleep disorders, executive function, attention fluctuations and mental flexibility are also reported. The responses of the nursing staff revealed the challenges and the obstacles pertaining to the care of people with DLB. The necessity of a holistic nursing approach safeguarding support, safety and prevention of falls became evident for the management of DLB symptoms. Unfortunately, existing care strategies were not found to address always the needs of people with DLB due to the common lack of a nursing care plan.

Conclusion:

Overall, specialized nursing care tailored to the individual needs of people with DLB is necessary for managing symptoms and ensuring quality of life of both people with DLB and their care partners. Given the complex clinical phenotype, the integration of nursing care into personalized multiprofessional care plan is of paramount importance.

The Lewy Body Society - 19 years of Impact

Jacqueline Cannon [1]

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Background:

The community for people with **"The most common type of dementia you have never heard of"**, their families and carers, health care professionals and researchers.

We are the only charity in the UK – and the first in Europe – dedicated exclusively to Lewy body dementia.

Methods:

We campaign to raise awareness of Lewy body dementia in those who need to understand the disease and its impact – people living with Lewy body dementia and those who can make a difference to their futures.

Results:

Experiences of Lewy body dementia can differ but for everyone, it is life-changing.

We are sharing the personal stories of people who are living with a diagnosis, their family members and friends to inspire and instil confidence in others in a similar situation and educate those who are less familiar.

Conclusion:

We are the small charity with a global reach, campaigning tirelessly to highlight Lewy body dementia.

As the first Lewy Body dementia charity in Europe, we have been leading the way in supporting research and raising awareness since 2006.

Thanks to the donations we receive we have been able to fund research projects totaling £2.2 million to date. The first research we funded was in 2007 with a PhD studentship at Newcastle University and we have since sponsored a further 21 projects. Through these studies, researchers have made significant strides forward in identifying the causes of Lewy body dementia and ways in which the disease might be more effectively identified and treated.

We also produce information materials which are available both in hard copy and downloadable from our website, to help those affected by Lewy body dementia. We also support the Admiral Nurse Dementia Helpline so that people with the disease and their carers can get expert advice and support.

Understanding personal experiences of diagnosis and care for Lewy Body Dementia in Ireland.

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Background:

This project is the first comprehensive exploration of the diagnostic and care pathways for individuals with Lewy Body Dementia (LBD) in Ireland. Through interviews with patients, carers, and healthcare professionals, it aims to identify gaps and areas for improvement.

Methods:

Semi-structured interviews were conducted with 11 individuals diagnosed with mild to moderate LBD. Interviews were transcribed verbatim, anonymised, and analysed using a descriptive phenomenological approach focusing on 'diagnosis', 'post-diagnostic support', and 'awareness'. Subsequently, we interviewed 15 care partners are in the process of interviewing healthcare professionals from diverse occupations, including Geriatricians, Geriatrician Trainees, Psych Nurses, Psychiatrists, Psychiatry Trainees, Palliative Care GPs, Falls Unit Staff, Physiotherapists, Memory Nurses, Neuropsychologists, Occupational Therapists (OT), Social Workers, Parkinson's Disease (PD) Nurse Specialists, and Neurologists.

Results:

Interviews with LBD patients revealed significant delays in diagnosis due to complex symptoms, lack of awareness, and societal stigma. Post-diagnostic support predominantly relied on informal care, with an evident need for additional formal care services. Carer partners echoed these themes, highlighting diagnostic pathway difficulties, inadequate service availability, and insufficient support and information. Notably, carers emphasized the lack of support for themselves, including difficulties in accessing allied healthcare appointments and a lack of mental health support, which left them feeling isolated. Preliminary insights from healthcare professionals reflected these challenges, emphasizing the need for better diagnostic tools, comprehensive support services, and improvements in the Irish healthcare system.

Conclusion:

The findings call for increased awareness, improved diagnostic resources, and tailored support services for LBD in Ireland. This research marks the first comprehensive exploration into the LBD pathways to diagnosis and care, offering valuable insights that set a new standard in the field. The need for systemic changes in the Irish healthcare system is evident, requiring policy makers to address current deficiencies and implement strategies to enhance care for both patients and carers.

The high cost of care and limited evidence on cost-effective strategies for Lewy body dementia: systematic review of evidence

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Background:

Lewy body dementia (LBD) is a prevalent yet frequently underdiagnosed form of dementia, accounting for up to 15% of all dementia cases. This study aims to increase awareness and advocacy for LBD by gathering and critically assessing the economic evidence, including the cost of illness and cost-effectiveness of interventions for managing LBD.

Methods:

A systematic literature review was undertaken with EMBASE, Medline, CINAHL, PsycINFO, NHS Economic Evaluation Database and EconLit. This search was supplemented by grey literature on Google Scholar and reviewing the reference lists of identified studies. The papers included in the review were published between 2008 and 2023, and involved participants with LBD (dementia with Lewy bodies or Parkinson's disease dementia), which either addressed the cost of illness or conducted an economic evaluation.

Results:

Thirteen papers were included, comprising ten cost-of-illness studies and three economic evaluations. The cost of LBD tends to be higher than that of other forms of dementia, such as Alzheimer's disease, and these costs escalate more steeply as the disease progresses. These cost differences may not be solely influenced by the subtype of dementia, but possibly also by patient characteristics like physical and cognitive abilities. Costeffectiveness of potential interventions for LBD is limited.

Conclusion:

Despite numerous drug trials and other interventions for dementia, very few have targeted LBD, let alone explored the cost-effectiveness of such therapies for LBD. This disparity highlights the urgent need for cost-effective strategies and interventions targeting LBD. We propose the establishment of universally accepted standards for LBD research.

The EMERALD-Lewy research program: Improving the diagnosis, management, and lived experience of Lewy body dementia in Ireland

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Background:

The Lewy body dementias (LBD), including Parkinson's dementia and Lewy body dementia, account for >20% of the nearly 65,000 people with dementia in Ireland; however, an estimated fewer than 5% of those affected receive a formal diagnosis. LBD is characterised by cognitive-behavioural and physical changes which significantly impact quality of life and care burden. Knowledge, awareness and support in Ireland for LBD is low.

Methods:

Interdisciplinary multiple methods across different work streams include implementation science, observational cohorts, real-time data collection/ecological momentary assessment, health services research, quality of life evaluations, policy economic analysis, and knowledge translation.

Results:

The 4-year EMERALD-Lewy program (2024-2028) is shaped by UK's 'Living Well with Dementia' framework, across 3 workstreams: (1) 'Diagnosing well', is scoping low diagnosis rates in Ireland, to achieve a 'good diagnosis' (timely/accurate/person-centered) and is investigating novel methods to improve diagnostic accuracy. (2) 'Living well' is exploring the meaning of 'quality of life' in LBD and it's measurement, is investigating daily lived experiences in real-time using a smartphone app, and is developing and evaluating peer support; (3) 'Participating and translating knowledge well', is impacting health practice and policy in Ireland by enhancing public awareness and knowledge of LBD, and meaningfully including patient and public involvement throughout the program.

Conclusion:

The EMERALD Lewy program aims to improve diagnostic rates and quality of care for LBD in Ireland, aligning with existing policy and practice.

Keepsake Chronicles for Lewy Body Dementia: An arts-based intervention to value personhood

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Background:

Most research in Lewy Body Dementia (LBD) has focused on the biomedical model, overlooking the lived experience (LE) of this progressive condition, which can significantly alter a person's identity. This study piloted "Keepsake Chronicles," an arts-based storytelling approach, to explore how it might support individuals with LBD and their care partners in integrating their experiences and finding meaning in their challenges.

Methods:

The project involved storytelling groups led by a writer, photographer, and nurse. Participants brought meaningful objects and shared stories centered around these objects, allowing for personal control and expression. The resulting outcomes included a portrait of the person, a photograph of the object, and a visual representation of the story's setting, accompanied by short stories or poems crafted solely from the participant's words, which were shared back with the participants. These elements were compiled into a personalized book, serving as a record of the participant's story and a tool for preserving their essence as the disease progresses.

Results:

Key outcomes were: (1) the sessions were cognitively stimulating, enjoyable, and promoted a strengths-based approach, celebrating personhood; (2) the outputs were a celebration of personhood in the context of a progressive neurodegenerative condition, and could be shared with individual’s families and the wider support circle; and (3) families valued the resulting book as a cherished keepsake that could help them hold onto the person’s identity through the progression of LBD.

Conclusion:

"Keepsake Chronicles" produced outputs that honored individuals with LBD, recognizing their personhood and demonstrating that, despite the challenges of the condition, moments of joy and meaningful self-expression are possible through storytelling. Such stories can provide valuable data revealing gaps in care, unmet needs, and inspire new approaches to treatment and societal understandings that are more closely aligned with the lived experiences of those with progressive neurodegenerative conditions.

Feasibility and benefits of an online psychosocial group for family carers of people with Lewy body dementia

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Background:

Family carers of people with Lewy body dementia (LBD) often experience poor mental and physical health, reduced quality of life and high levels of strain/burden. Effective carer interventions include psychoeducational or psychotherapeutic tailored to individual needs, with group interventions evaluated as the most effective. However dementia carer interventions rarely address the symptoms of LBD, despite some evidence indicating specific group interventions can enhance understanding and reduce social isolation

Methods:

The Lewy body dementia Admiral Nurse service is a UK based dementia specialist nurse model. Referrals via a national helpline are offered individualised, multicomponent interventions including psychoeducation and coping strategies. Support is delivered remotely through telephone or online video calls.In 2021 the service developed on online psychosocial group programme for family carers at earlier stages of their caring. This included 6 x 2 hour sessions aimed at supporting understanding of LBD, coping strategies, addressing emotional impact of caring and planning for the future. Mutual support and self -care was facilitated via small group sizes. Carers were assessed prior to attending to ensure suitability. Feedback was gathered via an anonymised survey and wellbeing measured using Warwick Edinburgh Mental Wellbeing Scale.

Results:

The programme has been offered to 4 separate groups (4-6 participants). Survey feedback (n= 15) indicated a positive difference to understanding of the condition, increased confidence in coping, development of new skills and feeling supported / connected with others across all respondents. Wellbeing scores improved overall on average, by approximately 6 points (43.3 – 49.1).

Conclusion:

Initial feedback and outcomes indicate this intervention was acceptable and made a positive difference to coping and wellbeing for those who took part. Further research is required to fully evaluate the impact and benefits of online psychoeducational groups for family carers of people with Lewy body dementia at different stages of their role.

Is air pollution associated with physical activity and sleep parameters in participants with dementia with Lewy bodies?

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Background:

Devices that measure activity and sleep may be useful tools for differentiating dementia with Lewy bodies (DLB) from Alzheimer's disease (AD), but the effects of air pollution (AP) on activity or sleep are unknown.

Methods:

We measured activity, sleep, and AP exposure in participants with probable DLB (n=9) and AD(n=7) who live in the Pacific Northwest, where AP exposure tends to be less than many other US cities. We used the wGT3X-BT to obtain 2 weeks of step count data and the Sleep Profiler X8 to obtain 2 nights of rapid eye movement (REM) and non-REM hypertonia (NRH) sleep data. We calculated AP exposure using participant addresses at study enrollment, publicly available AP estimates, and land use regression (LUR) models.

Results:

Participants with DLB were more likely to have lower daily step counts (mean=4,750 vs. 5,020, p=0.82), less REM sleep (mean=6.91% vs. 18.00%, p<0.01), and higher % NRH (mean=12.7% vs. 4.8%, p=0.08) than participants with AD. There were no significant differences in AP exposure between groups. Among participants with DLB, we observed suggestive correlations (p<0.10) between %REM and nitrogen dioxide (NO_2; r=0.58), particulate matter ($PM_{2.5}$; r=0.58), and particle number concentration (PNC; r=0.62); suggestive correlations between %NRH and carbon dioxide (CO; r=-0.59), NO_2 (r=-0.62), PNC (r=-0.60), and sulfur dioxide (SO_2; r=-0.61); and a suggestive correlation between daily number of steps and PNC (r=0.55). Among participants with AD, we observed a suggestive correlation between %NRH and O_3 (r=0.70) but no correlations between daily number of steps and exposures.

Conclusion:

Although our findings suggest that AP may be associated with sleep disturbances in DLB and physical activity measures in AD, larger studies are necessary to explore these associations.

Lewy body dementias research in Latin America: A scoping review

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Background:

Research endeavors in Latin America (LA) have primarily focused on Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD), leaving Lewy body dementias (LBD) in oblivion. We aimed to review the evidence related to LBD in LA, with the objective of providing a comprehensive perspective to understand if this is due to a lack of reports or to specific nuances of this region.

Methods:

A scoping review was conducted to identify research on LBD in LA. PubMed, EMBASE, LILACS, and Web of Science were searched. Original studies that explicitly informed the inclusion of participants with LBD were included and analyzed.

Results:

Out of 1388 identified studies, 70 were included in the review. Of them, 64 had a cross-sectional design, 3 were cohort studies, 2 had a case control methodology and only 1 was an open essay clinical trial. These studies primarily focused on clinical manifestations, neuropsychiatric symptoms, biomarkers, diagnostic tools, prevalence and risk factors of LBD in LA. 52 studies had data from Brazil.

Conclusion:

There is an underrepresentation for LBD research, with Brazil leading in publications, while other countries lag behind. Most studies evaluated associations, and causality establishment was rare. Challenges included the lack of robust designs, limited clinical trials, and unclear differentiation within the LBD spectrum. Addressing these gaps requires concerted efforts to bolster research capacity and foster international collaborations.

A Matching Profile Tool and Computer-Driven Algorithm for Compatible Peer-to-Peer Caregiver Support

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Background:

Caregivers can be a valuable resource to each other, potentially reducing caregiver stress and optimizing wellbeing. Current phase 2 study evaluates emerging data of a matching profile tool for a computer-driven algorithm designed to help caregivers find compatible peer-to-peer support.

Methods:

Current and/or former dementia caregivers were enrolled. Using a randomized controlled intervention trial method, participants completed questionnaires at baseline assessing factors related to their own health and well-being. Following a 3-month wait period (i.e. self as control) questionnaires were re-administered and participants completed the *C2C matching profile*. Study participants were then randomized to either receive matches with a high compatibility score (CM) or were randomly matched (RM) without consideration of their preferences. All caregivers received four matches. Questionnaires administered again at 6 and 15 months.

Results:

Dementia caregivers (n=189) were commonly female (75.9%), mean age 60.6 at baseline enrollment, most caring for a spouse/partner (72.0%) or a parent (13.2%). Types of dementia include AD (34.4%), LBD (21.7%) and FTLD (21.2%), and a small number of other diagnoses. Twenty-nine (15.3%) caregivers dropped out of the study. The drop rate from the RM group (21%) was about twice that of the CM group (11%). Qualitative findings of those who dropped and voiced dissatisfaction with their matches were predominantly from the RM group (83%). For LBD caregivers (n=42), only 1 dropped and was from RM.

C2C profile data suggest the most preferred characteristic to be matched with is a caregiver caring for someone with the same diagnosis; 79% of LBD caregivers ranked it as very or extremely important (62% for caregivers overall).

Conclusion:

Being matched using the *C2C matching profile* and computer-driven algorithm significantly reduces attrition indicating that the C2C tool may be valuable in matching caregivers for peer-to-peer support that is tailored to their needs and preferences.

Sociodemographic and clinical characteristics of a Lewy Body Disease population in a specialized Latin American center

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Background:

The burden of dementia is increasing, especially in Low- and Middle-Income Countries. Alzheimer's Disease (AD) and Lewy Body Disease (LBD) are among the most prevalent dementias worldwide, but accurate prevalence data for LBD in Latin America is lacking, with some estimates being surprisingly low. This gap may result from misdiagnosis due to limited trained personnel, variability in clinical presentation, and a primary focus on memory and executive impairments, often neglecting motor and neuropsychiatric symptoms that signal early neurodegeneration. Thus, distinguishing between dementia types is crucial. Our study aimed to address this gap by determining the prevalence of LBD at a Memory Clinic in Bogotá, Colombia, and comparing it with other neurodegenerative conditions like AD, frontotemporal dementia (FTD), and vascular dementia.

Methods:

We included patients from the memory clinic diagnosed with LBD between 2018 and 2022, along with those diagnosed with AD, FTD, and vascular dementia, in a 4:1 ratio. We assessed their functional, cognitive, and executive performance and neuropsychiatric symptoms. Differences were analyzed using ANOVA and Chi-square tests.

Results:

We identified 77 individuals with LBD, yielding a prevalence of 1.34%. Most were male. Compared to other dementias, notable differences were observed in the age of onset: FTD patients showed symptoms earliest, while AD patients had the latest onset. Variations were also found in functional, motor, and cognitive performance. LBD patients had higher scores for hallucinations, especially visual and auditory. Motor disturbances were more pronounced in the FTD and LBD groups. Visual hallucinations were most common, followed by auditory ones.

Conclusion:

Accurate differential diagnosis is vital, particularly in early dementia stages, due to the shared prodromal symptoms across neurodegenerative diseases. Precise diagnosis is essential for personalized management and to avoid inappropriate medication, which can increase risks and economic burdens on healthcare systems.

The landscape of dementia with Lewy bodies research: A scoping review of approaches and topics related to the perspectives of those affected by the disease

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Background:

Dementia with Lewy bodies (DLB) poses unique challenges due to its complex clinical presentation. Effective person-centered care and research necessitate incorporating the perspectives of those directly affected by DLB. Although various methods exist to capture these perspectives, their application and scope in DLB research remains unexplored. This scoping review aimed to map the extent, type and nature of research focusing on the perspectives of individuals with DLB and their care partners.

Methods:

Following the Arksey and O'Malley framework and Joanna Briggs Institute methodology, a comprehensive search was conducted across six databases and two grey literature sources. The inclusion criteria targeted studies that went beyond clinical symptom characterisation and measurement, excluding sources that relied solely on unidimensional symptom scales. Two reviewers independently applied selection criteria. Data were extracted, charted and analysed using descriptive numerical analysis and basic qualitative content analysis.

Results:

140 sources were included in the review. Of these, 89.3% were research articles, 67.9% used a quantitative approach, and 62.9% used a cross-sectional design. The most common method was standardised measures assessing multidimensional concepts, such as caregiver burden. Of these, the Zarit Burden Interview was the most cited. Interviews were the most common qualitative approach. A total of 28 topics were identified, with emotional and psychological well-being—particularly caregiver burden, stress and/or distress—being the most widely investigated topic. 14 topics were investigated three times or less.

Conclusion:

The review highlights a lack of methodological diversity and a disproportionate focus on certain topics, resulting in research gaps, many of which align with those identified as research priorities by individuals with DLB and care partners. We recommend exploring novel methods for systematically capturing patient and care partner perspectives in DLB cohorts, particularly on topics of highest priority to those affected by DLB.

Understanding LBD Speech: Towards an Adaptive Voice Assistant for Enhanced Communication

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Background:

Dementia, particularly Lewy Body Dementia (LBD), poses significant challenges for individuals, impacting their daily lives, overall well-being, and ability to communicate effectively. The complexity of enhancing communication for People with Dementia (PwD) has increased, driving the exploration of innovative solutions such as voice assistants. Understanding the unique speech features and conversational content of PwD is crucial for improving their communication experiences. Analyzing these speech features provides valuable insights that are essential for tailoring interactions and developing more effective support systems for PwD.

Methods:

This study analyzes speech recordings from the ADReSSo database, which includes speech samples from both dementia patients and healthy aging individuals. We aim to investigate various speech features from the time and frequency domains associated with dementia disease. These features will prove beneficial in distinguishing between dementia patients and healthy individuals. Furthermore, leveraging machine learning techniques such as Support Vector Machines (SVM), we explore the potential of these features in dementia detection. Additionally, through speech emotion recognition, this study delves into the array of emotions exhibited during conversations.

Results:

The findings reveal that several speech features, such as root mean square, zero-crossing rate, and fundamental frequency, exhibited significant differences between individuals with dementia (PwD) and healthy individuals. These speech features not only aid in identifying dementia but also reflect the distinct speaking patterns of PwD. Moreover, there are significant differences in speech emotions between PwD and healthy aging individuals.

Conclusion:

Our investigation highlights key differences in speech features and emotional expressions between individuals with dementia and healthy counterparts. These differences provide valuable markers for dementia detection and enable more empathetic interactions with voice assistants. Utilizing these insights, future personalized voice assistants could greatly improve communication for individuals with dementia and aid in early diagnosis, advancing both dementia research and the role of technology in healthcare.

Lewy Body International - a coalition of Lewy body voices and action

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Background:

The possibility of an international coalition of Lewy body organisations was first floated at the 2015 ILBDC in Fort Lauderdale. It was on the agenda and the session was attended by a professor and a carer from Japan and the founder and chair of the trustees of the Lewy Body Society (UK). The only other known LB charity, the US Lewy Body Dementia Association, who co-hosted the conference, did not send a representative. We quickly concluded that there were simply not enough LB organisations to consider a federation at that time.

Fast forward 7 years and organisations or information/advocacy resources were now established in Australasia. Canada, France, Ireland , Spain and a second in the US.

That time had come.

Lewy Body International was formally launched at the ILBDC in Newcastle in 2022.

Argentina , Belgium and Sweden soon followed and Lewy Body International's inaugural cooperative project was the first ever World Lewy Body Day on 28 January 2023. The day was marked by conferences, campaigns, a book launch, a social media blitz and buildings lit up across the globe.

The constituent members of LBInt range from one-person operations to a large, corporate organisation but each voice holds the same weight and and together we can make a louder noise

January 28 was chosen because it is Dr Lewy's birthday. It is also the day before this conference starts and a presentation about LBInt and World Lewy Body Day would be very appropriate.

Methods:

Results:

Successful start

Conclusion:

Lewy Body International is work in progress. More countries are welcome as they form LB dedicated groups and members help this where they can. The first World Lewy Body Day was an encouraging start and we look forward to continuing to work together globally shining a light.

Long term cognitive outcome of prodromal and mild dementia with Lewy bodies: a cohort study

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Background:

The cognitive evolution of early dementia with Lewy bodies (DLB) is less well known than that of Alzheimer's disease (AD). During dementia, DLB progresses like AD. The aim of this study was to analyze the long-term cognitive decline of early DLB.

Methods:

Participants were recruited for either mild cognitive impairment or mild dementia with a suspicion of DLB or AD, or as healthy older subjects (AlphaLewyMA study, NCT01876459, 2013). Using beta regression, we compared the slope of the Mini-Mental State Examination (MMSE) score of 110 DLB patients (DLB group), 57 AD patients (AD group), 19 DLB and AD patients (DLB+AD group), 30 patients with other cognitive diseases (DC group), and 31 healthy older controls (HC group).

Results:

The mean follow-up was 4.9 years. All patients' groups had a significant decrease in MMSE score. The slope of MMSE decline of the DLB group (-0.49 point a year) was higher than the HC group (+0.03; *P*<.0001), lower than that of the AD (-2.78; *P*<.0001) and DLB+AD (-2.92; *P*<.0001) groups and not different from the DC group (-0.29; *P*=.8000). The variability of annual variations in MMSE score was greater in the DLB group (2.13 points) than in the AD group (1.73 points). There was no difference between patients' group in terms of death or admission to a nursing home.

Conclusion:

Patients with early DLB decline cognitively more slowly while fluctuating, whereas AD and DLB+AD patients decline markedly. These results suggest that there is a more dysfunctional than neurodegenerative phase at the beginning of DLB.

Overview of Low- and Middle-Income Country Authorship for Dementia with Lewy Bodies Research

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Background:

Lack of diversity in research groups is a significant barrier in dementia with Lewy bodies (DLB). We aim to identify underrepresented DLB centres and expand global collaborations.

Methods:

We performed a PubMED search on August 21, 2024, for articles from the past five years including “dementia with Lewy bodies”, “Lewy body dementia”, or “Lewy bodies” with author affiliations including low- and middle-income countries (LMIC), defined by the World Bank for 2025. R packages “rentrez” and “XML” were used to extract first authors’ affiliations.

Results:

In total, 665 publications included at least one author from an LMIC. Only 3 publications had first authors from a low-income country (3 Sub-Saharan Africa, all Rwanda). One hundred nineteen publications had first authors from lower-middle-income countries (1 East Asia, 9 North Africa, 10 Sub-Saharan Africa, 99 South Asia). With 94 publications, India was the most prolific lower-middle-income country. Four hundred twenty-six publications had first authors from upper-middle-income countries (5 Sub-Saharan Africa, 24 Middle East and North Africa, 33 Europe and Central Asia, 70 Latin America, 294 East Asia). With 285 publications, China was the most prolific higher-middle-income country. One hundred seventeen publications had first authors from high-income countries (9 Middle East, 14 East Asia & Pacific, 46 North America, 53 Europe).

Conclusion:

Authors from LMICs significantly contribute to DLB research, although many LMICs are not adequately represented in international DLB networks. There is a need to establish strategies through which international DLB research networks can be developed, specifically supporting researchers from LMICs to participate in the global community. Systematic searches of DLB publications may present an opportunity to identify DLB organizations, clinicians and scientists from LMICs who could enrich and diversify our networks.

From data to dialogue: an AI-assisted approach to setting research priorities for Lewy Body Dementia

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Background:

By combining AI-assisted topic modelling and community engagement, this study aims to advance the research landscape for Lewy Body Dementia (LBD), a condition that remains under-recognized and under-researched, despite its significant care partner burden and reduced quality of life compared to other dementias.

Methods:

A two-stage approach included AI analysis of global LBD literature and its evolution post-2017 diagnostic guidelines, integrating Latent Dirichlet Allocation, followed by feedback from LBD community in Ireland through cross-sectional survey, public involvement event, and consensus meeting (PPI).

Results:

LBD research, over the last 17 years, has shifted from genetic factors and protein aggregation to advanced neuroimaging and AI for diagnostics. PPI identified critical gaps in multidisciplinary research, prevention, palliative care, policy development and set future priorities on diagnostic tools, care coordination, and non-pharmacological treatments for impactful progress.

Conclusion:

Integration of lived experiences, policy, and innovative is crucial to transform LBD management and patient outcomes.

Developing an integrated care pathway (ICP) for Lewy Body Disease in Ireland

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Background:

It is estimated that fewer than 5% of people with LBD (Lewy body dementia) in Ireland receive a formal diagnosis and many are misdiagnosed or have delayed diagnosis, leading to poorer outcomes. The EMERALD Lewy research program aims to improve diagnosis and care for people with LBD in Ireland. A key output is a nationally agreed integrated care pathway (ICP), co-produced with service users and fully integrated into existing/developing pathways and services. This would map patient care from initial presentation to end of life, to enhance healthcare quality, coordination, efficiency and patient satisfaction.

Methods:

Guided by an ICP expert, a multi-stakeholder team (including service users and families), we co-produced the ICP, linked to ongoing policy and service development through Ireland's National Dementia Service, and incorporating the DIAMOND Lewy diagnostic-management framework, adapted for Ireland. Consensus and expert opinion was gained through iterative steps, including: (1) Preliminary pathway development - to identify key care to be delivered and map care flows and activity; (2) Systematic problem identification - to understand people with LBD's priority care elements, and most concerning problem areas; and (3) Pathway refinement - to obtain expert panel input using a modified Delphi iterative review process.

Results:

The developed ICP is aligned with Ireland's developing network of memory, movement disorder, and related health services and designed to reduce unwarranted variation and improve the quality of service/support for people with LBD and their families. It enables health care services to scope service provision gaps, making explicit, at a system level, the services required to effectively manage LBD.

Conclusion:

The EMERALD Lewy ICP will be the basis to improve diagnosis and care for people with LBD in Ireland. Next steps involve structured implementation, and evaluation, across health services in Ireland.

Therapy

Oral Abstracts

What matters most? Exploring the treatment preferences of people with dementia with Lewy bodies and their care partners: a stated preference study

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Background:

Integrating stakeholder preferences into the selection of trial outcomes in dementia with Lewy bodies (DLB) is essential. Acknowledging that treatment of one symptom may exacerbate another, this study employs a discrete choice experiment (DCE) to elicit treatment preferences of individuals with DLB and their care partners, including their willingness to accept trade-offs between different symptoms. It will also determine the maximum acceptable risk (MAR) associated with treatment of these symptoms.

Methods:

A DCE survey instrument was developed in collaboration with a DLB research advisory group, pretested, and administered online. Six attributes were included: severity and functional impact of the four core DLB symptoms, rate of cognitive and functional decline, and risk of adverse events (for which amyloid-related imaging abnormalities (ARIA) were chosen as an example). The experimental design comprised six blocks, each with eight choice sets comparing two hypothetical treatments and a 'no treatment' option. Preliminary DCE data were analysed using a multinomial logit model to estimate the relative attribute importance.

Results:

At interim analysis, 50 respondents, aged 38-76, had participated (n=11 individuals with DLB; n=39 care partners; 88% female). Visual hallucinations was identified as the most important attribute for treatment to target; however, improvements in all core symptoms, as well as cognition and functioning, positively and significantly influenced respondents' utility (all $p < 0.000$). As expected, the risk of ARIA was associated with a negative, but not significant utility ($p = 0.7372$).

Conclusion:

Visual hallucinations should be prioritised as a primary or secondary outcome in clinical trials. Although respondents viewed the risk of adverse events (ARIA) unfavourably, it did not have a significant effect on their preference for treatments offering improvements in core symptoms. Establishing MAR is critical for assessing the feasibility of DLB trials and the clinical adoption of new therapies; more research on MAR is required.

tACS and its Influence on Cognitive Performance and Alpha Oscillations in Dementia with Lewy Bodies

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Background:

The study aims to evaluate the effect of a single-session (sham-controlled) of transcranial Alternating Current Stimulation (tACS) at alpha frequency (12 Hz) over the parieto-occipital cortex on resting-state EEG and cognitive attentional performance in patients with Dementia with Lewy Bodies (DLB). We hypothesized that, compared to a healthy control group, DLB patients would benefit from tACS in terms of increased alpha power and improved cognitive performance.

tACS is a non-invasive technique used to modulate brain activity, influencing brain oscillations related to cognitive functions such as memory, perception, and attention.We used the Starstim® tES-EEG system, which allows simultaneous tACS induction and monitoring of alpha power brain oscillations through a 19-channel EEG. We administered the Visual Search task to measure cognitive performance in terms of selective attention and visuo-spatial abilities.

Methods:

We collected socio-demographic data and administered the BDI-II and PANAS mood questionnaires. For DLB patients, global cognitive functioning (MoCA) and daily-life autonomy (ADL, IADL) were also assessed. Resting-state EEG was recorded as a baseline. Participants then received 20 minutes of alpha tACS at 1.5 mA over the parieto-occipital cortex (P3, P4, CZ) while completing a computerized Visual Search Task. Post-stimulation resting-state EEG was recorded to analyze alpha power changes. The procedure was later repeated, with sham tACS (placebo) replacing alpha tACS.

Results:

A 2x2 repeated-measures ANOVA analyzed differences in the Visual Search Task, comparing the experimental groups and the stimulation conditions. We found a significant improvement in reaction times (RT) only for DLB patients during tACS compared to sham, with no differences in accuracy. Additionally, we observed a modulation in pre-alpha power (7-8 Hz) following the tACS session in DLB patients.

Conclusion:

Alpha tACS can improve cognitive attentional performance in DLB patients. This technique shows potential for modulating brain activity and restoring alpha oscillations, which are reduced in DLB.

Efficacy and safety results of the RewinD-LB phase 2b clinical trial of neflamapimod in dementia with Lewy bodies (DLB)

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Background:

The RewinD-LB phase 2b clinical study (NCT05869669) of neflamapimod (oral p38α kinase inhibitor targeting cholinergic degeneration) was initiated to confirm phase 2a results (Jiang et al, Nature Communications, 2023; Prins et al, JPAD, 2024), in which neflamapimod demonstrated positive effects in patients with mild-to-moderate DLB on multiple clinical endpoints measuring cognition and/or function, most prominently in patients without evidence of advanced disease (as assessed by plasma levels of the neurodegeneration biomarker ptau181; Alam et al, Neurology, 2023).

Methods:

16-week, double-blind, placebo-controlled clinical trial, with 32-week open-label-extension. Patients: DLB by 2017 consensus clinical criteria, with very mild or mild dementia (global CDR=0.5 or 1.0) and plasma ptau181 at screening < 2.4 pg/mL. Treatment: neflamapimod 40mg or matching placebo capsules, three-times-per-day, randomized 1:1, stratified by background therapy [none, acetylcholinesterase inhibitor (AChEI), or memantine]. Primary endpoint: change in CDR-SB vs. placebo during the placebo-controlled phase of the study. Secondary endpoints: Timed up and go (TUG) test, a cognitive-test battery, and ADCS-CGIC. 43 investigational sites (32 USA, 8 UK, 3 Netherlands). Primary funding: US National Institute of Aging Grant R01AG080536.

Results:

159 participants randomized between August 2023 and June 2024. At baseline, mean (SD) age=71.4(6.1), CDR-SB=4.4(2.0), MMSE=23.3(4.4), TUG=14.2(15.1) seconds, NPI-10=11.5(13.8); 85% male; prevalence of core clinical features: fluctuations=73%, visual hallucinations=57%, REM sleep disorder=78%, parkinsonism=87%; 75% were receiving AChEI therapy (of which 15% were also receiving memantine) and 3% were receiving memantine without AChEI.

Conclusion:

The study successfully enrolled in a short period a non-advanced disease (i.e., without elevation in plasma ptau181) DLB patient population. The last-patient, last-visit for the 16-week placebo-controlled treatment period is to take place in October 2024 and the top-line efficacy results are expected in December 2024. Efficacy (all major clinical and biomarker results) and safety findings during the 16-week placebo-controlled phase of the study will be presented.

Cognitive and behavioral outcomes in patients with dementia with Lewy bodies treated with nilotinib

Charbel Moussa [1], Fernando Pagan [2] Yasar Torres-Yaghi [2], Michaeline Hebron [1], Barbara Wilmarth [1], Raymond Scott Turner [3], Sara Matar [1], Xiaoguang Liu [1], Dalila Ferrante [1], Giuseppe Esposito [2], Jaeil Ahn [1]

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Background:

We evaluated the safety, tolerability and efficacy of a potential disease-modifying treatment for individuals with dementia with Lewy bodies (DLB).

Methods:

We conducted a single-center, phase 2, randomized, double-blind, placebo-controlled study. 43 participants were randomized 1:1 into nilotinib, 200mg, or matching placebo groups. Study drug was taken orally once daily for 6 months followed by one-month wash-out. We hypothesized that nilotinib is safe and can improve cognitive and/or behavioral features in DLB.

Results:

Of the forty-three (43) individuals enrolled, fourteen (14) were women (33%), age (mean±SD) was 73±8.5 years. Nilotinib was safe and well-tolerated and more adverse events were noted in the placebo (74) vs nilotinib (37) groups (95% CI, 0.98 to 2.32, p=.054). The number of falls were reduced in the nilotinib (six) compared to placebo (21) group (95% CI, 1.30 to 10.12, p=0.006). ADAS-cognition 14 scores improved by 2.8pts (ADAS-Cog14; 95% CI, 0 to 6.34, p=0.037) in nilotinib versus placebo. Psychiatric features, irritability and cognitive fluctuations were worse in placebo compared to nilotinib. No differences were observed in MDS-UPDRS part II and III, but part I (cognition) improved (0.9 pts, 95% CI, 0 to - 2, p=0.044) in nilotinib compared to placebo. Other cognitive and functional scores, including MoCA (1.5pts, 95% CI, 95% CI, 0 to - 3, p=0.061) and ADCS-ADL, (-3.3 pts, 95% CI, -5 to - 1, p=0.084) trended towards an improvement. CSF HVA as a marker of dopamine level was increased (98.53nM, 5% CI, 27.81 to 169.3, p=0.004). The CSF ratio of pTau181/Aβ42 was reduced (Fig. 3E, -0.13nM, 5% CI, -0.27 to 0.01, p=0.034).

Conclusion:

Nilotinib has shown favorable safety and efficacy in patients with LBD supporting a multi-center phase 3 trial for individuals with DLB or advanced Parkinson’s disease with dementia.

Results from cog1201: A Proof-of-Concept Study of CT1812 in Participants with Mild-to-Moderate Dementia with Lewy Bodies

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Background:

CT1812 is an experimental small molecule oligomer antagonist in clinical development for the treatment of dementias driven by the buildup of oligomers of alpha-synuclein and beta-amyloid, both of which are present in many patients with dementia with Lewy bodies (DLB).

The COG1201 'SHIMMER' study is the first clinical trial of CT1812 in patients with DLB and is designed primarily to explore safety and tolerability and identify signals of benefit in cognitive function, motor deficits, and behavioral changes including daytime sleepiness and fluctuations.

Methods:

COG1201 is a randomized, double-blind, placebo-controlled study (NCT05225415) that enrolled 130 individuals with mild-to-moderate DLB as defined by the 4th report of the DLB Consortium. Participants were randomized 1:1:1 to receive once-daily oral doses of CT1812 (100 or 300 mg) or placebo for six months. Participants were followed during the trial using the Montreal Cognitive Assessment (MoCA), Cognitive Drug Research (CDR) Battery, ADCS-ADL and -CGIC, Neuropsychiatric Inventory, Unified Parkinson's Disease Rating Scale (UPDRS) Part III, Clinician Assessment of Fluctuation, Epworth Sleepiness Scale and other standard measures.

Cognition Therapeutics is conducting COG1201 with University of Miami Miller School of Medicine and the Lewy Body Dementia Association under a grant from the National Institute of Aging (R01AG071643).

Results:

Change from baseline for the exploratory efficacy outcomes will be reported using a mixed model for repeated measures. We will also report alpha-synuclein via skin biopsies (CND Life Sciences); amyloid status via plasma phosph-tau217 and amyloid monomer ratio; and other plasma biomarkers changes including GFAP and NfL.

Conclusion:

This study completed enrollment in May 2024 and results are anticipated by YE 2024. This study will provide the first insights into the impact of CT1812 on clinical, behavioral and functional endpoints in people diagnosed with DLB.

Poster Abstracts

Neuromodulation for Cognitive Impairment in Lewy body-related cognitive impairment: Exploring Patient Acceptance

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Background:

Few interventions exist for Parkinson's mild cognitive impairment (PD-MCI) or prodromal DLB (DLB-MCI), despite the high risk of progression to Lewy body dementia (LBD). Non-pharmacological therapies are emerging as vital options for this group. Peripheral nerve stimulation methods, like vagus and greater occipital nerve stimulation (ONS) using transcranial direct current stimulation (tDCS), have been shown to enhance memory in older adults and are now being tested in Alzheimer's disease (AD). We aimed to extend this intervention to those with early-stage cognitive decline in Lewy body disease.

Methods:

To inform a future feasibility study of ONS in LB disease, participants (n=50) with PD-MCI or prodromal DLB were shown a short video about ONS as a novel therapy for cognitive decline. They then completed a 32-item survey on their attitudes toward the intervention, including potential concerns and willingness to try it, as well as their knowledge and experience with non-drug treatments for cognitive impairment.

Results:

Participants were 66% male and 34% female, with a mean age of 63.62 years (± 8.303) and an average diagnosis duration of 5.2 years (±3.65). Among respondents, 83.4% viewed non-pharmacological treatments as important for managing cognitive impairment in LB disease, and 83.7% found ONS acceptable based on the video. The top three factors influencing ONS acceptability were safety, clinician qualifications, and side effects. Conversely, the least significant factors included treatment duration and frequency, speed of onset, and supporting research evidence. The most concerning inconvenience was electrode usage, while the least concerning were device learning and the need for periodic clinic visits.

Conclusion:

This study reveals substantial interest in non-drug, non-invasive transcutaneous nerve stimulation within the PD and LBD population, emphasizing the need for further exploration in a feasibility-pilot study, followed by a larger-scale trial, if warranted. Neuromodulation is a potentially important therapeutic option for cognitive decline in LB disease.

Profiling of Aggregation-Prone Motifs in Alpha-Synuclein and Implication for Targeted Therapeutic Development

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Background:

Lewy bodies and neurites formed due to excessive accumulation of α-synuclein are the hallmarks of Parkinson's disease. Along with PD, α-synuclein aggregates have been prominently observed in Lewy Body Dementia (LBD), Multiple System Atrophy (MSA), and in a subset of Alzheimer's Disease (AD) patients. The structures of the fibrillar region across different synucleinopathies suggest the modification in each conformation is governed by the pathological condition. The structural heterogeneity between oligomers and fibrillar forms of aggregates derived from patient samples is still elusive. The cryo-EM structures of postmortem brain-derived samples of PD, LBS, and MSA patients have revealed the polymorphic nature of well-arranged fibrillar forms with overlapping stretches. The discordance in main aggregation forming segments remains unsolved even with numerous studies employing computational tools and experimental investigations of selected short peptides

Methods:

We have synthesized a series of offsetting 15-mer peptides covering the entire stretches from recently reported cryo-EM structures of fibrils isolated from patients with all major synucleinopathies. The congregation patterns were experimentally validated by in-vitro assays such as Thioflavin T assay and Congo red binding assay as well as microscopic methods such as CLSM, SEM, and AFM.

Results:

Our study aims to identify the sticky peptide regions which can act as nucleation points. By utilizing a ThT-based aggregation assay, we have thoroughly profiled aggregation propensity and zeroed in on two aggregation hot spots, which could be the

nucleation centres.We have also discovered that the aggregation propensities are highly modulated by the flanking regions and post-translational modifications particularly focusing on acetylation and carbamylation that render the lysine residue chargeless.

Conclusion:

We are further utilizing the offsetting peptide library as a target detection tool for potential therapeutic development. The mildly aggregation-prone sequences appear to be of high interest as they can be utilized as standalone inhibitors or a potential target site for degrader development.

The efficacy of electroconvulsive therapy in patients with Lewy Body Diseases: A retrospective study

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Background:

Lewy Body Diseases (LBD), including Dementia with Lewy Bodies (DLB), prodromal DLB (pDLB) and Parkinson's Disease (PD) frequently present with psychiatric symptoms which sometimes need electroconvulsive therapy (ECT). However, the efficacy of ECT for those symptoms in patients with LBD, especially with DLB and pDLB is only implied by several reports targeting a small number of cases. In this study, we aimed to examine the efficacy of ECT in patients with LBD by comparing with other primary psychiatric disorders including mood disorders and schizophrenia, with a larger number of cases.

Methods:

The participants with LBD, mood disorders and psychotic disorders were selected from the patients who underwent ECT for the first time between 2012 and 2023 in Sunagawa City Hospital, Japan. Those who had comorbid brain organic diseases other than LBD and whose psychiatric symptoms were not the main target of ECT were excluded. Outcome was measured by Clinical Global Impressions (CGI) evaluated retrospectively and independently by multiple experienced psychiatrists and readmission rates. We compared them between the three groups and performed multivariate analysis with CGI as the objective variables.

Results:

119 patients underwent ECT for the first time during the period, and among them, 101 subjects were selected following the criteria. Thirty-two patients were diagnosed with DLB, with a mean (SD) age of 77.6 (7.0) years old and 68.8% were female. 65%, 31% and 38% had psychosis, catatonia and mood symptoms, respectively, at the time of ECT introduction. We will report other results including the outcome concerning the other Lewy Body Diseases (PD and pDLB) and the comparisons with other diseases, on the conference.

Conclusion:

In this study, we could include a large number of LBD patients compared to previous reports. We will report whether ECT is effective for LBD and identify the candidate predicting factors of ECT in LBD.

Occipital nerve stimulation for cognitive impairment in Parkinson's Disease - an open-label field study

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Background:

Mild cognitive impairment (MCI) may be a presenting feature of Parkinson's Disease (PD) or may develop over the course of progression of the disease. Greater occipital nerve stimulation (ONS) utilising tDCS has been shown to enhance performance of older adults in an associative memory task. We aimed to test the tolerability and feasibility of an ONS intervention protocol in a PD-MCI cohort.

Methods:

Patients with PD-MCI were recruited from a PD neuropsychiatry clinic. The intervention comprised three study visits over 28 days. Visits comprised a cognitive battery, ONS administration and carrying out a paired language task (visit 1), repetition of the paired language task (visit 2), and repeat cognitive battery (visit 3). Safety, tolerability, and acceptability of the intervention were measured using Brunoni's proposed tDCS adverse events questionnaire and a follow-up semi-qualitative survey.

Results:

5 participants with PD-MCI completed the intervention. Patients reported excellent safety and tolerability, with all adverse events rated as 'absent' on the tDCS adverse events scale. All patients found the intervention safe and acceptable**.** A lower Likert scale rating was given for convenience, on account of travel to the study site.

Preliminary evidence of efficacy was observed in cognitive testing, with statistically significant improvement in Total Learning on the CVLT-II. Trends to improvement were also observed in the MMSE and WAIS digit span Total Recognition Score.

Conclusion:

This was an open label field study, with a goal of assessing the feasibility and acceptability of an ONS trial protocol in the PD-MCI population. Patients reported positive impressions of the intervention, with excellent patient ratings of safety and acceptability. All patients who completed the trial indicated that they would very likely choose ONS or similar non-invasive neuromodulatory intervention as a treatment for their PD-related cognitive impairment, if such an intervention was found to be effective.

Deep Brain Stimulation for MOtor symptoms in patients with Parkinson's disease DEmentia (DBS-MODE)

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Background:

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for disabling motor symptoms of Parkinson's disease (PD) that persist despite optimal pharmacological treatment. Currently, DBS is not performed if there is concomitant significant cognitive impairment based on concerns of cognitive deterioration, higher complication rate and less functional improvement. However, this has not been investigated so far.

Methods:

A single center, prospective, randomized, open-label, blinded end-point (PROBE design) pilot clinical trial is being performed. Patients are eligible for the trial if they have PD dementia (PDD), are able to provide informed consent, and experience disabling motor response fluctuations, bradykinesia, dyskinesia, or painful dystonia, despite optimal pharmacological treatment. In total 44 patients will be randomized to either STN-DBS accompanied by best medical treatment (DBS group) or to best medical treatment alone (BMT group). The primary outcome measure is the change from baseline to 30 weeks on the Movement Disorder Society—Unified Parkinson's Disease Rating Scale part III score in a standardized off-drug phase. The main secondary outcome measures consist of scales assessing cognitive aspects of daily living, neuropsychiatric symptoms and impulsive compulsive disorders. Additional secondary outcome measures include motor signs during on-drug phase, dyskinesia, motor fluctuations, cognitive performance, (severe) adverse events, treatment satisfaction, and caregiver burden. Patients will be followed during 52 weeks after randomization.

Results:

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Conclusion:

The Deep Brain Stimulation for MOtor symptoms in patients with Parkinson's disease DEmentia (DBS-MODE) trial directly compares the effectiveness and safety of DBS with BMT in patients with PDD.

User satisfaction with digitalization and development of new exploratory digital biomarkers in a clinical drug trial testing Ambroxol in Dementia with Lewybodies

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Background:

The mechanisms behind dementia with Lewy Bodies (DLB) are not well understood, and disease-modifying treatments are unavailable. Current biomarkers lack the precision to diagnose prodromal DLB, are costly, time consuming, and insensitive to symptom fluctuations.

Methods:

The ANeED Joint Effort21 study aims to objectify DLB symptoms and disease progression using digital biomarkers in the double-blind, placebo-controlled randomized clinical drug trial, *The ANeED study* (ClinicalTrials.gov Identifier: NCT04588285), assessing the efficacy of the drug Ambroxol on DLB symptoms over a period of 18 months. ANeED Joint Effort21 is a case-control study including prodromal/mild/moderate DLB-patients and family caregivers already included in the ANeED study. Participants will continuously wear a smartwatch and utilize a digital application for passive monitoring, to track drug compliance, side effects and to perform cognitive assessments. Additionally, in between the 8 scheduled visits, participants will obtain movement sensors (Axivity AX6, sacrum and wrist placement) and sleep sensors (Vitalthings Somnofy), for 7-days consecutive real-time monitoring during 4 time points for patients (screening, week 24, week 52, month 18), and only once for caregivers. Additionally, caregivers will be offered a psychoeducation-based intervention.

Results:

In the pilot phase of the study, 8 patients have collected 15 real-time sleep- and movement data samples, as well as 3 caregiver samples. The anticipated recruitment start for all seven sites is autumn 2024 and aims to include 100 patients and their caregivers. A patient and public involvement program aims to promote recruitment. Data from the digital sensors is used to develop new digital biomarkers and algorithms to advance prognosis, diagnosis, and management of DLB.

Conclusion:

ANeED Joint Effort21 is the first study focusing on advancing novel biomarkers in a cohort of DLB patients and their caregivers in real-world surroundings and has the potential to make a big impact on the future of DLB management.

The ANeED Study: Challenges in Recruiting Lewy Body Patients for a Clinical Trial

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Background:

The ANeED-study is a multicenter, phase IIa/b RCT placebo controlled clinical trial recruiting 156 patients with prodromal and mild dementia with Lewy bodies (DLB) across eight neurological, geriatric, and old age psychiatric departments in Norway (1). At St. Olav University Hospital in Trondheim, the Department of Old Age Psychiatry is participating, with the goal to include 20 patients during two years. However, recruitment of persons with dementia to medication trials is challenging (2).

Methods:

A dedicated study team at our site recruited patients by informing local psychiatric, neurological and geriatric departments, primary care units and patient organisations. We held oral presentations, spread leaflets about the trial with contact information and used social media. The trial has been mentioned in newspapers. These recruitment strategies are in line with recommendations in literature (2).

Results:

Patients pre-screened at our site so far (n= 84) come from the departments of psychiatry (56%), geriatrics (18%), primary health care (15%) and neurology (10%), and one patient made personal contact. The included patients (n=12) are from the neurological (5), geriatric (4) and psychiatric departments (3). Screening failures (n=72) are due to MMSE <15 (29%), somatic disease (18%), no DLB (13%), geographic location (13%), rejection to participate (13%), age >85 (12%), mental health (11%), use of anticoagulation (6%) and no close relative (6%). Recruitment is still ongoing.

The pre-screening of less patients from the geriatric and neurological departments is because their specialists evaluate patients before referring to the trial, possibly reducing the representativeness of the data. However, the barriers for participation are present in patients from all departments.

Conclusion:

A number of patient-related and procedural factors limit recruitment significantly. These findings support addressing barriers to participation and demonstrate the need to cooperate across medical specialities in studies on DLB.

Compound Screening for Alpha-Synuclein Directed Small Molecules

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Background:

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 oligomerisation or 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 a standard 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 small molecules 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.

Conclusion:

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 additionally produce false positive reactions without preventing aggregation. Our results indicate that careful selection of small molecule concentration, solvent type and concentration, and aggregation assay readouts, are needed for the identification of much needed small molecules targeting alpha-synuclein aggregation.

Patient and Public Involvement and Engagement (PPIE) in the COBALT* trial - Motivation and Experiences of members *Combining memantine and cholinesterase inhibitors in Lewy body dementia treatment trial

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Background:

PPIE is integral in COBALT, a UK and Australian clinical trial designed to determine whether adding memantine to a cholinesterase inhibitor improves overall health and functioning for people with Lewy Body Dementia (LBD) including Dementia with Lewy Bodies and Parkinson's Dementia. PPIE groups, comprising people living with LBD and Parkinson's and current/former carers, along with a designated facilitator have made positive contributions to the trial. Here PPIE members report on the experiences and motivations of their peers.

Methods:

PPIE members completed annual online surveys, most recently in December 2023. Survey questions included experiences of involvement; perceived impact on the research; motivations for involvement, and personal benefits of membership and participation.

Results:

Twenty-five (96%) PPIE members completed the latest survey. All reported improved knowledge about Lewy body conditions, international LBD research and/or research in general, including trial processes and conduct. Most (68%) found the time commitment about right, and 80% would recommend joining a PPIE group. Members felt their input had improved study documents thus enhancing their understanding for trial participants, and, that they had provided a broader perspective based on their experiential knowledge. Reported motivations included to contribute to something worthwhile and make a difference to others. Personal benefits included gaining organisational skills, meeting interesting people, feeling valued and respected and finding a sense of purpose.

Conclusion:

COBALT PPIE members have varied motivations for involvement. They have positively impacted the trial conduct and we would recommend PPIE groups be established for other clinical trials. Key to success has been having a designated facilitator for support, recruitment, and to adapt activities so that all members can contribute. We acknowledge our reliance on members' ability to engage digitally, read documents, speak in a group, and possess appropriate equipment. Offering prospective members technology loans and skills development around online meetings may encourage even wider inclusion.

Addressing the distinctive needs of people with Lewy Body Dementia and their families: the lived experiences of the COBALT* clinical trial patient and public involvement and engagement (PPIE) group *(COmBining memantine And cholinesterase inhibitors in Lewy body dementia Treatment).

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Background:

NHS (UK) primary care dementia figures suggest that between 73,000 and 109,000 people over 65 have dementia with Lewy bodies in England, but only 15,000 have a recorded diagnosis. People with lived experience of Lewy body dementia (LBD) are acutely aware of the personal impact of the poor rates of diagnosis and lack of effective management. In response, many are keen to support research for example through public-patient involvement and engagement (PPIE) for COBALT, a joint UK/Australia clinical trial assessing the impact of adding memantine to commonly used dementia drugs. This group undertakes many trial related tasks and also initiates activities arising from their experiences.

Methods:

PPIE group members collected case examples of challenges they encountered in their experiences of health and social care. They considered what mattered most to them about the conduct and outcome of these interactions. Ways to optimise similar situations in future were identified. Collection of case example is on-going to identify common themes.

Results:

Concerns included a lack of knowledge of the core features of LBD notably among therapists and adult social care practitioners, diagnostic delays leading to missed opportunities for timely treatment of symptoms, lack of awareness of drug contra-indications commonly encountered with LBD, and a lack of understanding of LBD progression and the challenges posed by its unpredictable nature. Solutions included raising awareness of LBD, greater focus on person-centred care, more involvement of family carers and increased learning opportunities directed towards practitioners less familiar with LBD.

Conclusion:

Understanding the significance and impact of gaps in LBD knowledge and care delivery from the perspectives of people personally affected is crucial. The identification of research topics and collection of data by people with lived experience can ensure that research is conducted which matters most to those most significantly impacted. This process is currently underutilised within LBD research.

Gamified Data Collection for Lewy Body Dementia: A Smart, Non-Obtrusive Approach to Longitudinal Monitoring and Insight Discovery

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Background:

Traditional diagnostic tests and clinical visits for dementia are often infrequent and subject to limitations such as subjectivity, cultural bias, and "white coat syndrome." While current digital data collection methods address some of these challenges, they typically focus on singular data types, failing to capture the holistic and interconnected nature of dementia symptoms. Additionally, maintaining patient engagement with these methods can be difficult, leading to non-compliance and fragmented data collection.

Methods:

This study proposes an innovative approach using gamification and serious games to address these issues. The games embed various cognitive, behavioral, and motor tasks into interactive, adaptive scenarios, transforming standard diagnostic tests into engaging activities designed to sustain patient interest over the long term. The platform integrates smartphone sensors and wearable devices to collect diverse data types, including motor function, heart rate variability (HRV), and temperature, enabling the continuous and simultaneous collection of multiple symptoms over extended periods. The data is analyzed using artificial intelligence (AI) to detect patterns and relationships among different symptoms.

Results:

This approach is particularly beneficial for patients with Lewy Body Dementia (LBD), as it can capture symptom fluctuations, specific motor impairments, autonomic dysfunction, and the interconnected nature of multiple symptoms. The system’s ability to track and integrate these diverse data types, in real-time, provides novel insights into disease progression that are often missed by traditional diagnostic methods.

Conclusion:

By continuously monitoring patients and analyzing data through AI, this gamified system improves long-term patient engagement and offers a more detailed, comprehensive view of patient symptoms. This approach reduces the risk of misdiagnosis and advances personalized care and treatment assessment. Additionally, it holds the potential to discover new digital biomarkers, providing deeper insights into both the disease and the individual patient's condition, beyond what is achievable with traditional clinical visits or single-focus digital methods.

COmBining memantine And cholinesterase inhibitors in Lewy body dementia Treatment (COBALT)

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Background:

The pharmacological management of Dementia with Lewy bodies (DLB) and Parkinson's Disease Dementia (PDD) is hugely challenging, resulting in significant unmet therapeutic needs for these patients.

Acetylcholinesterase Inhibitors (AChEI) are commonly prescribed to treat DLB and PDD symptoms and Memantine, an NMDA receptor agonist, is another potential treatment. Previous trials and studies of memantine, either alone or in combination with AChEIs have been inconclusive in regard to the benefits of this agent, and it is not clear whether there is a differential response to memantine between DLB and PDD.

COBALT comprises two separately powered trials; COBALT- DLB and COBALT- PDD utilising a master protocol, basket design. Both parallel-arm, double-blind RCTs will assess the clinical and cost-effectiveness of combining memantine and AChEI.

Methods:

Patients with a DLB (n=186) or PDD (n=186) diagnosis on a stable dose of AChEI will be randomised (1:1) to memantine or placebo for 52 weeks.

The primary outcome, a modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scale, is completed at 26 weeks. Secondary and exploratory outcomes include cognitive, neuropsychiatric, sleep, QOL, and health economic measures, completed at 26 and 52 weeks with repeat assessment of ADCS-CGIC at 52 weeks.

COBALT- DLB and COBALT- PDD are actively recruiting at 23 UK centres and one centre in Melbourne, Australia.

Results:

Separate power analyses were conducted for the two trials to detect an ADCS-CGIC score difference of 0.7 between groups at 26 weeks.

For each trial, Intention-to-treat analysis will be performed on ADCS-CGIC scores at 26 weeks; secondary and exploratory outcomes will be evaluated for data collected at 26 weeks and 52 weeks.

Conclusion:

COBALT will answer an important question regarding the pharmacological management of patients with Lewy Body Dementia.

Eligibility Criteria of Previous Randomized Clinical Trials in Patients with Dementia with Lewy Bodies

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Background:

Currently there are no disease modifying therapies for Dementia with Lewy Bodies (DLB), though several agents have been investigated in randomized clinical trials (RCTs). It is unknown how their selection criteria relate to each other and to what extent they are clinically applicable. We therefore aimed to establish an overview of selection criteria of existing DLB-RCTs and illustrate the effect of these criteria on eligibility for enrollment.

Methods:

ClinicalTrials.gov was searched for previous phase 2/3 DLB-RCTs. Selection criteria were clustered into themes. A combination of common themes was applied to the extensively phenotyped DLB cohort-study 'DEvELOP' (n=186) to illustrate the eligible proportion after application. Additionally, three scenarios for one common theme (least/most restrictive, most common) were applied to elucidate varying eligibility that arises with the diversity of parameters among DLB-RCTs.

Results:

Thirty RCTs were identified. There was notable heterogeneity in definitions, measurement tools and associated parameters among and within the criteria in the themes. Five prevalent themes (present in 30-100% of the studies) were: age, medical comorbidities, medication use, cognitive scores and caregiver involvement. The combination of common selection criteria: cardiovascular comorbidities, cholinesterase-inhibitor use and an MMSE-score of 14-26 (most common) resulted in 18% eligibility from DEvELOP-patients. For the MoCA, the least restrictive range ($\geq$14) resulted in 92% eligibility, the most restrictive range (18-24) resulted in 57% eligibility and the most common range ($\geq$18) resulted in 77% eligibility.

Conclusion:

Our results suggest that a combination of common selection criteria results in a substantial decline of eligibility. Moreover, diversity in the operationalization of criteria results in varying eligibility. This could negatively affect generalizability to the clinic and the comparison between RCT results. Ultimately, hampering drug development. The influence of selection criteria on eligibility of patients and inclusion characteristics should be taken into account in future trial design, to ensure external validity of trial outcomes.

ANeED Study - Ambroxol in New and Early Dementia with Lewybodies Study - a status update on recruitment, safety, and tolerability

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Background:

No disease modifying treatment is yet available for dementia with Lewy bodies (DLB). DLB patients have a more rapid disease progression to the end stage of severe dementia, nursing home admission and death than persons living with Alzheimer's disease (AD) (1).

Reported findings suggests reduced glucocerebrosidase (GCase) activity may be involved as a central disease mechanism in the α-synucleinopathies including DLB. Ambroxol is a well-known drug able to enhance GCase activity and thus increases synuclein clearance in the CNS (2,3).

Methods:

The ANeED study is a national, multicentre, phase IIa/b randomized, and placebo controlled clinical drug intervention trial including patients with prodromal and mild DLB with MMSE >14 (NCT04588285). The drug intervention is 1260 mg/d Ambroxol or placebo and treatment duration is 18 months. We stratify participants based on genotypes for *APOE* and the CSF biomarker amyloid-beta. Allocation ratio 1:1 for Ambroxol and placebo.

Results:

The study started in May 2021. As of September 2024, all eight Norwegian sites have started recruitment. Recruitment rate was 3-4 patients every month. Of 95 included patients 90 started treatment with compliance >90%. 40 patients completed the RCT after 18 months and continue in the extended open label phase with Ambroxol for additional 12 months. 10 participants completed all 30 months. Adverse events reported are falls, nausea and sleep disturbances, but the relationship with Ambroxol is uncertain. The goal for inclusions is 156 participants. Demographics, clinical and safety and tolerability data will be presented at the conference.

Conclusion:

The ANeED study continues to recruit patients as at a low and steady rate. We have not registered any serious adverse events judged to be related to the study medication. The compliance is high and the tolerability and safety good.