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O07.4

Development and validation of the Dutch Mini-Linguistic State Examination (MLSE-NL) in primary progressive aphasia

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State of the art
Differentiating between primary progressive aphasia (PPA) subtypes is complicated by the lack of good language assessment tools. Patel [Brain Comms 2022; 4(1-11)] developed a comprehensive PPA screening test, the Mini-Linguistic State Examination (MLSE). The MLSE consists of 11 subtests, the total score is 100. Five error types are scored (motor speech, phonology, semantic, syntax, working memory). This study aimed to develop and validate the Dutch version (MLSE-NL). This study is a collaboration between the Erasmus Medical Centre, University of Antwerp, and Radboud Medical Centre.

Methodology
We administered the MLSE-NL to 21 patients with PPA (6 svPPA/10 nfvPPA/5 lvPPA) and 85 controls. We investigated its psychometric properties. The control's cumulative frequencies and percentile scores were calculated. We compared between-group differences, controlling for sex, age, and education.

Results
Internal consistency (α=0.71-0.88) and interrater reliability (ICC=0.91-0.98) were good. The MLSE-NL cutoff was <91. MLSE-NL total scores were 33-91 (70.1±16.1) in patients and 83-100 (97.3±2.9) in controls. Patients with PPA scored lower than controls on MLSE-NL total and subtests ($p<0.001$). Lowest MLSE-NL total scores were measured in patients with nfvPPA. Patients with nfvPPA had more motor speech, phonology, and syntactic errors than lvPPA/svPPA, patients with lvPPA had more working memory errors than nfvPPA/svPPA, and patients with svPPA had more semantic errors than nfvPPA/lvPPA ($p<0.05$).

Conclusion
The MLSE-NL is a promising PPA screening tool, showing good psychometric properties and differential diagnostic abilities. Further investigation and validation across larger cohorts, including atypical PPA forms and other FTD spectrum disorders, are currently ongoing.

O08.1

Detection of TDP-43 seeding activity in the olfactory mucosa from patients with Frontotemporal Dementia

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State of art.
TDP-43 aggregates could be recovered in the olfactory bulb of Alzheimer's patients, and additional post-mortem observations indicated that TDP-43 inclusions in the olfactory bulb might induce odor impairment in ALS patients. Thus, the olfactory mucosa could represent a valuable source for testing TDP-43 aggregation capacity, and it may represent an easily accessible tissue to study aberrantly misfolded or modified TDP-43. We assessed TDP-43 seeding activity and aggregates detection in the olfactory mucosa of patients with FTLD-TDP by TDP-43 Seeding Amplification Assay (TDP43-SAA) and immunocytochemical analysis.
Methodology
The TDP43-SAA was optimized using frontal cortex samples from sixteen post-mortem cases with FTLD-TDP, FTLD-tau, and controls. Subsequently, olfactory mucosa samples were collected from seventeen patients with FTLD-TDP, fifteen healthy controls, and three patients carrying MAPT variants.
Results
TDP43-SAA discriminated with 100% accuracy post-mortem cases presenting or lacking TDP-43 neuropathology. TDP-43 seeding activity was detectable in the olfactory mucosa, and 82.4% of patients with FTLD-TDP tested positive, whereas 86.7% of controls tested negative ($p<0.001$). Two out of three patients with MAPT mutations tested negative. In TDP43-SAA positive samples, cytoplasmatic deposits of phosphorylated TDP-43 in the olfactory neural cells were detected.
Conclusion
TDP-43 aggregates can be detectable in olfactory mucosa, suggesting that TDP43-SAA might be useful for identifying and monitoring FTLD-TDP in living patients.

O09.1

Synaptic dysfunction in FTD patient-derived iPSC-neurons

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State of the art: Synaptic dysfunction is proposed to associate with frontotemporal dementia (FTD) pathogenesis already in the early stages and with the C9orf72 hexanucleotide repeat expansion (C9-HRE), the most common genetic cause underlying FTD. C9-HRE leads to distinct pathological hallmarks, including C9orf72 haploinsufficiency and accumulation of toxic RNA foci and dipeptide repeat (DPR) proteins. FTD patient brains, including those carrying the C9-HRE, are also characterized by TDP-43 and p62 neuropathology. Methodology: Here, we examined induced pluripotent stem cell (iPSC)-derived cortical neurons from C9-HRE-carrying and sporadic FTD patients and healthy control individuals. The neurons were characterized by immunocytochemical methods and global RNA sequencing. Dendritic spines were quantified from confocal microscope images and synaptic function was assessed by calcium imaging. Results: iPSC-neurons from C9-HRE carriers developed typical C9-HRE-associated RNA foci and DPR proteins. All FTD neurons demonstrated increased TDP-43 nucleus-to-cytosolic translocation and p62 accumulation, and changes in nuclear size and morphology. Additionally, they displayed reduced number and altered morphologies of dendritic spines and a significantly decreased response to GABA stimulation. These synaptic disturbances were accompanied by upregulated expression of genes related to synaptic structure and function compared to control neurons. Oppositely, pathways involved in DNA repair were significantly downregulated in the FTD neurons. Conclusion: Our results show that the FTD iPSC-neurons recapitulate key pathological and functional changes of the FTD brain and strongly support the hypothesis of synaptic dysfunction as a crucial contributor to disease pathogenesis in sporadic and C9-HRE-associated FTD.

O12.2

Utility of case review meetings in Japanese FTD Consortium FTLD-J

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State of the art: To facilitate frontotemporal dementia (FTD) research and clinical trial, we established a Japanese FTD registry, named FTLD-J, which consists of 25 institutions of psychiatry and neurology across Japan. Since FTLD-J includes diverse institutions, consistency of diagnosis needs to be assured.

Methodology: To date, FTLD-J has held 13 diagnostic case review meetings open to all participating facilities, at which the clinical course, neurological-neuropsychological evaluations, and neuroimaging analysis of each case was presented from each facility, and experts in each field actively exchanged their opinions. Here we examined how the diagnosis of each case changed through the meetings.

Results: Between February 2016 and January 2024, we recruited 256 participants as behavioral variant FTD (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA). The diagnoses of 196 participants were reevaluated at the meetings based on the international diagnostic criteria. Of the 103 participants initially enrolled as bvFTD, 61 fulfilled FTDC criteria and passed the case review. In the remaining 42 cases; however, the initial clinical diagnosis of bvFTD was not retained. Of the 82 participants enrolled as SD, 72 were confirmed as SD, and in 10 cases, the diagnoses were changed through the meeting. Of the 11 participants enrolled as PNFA, 10 cases were confirmed as PNFA. bvFTD had predominantly higher rate of diagnosis changes than SD ($p<0.001$).

Conclusion: Our results suggested that case review meetings in a nationwide multicenter study for FTD improve the diagnostic consistency of the cohort, especially with regard to bvFTD.

O13.5

Blood-based inflammation markers relate to neuroinflammation and survival in syndromes associated with frontotemporal lobar degeneration

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State of the art: Neuroinflammation is an important pathogenic mechanism in neurodegenerative diseases, including frontotemporal lobar degeneration (FTLD). Neuroinflammation is proportionate to symptom severity and rate of progression. Here we assess inflammatory patterns of serum cytokines from 214 patients with clinical syndromes related to FTLD, as compared to 29 healthy controls, and their association with regional neuroinflammation (TSPO PET) and survival.

Methodology: Serum assays used the MesoScale Discovery V-Plex-Human Cytokine 36 plex panel plus five additional cytokine assays. A sub-group of patients underwent TSPO PET imaging, as an index of microglial activation. A Principal Component Analysis (PCA) across all participants was used to reduce the dimensionality of cytokine data. Frequentist and Bayesian analyses were performed on the resulting components to compare each patient cohort to controls, and test for associations with central inflammation, neurodegeneration-relevant plasma markers and survival.

Results: The first component on cytokine data (explaining 21.5% variance) was strongly loaded by pro-inflammatory cytokines, including TNF-α, TNF-R1, M-CSF, IL-17A, IL-12, IP-10 and IL-6. Individual scores of the component showed significant differences between each patient cohort and controls. Higher pro-inflammatory profile scores were associated with higher microglial activation in frontal and brainstem regions, and with lower survival, even when correcting for baseline clinical severity.

Conclusion: This data-driven approach identified a pro-inflammatory serum profile across the FTLD spectrum, which was associated with central neuroinflammation and shorter survival. This pilot data approach will be taken forward in the Open Network for Frontotemporal dementia Inflammation Research (ON-FIRE), over 20 UK-based centres.

O02.1

Uncovering distinct trajectories of brain atrophy and tau deposition in Progressive Supranuclear Palsy

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State of the art: Subtype and Stage Inference (SuStaIn) is a novel unsupervised machine learning algorithm that separates data-driven disease phenotypes distinguished by diverse temporal progression patterns. We applied SuStaIn using MRI and flortaucipir (FTP) tau PET data to a heterogeneous cohort of Progressive Supranuclear Palsy (PSP) patients. We aimed to interpret various PSP subtypes in terms of their progression over time across different modalities, tracking trajectories of both FTP uptake and neurodegeneration.
Methodology: 150 PSP patients were recruited (n=66 Richardson's syndrome (PSP-RS), n=26 parkinsonism (PSP-P), n=25 speech-language (PSP-SL), n=13 progressive gait freezing, n=10 corticobasal syndrome, n=3 frontal, n=1 oculomotor and n=6 postural instability) and underwent 3T MRI and FTP PET. Using 102 healthy controls, age-, gender- and scanner-adjusted W-scores were calculated for 15 regions-of-interest for atrophy (MRI) and FTP uptake and SuStaIn was applied.
Results: Two subtypes emerged across both modalities. Subtype 1 exhibited initial severe subcortical pathology from the pallidum and brainstem, spreading to other basal ganglia structures and eventually to the cortex. Subtype 2 exhibited simultaneous yet milder cortical and subcortical pathology, homogeneously distributed with advancing Stages. Both PET and MRI Subtype 1 mainly included PSP-RS and PSP-P, while Subtype 2 mainly featured PSP-SL. PET Stages appeared to anticipate MRI Stages. MRI Stages efficiently captured clinical severity progression. Patients in Subtype 1 had a shorter survival.
Conclusion: Differentiating in vivo tau and atrophy trajectories in PSP patients using cross-sectional data is feasible and correlates with different patterns of clinical progression and survival.

O05.2

Differentiating Sporadic behavioural variant Frontotemporal Dementia from late-onset Primary Psychiatric Disorders: the DIPPA-FTD study

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State-of-the-art

Sporadic bvFTD (s-bvFTD) is often misdiagnosed as late-onset primary psychiatric disorder (PPD) due to symptomatic overlap. The DIPPA-FTD study aims to identify clinical discriminators to distinguish s-bvFTD from PPD.

Methodology

DIPPA-FTD consists of a retrospective (s-bvFTD=508/PPD=152) and ongoing prospective (s-bvFTD=37/PPD=40) cohort. Logistic regression and ROC-curve analysis were applied to determine discriminative value per clinical marker in the retrospective – (i) neuropsychological features, (ii) visual brain atrophy rating, (iii) serum NfL+GFAP and (iv) all variables combined with no missing data – and (v) for clinical (bedside) tools in the prospective study (de Boer et al., JAD:2024;97(2):963-973).

Results

For (i) neuropsychology (s-bvFTD=217/PPD=75) higher letter fluency (OR:1.47, p<0.001), and global cognitive screening (OR:1.72, p=0.01) scores, but lower attention (OR:0.77, p=0.05) were significantly associated with PPD (AUC=0.77). For (ii) imaging (s-bvFTD=211/PPD=112) fronto-insula atrophy was the most useful discriminator (AUC 0.80). For (iii) blood markers (s-bvFTD= 275/PPD=82) NfL+GFAP levels were significantly higher in s-bvFTD. Discriminative performance was highest for NfL+GFAP 9 AUC=0.88), followed by NfL (AUC=0.87) and GFAP (AUC=0.79). In the combined model (iv) (s-bvFTD=120/PPD=40), increased NfL (OR:1.09, p<0.01), fronto-insula atrophy (OR:2.38, p=0.02) and enlarged ventricular space (OR:3.84, p=0.05) were strongest predictors for s-bvFTD. In the prospective study (v) high 'FTD vs. PPD Checklist' (OR:2.31, p<0.0001) and low ACE-III (OR:0.84, p<0.0001) scores, were significantly associated with s-bvFTD and combined reached highest AUC(=0.96).

Conclusion

Several clinical discriminative markers identified in the retrospective- and prospective DIPPA-FTD study demonstrate diagnostic value. Incorporating these discriminators into clinical practice enhance precise and timely differentiation between s-bvFTD and late-onset PPD.

O07.3

Criminal minds in dementia: A systematic review & quantitative meta-analysis

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State of the art: Subjects with dementia might exhibit criminal behavior (CB) in early disease, especially in frontotemporal dementia (FTD). This review/meta-analysis investigated CB prevalence across all dementia/neurodegenerative syndromes.
Methodology: Systematic literature search PubMed. Preregistration PROSPERO, PRISMA criteria. Quantitative meta-analysis with mean frequencies of CB for each syndrome, and odds ratios for CB in comparison between syndromes. Statistics re-calculated after normalization of CB prevalence to country-specific overall crime rates.
Results: Seventeen relevant out of 1,032 studies were identified. Studies originated from different countries, with dominance of U.S.A., followed by Scandinavia, Germany and Japan. Finally, 14 studies remained for systematic meta-analysis. Most studies investigated Alzheimer's disease (AD;12) and FTD (11), further studied behavioral variant (bv)FTD(6), semantic variant primary progressive aphasia (svPPA;3), vascular dementia (3), Parkinsonian syndromes (ParkS;3), and Huntington's disease (HD;2). Studies on AD and FTD dominated. In total, studies included 236,360 persons. All quantitative analyses revealed that prevalence of CB was highest in bvFTD (50%), followed by svPPA (40%), but rather low in vascular dementia (15%), HD (15%), AD (10%), and lowest in ParkS (less than 10%). Prevalence seems to be more frequent in early disease course than in the general population, but declines thereafter below population levels. Men seem to be generally overrepresented.
Conclusion: CB is a common symptom in dementia syndromes, in particular FTD. CB committed for the first time at mid-age could be an indicator of incident dementia, requiring earliest diagnosis and therapy. Large prospective international studies are warranted systematically applying homogeneous methods and standardized questionnaires.

O13.6

Effects of blood-brain barrier opening with ultrasounds combined to microbubbles on tau prion-like propagation

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Sate of the art: Tau pathology accounts for a large proportion of frontotemporal dementia (FTD) cases and is correlated to cognitive decline. No therapeutics targeting tau have proven clinical efficacy. One of the pitfalls in their development is the blood-brain barrier (BBB) which drastically restricts their brain penetration. BBB can be safely, transiently, and repeatedly opened using low-intensity pulsed ultrasounds with microbubbles (LIPU-MB). While beneficial effects have been shown in amyloid models, its effects on tau pathology remain less clear. Our study aims at evaluating the effects of LIPU-MB BBB opening on tau pathology and its prion-like propagation accelerated by intracerebral inoculation of human tau-purified brain extracts in P301S mice.

Methodology: P301S mice received stereotaxic injection of either human tau-purified extracts (18 mice) in right hippocampus. 2 weeks later, five sessions (one per week) of LIPU-MB were administered to 10 of these mice and the remaining 8 mice received sham procedure. All mice were sacrificed one week after the last session. Immunostaining of phosphorylated tau (AT8, AT100) were compared between the sonicated and non-sonicated groups.

Results: Intracerebral injection of human tau-purified extracts robustly induced, as expected, increased tau burden and spreading. BBB opening with sonication was able to decrease tau pathology in regions distant from the injected site (piriform cortex, amygdala) ($p<0.05$).

Conclusion: BBB opening with ultrasounds can reduce tau pathology and propagation in tau transgenic mice. Further investigations are needed to elucidate the underlying mechanisms of action, but these results could have therapeutic impact for tau-driven forms of FTD.

O13.7

Glymphatic dysfunction occurs across clinical phenotypes of motor neuron disease

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State of the art. Converging evidence supports a key pathogenic role of the glymphatic system in the accumulation of pathological aggregates in several proteinopathies, including amyotrophic lateral sclerosis (ALS). Our aim was to verify the presence of glymphatic function impairment, as shown by diffusion tensor imaging analysis along the perivascular space (DTI-ALPS), and to explore its clinical correlates in motor neuron disease (MND) phenotypes.
Methodology. Forty-nine patients with MND phenotypes (including 33 ALS, 7 with pure lower motor neuron and 9 with pure upper motor neuron clinical presentations) and 23 matched healthy controls underwent brain MRI on a 3 Tesla scanner. We obtained DTI-ALPS index from each individual, evaluating its relationship with clinical and cognitive features.
Results. Compared with healthy controls, MND patients showed significantly decreased DTI-ALPS index values (p=0.03). ALS patients with a bulbar onset of symptoms showed greater reduction of DTI-ALPS index values, as compared with individuals with a spinal onset (p=0.05). DTI-ALPS values were comparable across MND phenotypes. No significant correlations were found between DTI-ALPS and clinical disability, upper motor neuron burden or degree of cognitive impairment.
Conclusions. We confirm the presence of altered glymphatic function across MND phenotypes, with greatest damage in patients with a bulbar symptom onset, supporting a pathogenic involvement of this system for the accumulation of TDP-43 proteinopathy in MND.

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O02.3

Altered spatiotemporal dynamics of interoception associated with social cognition impairment in behavioural-variant frontotemporal dementia

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Start of the art
Emerging evidence suggests that allostatic-interoception, the processing of bodily signals in response to environmental demands, is dysfunctional in behavioral-variant frontotemporal dementia (bvFTD). These dysfunctions may be accompanied by altered intrinsic neural timescales (INT)(i.e.,delayed signal processing of interoceptive information). INT, however, have not been investigated in bvFTD or in interoception. This study aims to address this gap and explore associations with social cognition.

Methodology
Thirty-one bvFTD patients, 33 Alzheimer's Disease (AD) patients, and 49 Controls completed an interoception or exteroception task with simultaneous high-density-EEG recordings. INT were measured via autocorrelation windows (ACW), representing the correlation of the whole-brain EEG signal for each heartbeat with a time-lagged version of itself. A shorter ACW represents more efficient processing of the cardiac brain signals. Social cognition was measured via the Mini Social Emotion Assessment task.

Results
Spatiotemporal clustering analyses revealed that during interoception only, bvFTD patients had longer ACW durations than controls in bilateral temporal and occipito-parietal regions. In AD, longer ACW durations were observed in central and occipito-parietal brain regions than in controls. Social cognitive impairment was associated with slower interoceptive INT in bvFTD, $r(17) = .440$, $p < .038$, but not in AD or controls.

Conclusion
We provide evidence for altered INT in bvFTD during interoception related to social cognitive impairments. This evidence in bvFTD suggests a shared mechanism underlying both processes. Neural underpinnings of INT during interoception open a new methodological agenda for research. This study contributes to recent theoretical frameworks of dysfunctional allostatic-interoceptive processing in bvFTD.

O01.5

Predictors of survival in syndromes associated with Frontotemporal Lobar Degeneration: a European registry

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State of the art
Estimating survival for people with syndromes associated with Frontotemporal Lobar Degeneration (FTLD) is essential to plan trials and assess the efficacy of intervention. Population-based registers provide unique samples for estimating survival rates. The aim of this study was to assess survival and its predictors in incident cases of FTLD-disorders from the European FRONTIERS register based-study.
Methodology
Two-hundred sixty six incident cases with FTLD disorders were followed for up to five years. Patients with the behavioural variant FTD (bvFTD), primary progressive aphasia (PPA), progressive supranuclear palsy (PSP) or corticobasal syndrome (CBS), and FTD with motor neuron disease (FTD-MND) were included. The Survival Probability Score (SPS) was computed on the basis of independent predictors of survivorship.
Results
The median care home admission rate was 97 months (95%CIs=86-98) from disease onset, and 57 months (56-58) from diagnosis. The median survival was 90 months (77-97) from disease onset and 49 months (44-58) from diagnosis. Survival from diagnosis was shorter in FTD-MND (HR [95%CIs]=4.59 [2.49-8.76], p<0.001) and PSP/CBS (1.56 [1.01-2.42], p=0.044) as compared to bvFTD; no differences between PPA and bvFTD were found. The SPS proved high accurate in predicting 1-year survival probability (AUC=0.789, 95%CIs=0.69-0.87), when defined by age, European area of residency, extrapyramidal symptoms and MND at diagnosis.
Conclusion
In FTLD associated syndromes, survival rates differ according to clinical features and geography. Understanding the predictors of survival may help to improve patient stratification in clinical trials and contribute to better planning of public health service policies.

O03.3

An international COS-PPA: A consensus study to identify a Core Outcome Set for Primary Progressive Aphasia

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State of the art: Several symptomatic interventions have been developed to treat speech, language and communication difficulties in Primary Progressive Aphasia (PPA). Studies exploring the effectiveness of these interventions have used many different outcome measures, limiting comparability. Often, these measures do not assess what is important to key stakeholders, highlighting a need to develop a specific core outcome set (COS) for PPA.

Methodology: This three-stage study comprised: Stage 1 - systematic review to identify measures used to examine the effectiveness of interventions for PPA in the research literature; Stage 2 - Nominal Group Technique consensus to identify the most important outcomes for people with PPA and care partners across 15 countries; Stage 3 – e-Delphi consensus to identify a core outcome measurement set with researchers spanning 17 countries.

Results: The Stage 1 systematic review identified 145 papers and 90 different published or publicly available measurement tools. In Stage 2, 82 people with PPA and 95 care partners identified and prioritised core outcome constructs. These constructs were weighted alongside the ratings from 57 researchers in stage 3 resulting in a top five outcome constructs; 1. Participate in conversations with family and friends, 2. Get words out, 3. Be more fluent, 4. Convey a message by any means, and 5. Understand what others are saying. In Stage 3, researchers identified two measures corresponding to construct domains.

Conclusion: The development and adoption of this COS for PPA has the potential to ensure that research addresses the needs of this underserved population.

O11.1

Longitudinal behavioral and neuropsychiatric changes in genetic frontotemporal dementia: from presymptomatic to symptomatic conversion

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The frequency and the severity of behavioral and neuropsychiatric symptoms (NPS) differ among people with FTD caused by genetic mutations, such as those in chromosome 9 open reading frame 72 (C9orf72) or granulin (GRN). We compared the longitudinal changes of NPS among C9orf72 and GRN mutation carriers and noncarrier controls in the predementia phases.

N=10 GRN, N=23 C9orf72 carriers and N=49 noncarriers underwent annual examinations including the neuropsychiatric inventory-questionnaire (NPI-Q), the Iowa Scales of Personality Change (ISPC), the Beck Depression Inventory (BDI), and the Frontal Behavioral Inventory (FBI) for an average of 7.8 years. Group differences in the longitudinal changes of each NPS rating scale were compared using generalized linear mixed-effects models.

Carriers versus noncarriers had similar baseline NPS scores, and longitudinal comparisons suggested 1) higher rates of the ISPC total score and the emotional/social personality disturbance score increases over follow-up in GRN versus noncarriers, 2) higher rates of the ISPC dysexecutive personality disturbance score increases in C9orf72 versus noncarriers, and 3) higher rates of the BDI total score increases in both C9orf72 and GRN versus noncarriers. NPI-Q and FBI changes were similar among carriers and noncarriers.

Comparing the two carrier variants, GRN showed higher rates of NPI-Q affective subsyndrome and ISPC disturbed social behavior, emotional dysregulation, and distressed personality disturbances compared to C9orf72. Changes in other scales/domains were not significantly different between GRN and C9orf72.

Trajectories of NPS may differ among C9orf72 and GRN carriers compared to noncarrier controls prior to the onset of overt FTD.

Frontotemporal dementia (FTD) presents with heterogeneous neuropsychiatric symptoms (NPS), which often begin prior to the symptomatic onset. Familial FTD due to autosomal dominant genetic mutations might display mutation-specific NPS profiles. We hypothesized distinct NPS trajectories for chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN), and microtubule-associated protein tau (MAPT) mutation carriers during their transition from presymptomatic to symptomatic stages of FTD.

We analyzed 1662 participants from ALLFTD, including 342 C9orf72, 148 GRN, 168 MAPT mutation carriers and 1004 noncarriers. We categorized participants into four stages based on CDR plus NACC FTLD global scores: 1) Presymptomatic (CDR=0 throughout the follow-up), 2) Early conversion (began with CDR=0, then increased to 0.5), 3) Advanced conversion (began with CDR=0.5, then increased to >1.0), and 4) Symptomatic (CDR>1.0 throughout). The Neuropsychiatric Inventory-Questionnaire (NPI-Q) assessed changes in NPS over up to seven visits. Total NPI-Q scores were analyzed using a generalized mixed-effects model, adjusting for age and baseline scores.

NPI-Q trajectories were similar among carriers and noncarriers during presymptomatic stages. However, in the early conversion stage, C9orf72 and GRN carriers exhibited significantly higher NPI-Q score increases compared to MAPT carriers, primarily in the psychosis and hyperactivity domains. In the advanced and symptomatic stages, the rates of NPI-Q changes were similar across the groups.

People with familial FTD, particularly those predicted to have underlying TDP-43 pathology, may experience more severe NPS like psychosis or hyperactivity as they progress from presymptomatic to prodromal phases. This trajectory appears distinct from those with tau pathology or sporadic FTD.

O01.8

Sex differences in clinical phenotypes of behavioural variant frontotemporal dementia

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State of art: Differences in sex distributions between genetic and sporadic behavioural variant frontotemporal dementia (bvFTD) have been reported. Genetic bvFTD shows a relatively equal sex ratio, while sporadic bvFTD has a higher male prevalence, with a 2:1 ratio. We hypothesized differences in phenotypes between genetic and sporadic bvFTD females.

Methodology: To investigate this, we included symptomatic bvFTD patients with and without known FTD genetic mutations from the ALLFTD and GENFI cohorts (N=665, 256 females, 409 males). We compared neuropsychiatric and cognitive symptoms, as well as T1-weighted MRI grey matter volumes, between genetic and sporadic cases within each sex group.

Results: Overall, sporadic bvFTD exhibited more severe neuropsychiatric and cognitive symptoms compared to genetic cases. Sporadic bvFTD females showed more compulsive behaviour symptoms ($p<0.001$), language impairment ($p=0.0069$) and executive deficits ($p<0.001$) compared to genetic bvFTD females while sporadic males showed worse empathy ($p=0.033$) and apathy ($p=0.012$) compared to genetic bvFTD males. Genetic bvFTD females had smaller grey matter volumes than sporadic females, particularly in the left parietal lobe, driven by the C9orf72 group while no differences were apparent between males.

Conclusion: Sporadic bvFTD females differ in clinical phenotype compared to genetic bvFTD females and show less parietal lobe atrophy. Our results suggest the underrepresentation of a distinct female bvFTD phenotype in sporadic bvFTD females, a phenomenon not apparent in bvFTD males. Some bvFTD females without genetic mutations may be misdiagnosed due to lack of typical bvFTD symptoms from diagnostic criteria that may be more applicable for sporadic male bvFTD patients.

O06.3

Cryptic RNA/proteins as a reporter of TDP-43 pathology in neurodegenerative diseases

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State of the art
Loss of nuclear TDP-43 function is found in multiple neurodegenerative diseases. In FTLD-TDP, TDP-43 dysfunction leads to the accumulation of aberrant cryptic RNAs, which associates with shorter survival. Further, the presence of TDP-43 pathology in AD associates with greater disease severity. Thus, it is imperative that we better understand the contributions of TDP-43 to AD and FTLD, and identify means to discriminate cases with TDP-43 from those without.

Methodology
We assessed a cohort of FTLD-TDP and AD brains, with and without TDP-43 pathology, and normal controls to determine the extent of TDP-43 deposition and dysfunction across affected brain regions. Further, we evaluated the presence of a cryptic protein (HDGFL2) and its ability to discriminate TDP-43 positive from negative cases by using a novel antibody.

Results
We observed similar TDP-43 deposition in AD-TDP and FTLD-TDP cases, except frontal cortex accumulation was only observed in FTLD-TDP. Cryptic TDP-43-regulated RNAs identified in FTLD-TDP, significantly accumulated in AD regions affected by TDP-43 pathology, regardless of TDP-43 subtype classification. HDGFL2 cryptic proteins were also detected in the brains of cases with TDP-43 pathology but not in those without.

Conclusion
TDP-43 dysfunction and related changes in cryptic splicing could represent a common molecular mechanism shared between AD-TDP and FTLD-TDP, and potentially other TDP-43 proteinopathies. Cryptic RNAs/proteins may represent an intriguing new therapeutic and diagnostic target to distinguish individuals with TDP-43 pathology from those without, which in turn would inform the selection of ideal participants for clinical trials of potential TDP-43-based therapeutics.

O11.2

Differential Diagnosis of Motor Speech Disorders in Frontotemporal Dementia: A Case-Based Tutorial

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State of the art

Frontotemporal dementia (FTD) disorders pose significant challenges for differential diagnosis. Many phenotypes present with motor speech disorders (MSDs)- apraxia of speech and/or dysarthria- that carry diagnostic clues to help distinguish amongst the FTD clinical subtypes and from other neurological conditions. Different FTD syndromes have different prognoses and may benefit from different available and future interventions; therefore, misdiagnosis may lead to misinformation and missed opportunities.

Methodology

The session begins by outlining the clinical features characteristic of apraxia of speech and hypokinetic, spastic, and mixed dysarthrias which are commonly associated with primary progressive apraxia of speech, nonfluent/ agrammatic primary progressive aphasia, progressive supranuclear palsy, and corticobasal syndrome. Drawing upon clinical vignettes with video presentations, this session elucidates the distinctive and diagnostic features essential for discriminating these MSDs.

Results

Perceptual speech features and oral mechanism examination findings specific and sensitive to each MSD will be reviewed along with the number of overlapping features among them. The tutorial underscores the importance of the specificity of motor speech disorder characterization and a multidisciplinary approach, incorporating comprehensive speech-language assessments along with neurologic exams and neuroimaging for achieving an accurate differential diagnosis.

Conclusion

This tutorial serves as a resource for healthcare professionals involved in the evaluation and management of individuals with FTD, with the goal of facilitating timely diagnosis and targeted intervention strategies.

O08.3

CSF TMEM106B as a fluid biomarker in familial and sporadic frontotemporal lobar degeneration

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State of the art:
TMEM106B encodes a lysosomal protein and is a genetic susceptibility factor for frontotemporal lobar degeneration (FTLD). Its value as a clinical fluid biomarker is unexplored.

Methodology:
CSF TMEM106B and neurofilament light (NfL) were quantified with SOMAmer proteomics in a cohort of symptomatic and asymptomatic C9orf72, GRN, and MAPT mutation carriers and family non-carrier controls (ALLFTD, n = 182), and a cohort of neuropathology-confirmed sporadic cases and controls (UCSF, n = 96). Biomarkers were correlated with disease severity (CDR®+NACC-FTLD). In a subgroup with available T1-weighted MRI (n = 208), CSF TMEM106B was correlated with brain volumes using voxel-based morphometry, covarying for age, total intracranial volume, CDR®+NACC-FTLD, and scanner.

Results:
In both cohorts, CSF TMEM106B did not differ by sex, clinical phenotype, or neuropathological diagnosis. CSF TMEM106B did not correlate with age or NfL. CSF TMEM106B was lower in homozygous TMEM106B rs1990622 G/G allele carriers in C9orf2 and MAPT, but not in GRN mutation carriers. Regardless of disease-causing mutation, lower CSF TMEM106B correlated with worse disease severity. CSF TMEM106B positively correlated with brain volumes in bilateral frontal, temporal, and parietal regions, regardless of TMEM106B genotype, but was driven by C9orf72+GRN participants and symptomatic mutation carriers. Associations with CSF NfL were observed in frontotemporal regions when CDR®+NACC-FTLD was not used as a covariate.

Conclusion:
CSF TMEM106B levels vary by TMEM106B genotype, track with disease severity across genetic and sporadic FTLD, and correlate more strongly with brain volumes than CSF NfL, supporting its utility as an FTLD fluid biomarker.

O02.2

Mapping the staging of neuroimaging trajectories in frontotemporal dementia: New insights using fixel-based analysis

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State of the art: Neuropathology in frontotemporal dementia (FTD) shows 'prion-like' propagation, spreading along white matter pathways and aggregating in neuronal bodies. In-vivo mapping of white matter trajectories and associated grey matter changes can improve our understanding of disease mechanisms in FTD, but longitudinal studies are scarce due to methodological challenges. Here, we developed a novel approach to map staging of neuroimaging trajectories in FTD using fixel-based analysis (FBA), a new diffusion weighted imaging technique.

Methods: 23 bvFTD, 15 PNFA, 22 SD and 30 matched heathy controls underwent comprehensive clinical evaluations and multimodal MRI annually for up to 6 years. Changes in white matter (WM) fibre density and cross-section, and their associations with cortical thickness, were examined over time using whole-brain, spatiotemporal linear mixed effects models.

Results: FBA revealed more extensive WM changes than previously reported, which preceded and co-occurred with progressive cortical thinning across groups. In bvFTD, changes extended posteriorly over time, encroaching in tracts connecting subcortical and motor-association regions. In PNFA, baseline left-lateralised WM disruption extended anteriorly and inferiorly and into the contralateral hemisphere, mirroring baseline cortical atrophy over time. In SD, WM changes extended posteriorly and laterally, along the inferior and superior longitudinal fasculi and associated grey matter regions.

Conclusion: Our combined methodology uncovered time-sensitive relations of WM and grey matter changes in FTD, with syndrome-specific effects and improved biological interpretability. Our findings can inform better models of disease staging and provide targets for patient stratification and monitoring in trials of disease-modifying interventions.

O01.1

A cross-linguistic review of the quantitative markers of speech and language of the FTD Spectrum

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State of the art
Speech and language changes occur in the early stages of FTD and offer a potential non-invasive, early, and accessible diagnostic tool. The use of speech and language markers in this disease spectrum is limited by the fact that most studies investigate English-speaking patients.

Methodology
This systematic review examines the literature (publications until March 2023) on psychoacoustic and linguistic features of speech that occur across the FTD spectrum, including behavioral variant FTD, Primary Progressive Aphasia, Corticobasal Syndrome, Progressive Supranuclear Palsy and ALS-FTD, across as many different languages as possible. Features were grouped into 6 categories: phonetic-phonological, lexico-semantic, morpho-syntactic, syntactic, discourse-pragmatic and error typing.

Results
Seventy-six papers were identified that investigate psychoacoustic and linguistic markers in discursive speech. Seventy-five percent of these papers studied English-speaking patients, the other papers studied patients speaking Czech, Spanish, Italian, French, German, Dutch, Greek, Hindi or Korean. Forty-four features were studied in more than one language. Six generalisable features were identified across different languages: four belonged to the phonetic and phonological category (speech rate, articulation rate, pause frequency, and total pause duration), and two to the lexico-semantic category (noun: verb ratio, and total number of nouns).

Conclusion
While there are clear interlinguistic differences across patient groups, the results show promise for implementation of cross-linguistic markers of speech and language across the FTD spectrum, particularly for psychoacoustic features. We show a clear need for further investigation of speech and language markers in more non-English languages, especially non-Indo-European languages.

O01.2

Brain imaging profiles of apraxia of speech and agrammatism in Japanese and English speakers diagnosed with nonfluent variant primary progressive aphasia

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[State of the Art]
Japanese, an agglutinative language characterized by its intricate morphology, poses unique challenges in identifying apraxia of speech (AOS) and agrammatism. This study examined the neural correlates of early speech disturbances in Japanese and English speakers diagnosed with nonfluent/agrammatic variant primary progressive aphasia (nfvPPA).
[Methodology]
Japanese speaking nfvPPA patients (n=40) were sex– and disease severity–matched to English speaking nfvPPA patients (n=42) and 84 native language–matched healthy controls. All participants underwent whole brain MRI-T1 and completed a comprehensive speech/language battery. Voxel-based (VBM) and source-based (SBM) morphometry analyses examined brain changes associated with AOS and agrammatism within and between groups.
[Results]
Compared to controls, Japanese-speaking nfvPPA showed focal atrophy in the left motor and premotor cortex. In contrast, English-speaking nfvPPA exhibited widespread atrophy encroaching the left prefrontal and temporal cortex. Across groups, SBM analyses uncovered 18 distinct atrophy patterns involving language and speech production network regions. AOS was significantly associated with atrophy in the left posterior frontal lobe, whilst agrammatism involved a widespread network of left anterior frontotemporal regions in both groups.
[Conclusion]
We found region–specific patterns of atrophy underpinning AOS and agrammatism across a cross-linguistic cohort of nfvPPA cases. In contrast to English nfvPPA, the focal left premotor atrophy and its associations with AOS in Japanese nfvPPA suggest a higher occurrence AOS-dominant subtype, possibly reflecting the challenges of detecting agrammatism due to Japanese grammatical structure. Our findings underscore the importance of accounting for language structure and grammar to minimise diagnostic biases in nfvPPA.

O01.3

Navigating dysgraphia phenotypes in Chinese lvPPA: A clinical and imaging analysis

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State of the art
The diversity of language typology frequently leads to language-specific symptomatology. Distinct dysgraphia patterns have been reported between Chinese and English Primary Progressive Aphasia (PPA) patients. In this study, we explore the clinical and imaging phenotypes of Chinese logopenic variant (lv) PPA with and without profound dysgraphia.
Methodology
We first assessed the orthographic dictation performance of 32 Chinese lvPPA patients and 24 controls. individuals with lvPPA were then categorized into mild (mild-dysgraphia-lvPPA, n=14) and profound (profound-dysgraphia-lvPPA, n=18) dysgraphia groups based on their orthographic dictation scores, employing a threshold of eight standard deviations. Subsequently, we conducted a comparative analysis of their imaging, speech, and language characteristics.
Results
Chinese mild-dysgraphia-lvPPA patients accurately dictated 11-32 out of 34 words, while those with profound dysgraphia completed 0-8 words. Despite comparable age and educational background, profound-dysgraphia-lvPPA displayed lower performance in confrontational naming (p=0.001), semantic association (picture/word p=0.024, 0.010), and repetition test (p=0.002). Conversely, both groups exhibited similar proficiency in motor speech and syntax comprehension assessments. Furthermore, profound-dysgraphia-lvPPA patients exhibited more cortical thinning at left anterior and inferior temporal regions, whereas individuals with mild-dysgraphia-lvPPA displayed more cortical thinning over middle and lower frontal gyri.
Conclusion
In summary, this study elucidates distinct cognitive and neuroanatomical profiles among Chinese lvPPA patients, correlating with varying degrees of dysgraphia. These findings align with the literature of two partially distinct brain networks observed in English-speaking lvPPA patient. Given the stronger reliance on orthographic long-term memory in logographic script users, this differentiation is more accentuated among Chinese lvPPA patients.

O05.1

Disentangling Behavioral Problems in Dementia Subtypes: From Fixed Interests to Empathy Deficits

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State of the art: Fixed interest behavior (FIB) is often seen in individuals with behavioral variant frontotemporal dementia (bvFTD) and temporal variants such as semantic bvFTD (sbvFTD) and semantic variant primary progressive aphasia (svPPA). However, the phenomenology, nomenclature, and prevalence rates of these symptoms, and particularly differences across FTD subtypes, remains a topic of contention in the field.

Methodology: Utilizing chart reviews and the Yale-Brown Obsessive Compulsive Scale Self Report (YBOCS-SR) version, we compared characteristics and frequency of FIB in 135 early-stage (CDR≤1, MMSE≥20) persons with dementia (PWD) (17 Alzheimer's disease, 25 non-fluent PPA, 9 logopenic PPA, 8 progressive supranuclear palsy syndrome, 7 corticobasal syndrome, 38 bvFTD, 15 svPPA, 16 sbvFTD), with 88 older healthy controls (HC).

Results: Among PWD, only sbvFTDs showed statistically higher YBOCS-SR total-scores [mean(SD)=11.8(2.1)] than HCs ($p < 0.05$), though high YBOCS-SR total-scores were also observed in bvFTD [7.1(0.9)] and svPPA [(7.0(1.8)] compared to other PWD. Analysis of YBOCS-SR sub-scores in sbvFTD revealed high levels of "complete and willing compliance" with compulsions, with little concern about the impact on daily functioning. Chart reviews indicated that obsessions in sbvFTD were more aligned with overvalued ideas and hyper-focus on FIB, suggesting positive attributions towards FIB and a longer attention span during the execution of such behaviors.

Conclusion: FIB is more prominent in early-stage sbvFTD compared to other FTD subtypes. Unlike individuals with psychiatrically diagnosed obsessive-compulsive disorder, PWD have less anxiety, self-criticism, or insight, thus we advocate improved terminologies to phenotype the distinct characteristics of these symptoms in PWD.

O09.5

C9orf72 repeat expansion affects immune response in a xenografted microglia mouse model

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State of the art: A non-coding hexanucleotide repeat expansion (HRE) in the C9orf72 (C9) gene is the most common genetic cause of FTD and ALS. Increasing evidence suggests that aberrant microglia activation and neuroinflammation play a crucial role in neurodegeneration. C9 is highly expressed in microglia, but the role of microglia in disease pathogenesis remains poorly investigated.
Methodology: We differentiated both a C9 patient as well as a C9 knockout (C9KO) induced pluripotent stem cell lines into microglia (iPSC-MG) and examined their intrinsic phenotypes both in vitro and in an in vivo xenotransplantation model, where iPSC-MG are transplanted into the brain of mice. Our approach integrated in vitro assays alongside single-cell RNA sequencing (scRNA-seq) of isolated human microglia upon transplantation into mice brains.
Results: We observed enlarged lysosomes positive for CathepsinD and an increased number of intracellular structures consistent with storage lysosomes, as well as altered degradation of pHrodo particles in C9KO microglia. scRNA-seq sequencing of transplanted microglia from C9 patient line revealed endogenous transcriptomic alterations consisting of a reduction in C9 levels and dysregulation of immune-related pathways with downregulation of HLA-related genes. Moreover, we found evidence of altered genes related to the intracellular vesicular transport. Those alterations are mirrored upon C9 depletion, consistent with a loss-of-function mechanism.
Conclusion: Our data reveal an essential role of C9 in regulating microglial homeostasis in both in vitro and in vivo and complement our recent snRNAseq studies using spinal cord and motor cortex of C9 patients (Masrori, Bijnens et al., biorxiv, 2022).

O04.3

Investigation of genetic modifiers in the ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration Study

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State of the art. Intermediate expansions spanning 27 to 33 CAG repeats in ATXN2 are a risk factor for amyotrophic lateral sclerosis (ALS). In addition, ATXN2 is a modifier of TDP-43 pathology. We evaluated the distribution of intermediate expansions in ATXN2 participants enrolled through the ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study.

Methodology. ATXN2 repeat lengths were determined with fluorescently labeled primer PCR with capillary electrophoresis. Fisher's exact tests were performed to compare the proportion of intermediate expansion carriers across non-carrier controls, each genetic FTD group and sporadic FTD patients. To take into account family relatedness, mixed effects logistic regression analysis was conducted with pedigree as random effect.

Results. 8 % of C9orf72 expansion carriers also carried an intermediate ATXN2 repeat expansion (≥ 27 repeats), which is significantly different from non-mutation carriers (2 %) ($p < 0.05$, after adjusting for multiple testing). Carrying a pathogenic C9orf72 repeat expansion was significantly associated with the presence of ATXN2 intermediate expansions compared to GRN, MAPT and non-mutation carriers in logistic regression analysis ($p < 0.05$). Among the C9orf72 expansion carriers, intermediate repeat expansions were found in presymptomatic individuals, in those with mild cognitive impairment, bvFTD and PSP. Among the C9orf72 carriers, there are only two individuals with a clinical PSP phenotype. Strikingly, both individuals are also carrier of an intermediate ATXN2 repeat expansion.

Conclusion. The presence of genetic risk factors in individuals who also carry known pathogenic variants in C9orf72 suggests that the penetrance and presentation of disease in C9orf72 carriers is modifiable.

O01.7

Influence of Biological Sex on Cognitive Resilience in Genetic FTLD

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State of the art
Biological sex might influence symptoms within the spectrum of frontotemporal lobar degeneration (FTLD). However, research into the impact of biological sex during the early stages of FTLD is lacking.
Methodology
We included 275 mutation carriers (158 females; 127 with C9orf72, 68 with GRN, and 80 with MAPT mutations) and 161 non-carrier familial controls from the ALLFTD Consortium. Participants underwent baseline and longitudinal magnetic resonance imaging (MRI) and neuropsychological evaluations. MRI-derived regional volume estimates (RVE) were computed. Cognitive measures and RVE were normalized against sex-matched controls. The residuals approach was used to explore cognitive resilience by fitting a linear regression model for executive z-scores as the response value adjusting for age, education, and RVE.
Results
No differences were found for age, education level, disease severity, or mutation frequency between sexes. Most mutation carriers (188, 68%) were asymptomatic or mildly symptomatic at baseline. Female mutation carriers showed lower visuospatial performance at baseline (Cohen's d = -0.34, 95% CI[-0.58, -0.09], p=.001). This difference remained significant among asymptomatic GRN mutation carriers (p=0.003) but not in other mutations. The residuals approach showed that female mutation carriers presented higher executive performance than males for the same amount of frontotemporal and global atrophy (Cohen's d=0.45, 95 % CI[0.22, 0.67], p<.001). This was particularly pronounced in C9orf72 carriers (Cohen's d=0.77, 95% CI[0.35, 1.20], p<.001) but not significant in GRN (p=0.48) and MAPT carriers (p=0.0
Conclusion
Female sex might affect early cognitive performance and confer higher executive reserve in genetic FTLD.

O04.1

Multi-transcriptomic analyses reveal altered expression profiles in Pick's disease parietal tissue

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State-of-the-art:
Pick's Disease (PiD) is a rare neurodegenerative disorder characterized by dementia, frontotemporal degeneration and pathognomonic 3R tau inclusions observed at autopsy. PiD has remained significantly understudied due to its rarity and no previous studies have investigated its transcriptomic profile or disease-specific pathways.

Methodology:
We have performed the first multi-transcriptomics experiments on the parietal cortex of PiD cases (n=28), Progressive supranuclear palsy (n=25) cases and control (n=15) samples using bulk short-read (SR), long-read (Isoform sequencing; Iso-Seq), and single-nuclei (snRNA) RNA sequencing approaches. Significant differentially expressed genes (DEGs) from the SR analysis informed into differential transcript expression, cell-type-specific expression, network analysis, and immunohistochemistry studies.
Results:
Differential gene expression analysis of the SR data identified 14 DEGs (eg. CCL2, AZGP1) between PiD cases and controls. Iso-Seq data quantified transcript expression of the DEGs and revealed a novel AZGP1 transcript as the most abundant in PiD. The study of DEG expression with 3R tau burden scores highlighted significant positive associations with a subset of DEGs. Network analysis showed DEG enrichment in immune system-associated modules and snRNA data confirmed expression of DEGs in cell-types associated with brain immunity. Immunohistochemical staining against CCL2, showed significantly higher burden in PiD compared to PSP cases.
Conclusion:
Our data highlights the use of multi-transcriptomics to capture the unique transcriptome of 3R tau pathology in PiD and suggests the involvement of inflammatory processes in the disease pathophysiology. We are further investigating the relationship between the DEGs and utilizing spatial transcriptomics and whole-genome sequencing to better define 3R tau-specific pathways.

O06.2

Neuropathology-based approaches reveal novel pathogenic aspects of progressive supranuclear palsy

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State of the art: Progressive supranuclear palsy (PSP) is defined by uniform neuropathological features. Although Cryo-EM studies revealed one predominant type of tau filament in PSP, there are several clinical phenotypes and various duration of illness associated with this pathology and the pathogenesis is unclear.

Methodology: We used a complex approach to study the pathogenesis of PSP using cases from the UHN-Neurodegeneration brain disease collection including classical morphological studies using iron detection methods, antibodies against tau and neurodegenerative disease protein-related epitopes and lysosomal protases, complemented by immunogold electron microscopy, RNAscope for cellular MAPT gene expression changes, enzyme assays for cathepsin D, single nuclear RNA sequencing, seeding assays for 4R tau, proteomics, spatial transcriptomics, and astrocyte culture derived from PSP brains to study mitochondrial response.

Results: We demonstrate i) a distinct lysosomal response compared to that seen in Alzheimer's disease; ii) a dynamic response of MAPT gene expression in PSP affected cells; iii) that the molecular behavior of misfolded tau protein can be a basis for molecular classification of PSP; iv) the involvement of peripheral nerves in PSP; v) that the molecular signature of amyloid-beta as co-pathology is different in PSP; and vi) significant mitochondrial and iron-related pathway response in astrocytes in PSP brains.

Conclusion: Our neuropathology-based observations support the notion of molecular classification of PSP and show that the periphery might be a target for seeding assay-based detection of 4R tau and reveal a complex pathogenic scenario involving lysosomes, iron-, and mitochondrial-pathways.

O03.1

Platform trials for FTD and PSP

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State of the Art: Progressive Supranuclear Palsy (PSP) is a frequent cause of atypical parkinsonism, and less commonly, primary progressive aphasia or FTD. It is associated with FTLD-tau pathology. There are no effective treatments for PSP, however four large, multicenter clinical trials have been completed in the most common clinical syndrome, Richardson's (PSP-RS), and endpoints have been shown to be highly reliable and replicable. Platform (umbrella) trials evaluate multiple therapies versus a combined placebo arm, creating efficiencies in time, cost and participant burden.

Methodology: PTP is a randomized, placebo-controlled, Phase 2 platform trial in PSP-RS that will simultaneously test at least three different tau-related or neuroprotective therapies to determine safety, tolerability, and clinical proof of concept based on a multimodal clinical rating scale, the modified PSP Rating Scale (mPSPRS-15). 440 participants will be randomized 1:1:1 to one of three therapeutic regimens, and within each regimen, 3:1 drug to placebo. By pooling placebo arms, we estimate 80% power to detect a 33% slowing in decline on the mPSPRS-15 over 12 months, accounting for 20% attrition.

Results: PTP is planned to begin enrollment in 2025. We will present an update on the trial design and compounds selected for inclusion.

Conclusion: The PTP is a planned public-private partnership that will provide key data for decision-making about which therapies to pursue in larger efficacy trials, create a new research infrastructure to efficiently evaluate additional PSP therapies, and a resource for longitudinal PSP clinical and biomarker data, and biospecimens, to be shared with other researchers.

O07.1

Exploring Emotion and Emotional Variability as Digital Biomarkers in Frontotemporal Dementia Speech

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Frontotemporal Dementia (FTD) encompasses a diverse group of progressive neurodegenerative diseases that impact speech production and comprehension, along with higher-order cognition, behavior, and motor control. Traditional acoustic speech markers have been extensively studied in FTD, as have assessments capturing apathy and impairments in recognizing and expressing emotion. This work leverages machine learning for tracking changes in emotional content within the speech of individuals with FTD and healthy controls with the aim of assessing and monitoring emotional changes in individuals with FTD.
Methods: Analysis of a dataset comprising standard elicited speech tasks performed by 78 individuals diagnosed with FTD and 55 healthy elderly controls was performed. Emotion was analysed using an ensemble-based convolutional neural network classifier trained on the Interactive Emotional Dyadic Motion Capture dataset and then applying the classifier on short time windows from the FTD and healthy control narratives to facilitate a granular examination of emotional changes throughout longer speech samples.
Results: When compared to healthy controls, people with FTD demonstrated reduced emotional change in a monologue task describing a happy experience. During a picture description task, people with FTD displayed a slightly elevated average level of frustration ($p < 0.005$). Increased frustration levels experienced by people with FTD could potentially serve as an indicator of their difficulties in accomplishing the task.
Conclusions: Capturing the temporal evolution of emotional content offers a nuanced understanding of communication in individuals with FTD.

O07.2

The Signature Initiative 2 years later: towards the clinical recommendations for socio-cognitive assessment in neurocognitive disorders

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Background: Harmonising assessment for neurocognitive disorders (NCDs) is an urgent priority for both clinical settings and research. In 2022, we launched the SIGNATURE initiative with the aim to harmonize and optimise the use of socio-cognitive assessments in NCDs. Hereby, we report findings from the first phase of the initiative including the evaluation of the state-of-the-art in memory clinics. Methods: We drafted an ad-hoc online survey to explore practices, best known and used measures, perceived relevance and obstacles for their use. Data were aggregated and stratified by geographical regions and variables of interest. Results: 413 responses from 10 European and Latin American regions were recorded. 77% of responders reported having no or limited experience with socio-cognitive measures. However, all responders largely agreed (>85% agreement) on the their relevance for differential diagnosis and detection of new cognitive phenotypes. The Ekman-60 faces test (or its variants) was reported as the most well-known and used task (83% of responders), followed by Faux Pas (or its variants) (72%) and Reading the Mind in the Eyes (61%) tasks. Limited availability of standardized and validated measures in clinics was reported as the main obstacle (86% of agreement), followed by lack of guidelines (79%), time (77%), and education (67%). Discussion: Real-life barriers in neuropsychology practice and availability of measures influence the adoption of socio-cognitive testing. Our initiative supports a bidirectional collaboration between clinicians and researchers to fit the needs and constraints of clinical practice and to define a flexible set of recommendations that can facilitate consistent socio-cognitive assessment.

Background: Scientific work over the last decade strongly supports the presence of early socio-cognitive deficits in different neurocognitive (NCD) patients and confirms the DSM-5 guidelines, what stated that social cognition should be included in the core cognitive domains assessed in NCDs.

However, no guidelines exist for the socio-cognitive testing in NCDs. The international SIGNATURE initiative was recently set up to promote an advancement in this field. Hereby, we report consortium clinical guidelines based on available evidence from the literature and current state-of-the-art practice in memory clinics. Methods: Using the Delphi consensus method, 22 panellists from 13 countries and relevant scientific societies defined workflow assumptions. Two in-presence Delphi rounds were performed during the first hybrid SIGNATURE workshop in September 2023. Results: Supported by a systematic literature review and clinical evidence resulting from the SIGNATURE clinical survey, panellists defined the context of use, relevance, practice, obstacles and future priorities for socio-cognitive testing in NCDs. Conclusions: The present set of recommendations resulting from a bidirectional collaboration between clinicians from centres specialized in NCDs and researchers who are experts in social cognition drives the needed advancement in this field. Adopting harmonized recommendations may facilitate multisite international studies and consistent neuropsychological evaluation across countries. Future collaborative clinical research projects should overcome the current limitations and foster the use of more ecological and cross-culturally validated measures in clinics.

O13.1

Discovery of Novel Splicing Alterations in FTLD-TDP: Insights from Brain Transcriptomics Using Short- and Long-Read Sequencing

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State of the art

Dysregulation of TDP-43 as seen in TDP-43 proteinopathies leads to specific RNA splicing dysfunction. While discovery studies have explored novel TDP-43-driven splicing events in induced pluripotent stem cell (iPSC)-derived neurons and TDP-43 negative neuronal nuclei, transcriptome-wide investigations in FTLD-TDP brains remain unexplored. Such studies hold promise for identifying widespread novel and relevant splicing alterations in FTLD-TDP patient brains.

Methodology

We conducted the largest differential splicing analysis using bulk short-read RNA-seq data from frontal-cortex (FCX) tissue of 127 FTLD-TDP (A, B, C, GRN and C9orf72 carriers) and 22 neuropathologically normal subjects (Mayo Clinic Brain Bank; Illumina), using Leafcutter. Additionally, long-read bulk and single nuclei RNAseq (LR-snRNAseq) data was generated from FCX of 9/7 FTLD-TDP/controls and human TARDBP wildtype and knockout iPSC-derived neurons (ONT). Proteomics data was obtained from FCX (99/19 FTLD-TDP/controls), plasma (75/75 FTLD-TDP/FTLD-Tau), and CSF (50/50 FTLD-TDP/FTLD-Tau).

Results

1818 events were identified as differentially spliced (FDR<0.05, |dPSI|>0.1) in FTLD-TDP brains, of which 96 remained significant after adjusting for cell type proportion. FTLD-TDP_C and C9orf72 carriers exhibit similar splicing patterns, particularly in genes associated with neurodevelopment. Following exploration and characterization, 30 novel splicing events (including STMN2 and ARHGAP32) were selected as potential biomarkers for TDP-43 pathology, of which 18 were confirmed by LR-RNAseq. Predicted protein products are currently explored in existing proteomics data from brain, plasma, and CSF.

Conclusion

This study provides a significant advancement in the discovery of novel splicing alternations using integrative data analyses and will suggest novel biomarkers of TDP-43 pathology with high confidence.

O03.2

The Multidomain Impairment Rating (MIR) Scale: Comparison to the CDR+NACC FTLD in the ALLFTD Consortium

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State of the Art: The 12-item Multidomain Impairment Rating (MIR) scale was developed in 2016 to encompass all key manifestations of the FTLD spectrum disorders. The MIR involves elements of the CDR®+NACC FTLD (FTLD-CDR) plus 4 domains addressing concentration/multitasking, visuospatial functioning, psychiatric features, and motor features, and 3 domains (community life, home life, and personal life) reflecting impairment in activities of daily living due to cognitive, behavioral, and/or motor dysfunction.

Methodology: Demographic, clinical, FTLD-CDR, and MIR data from ALLFTD Consortium participants on their most recent visit were analyzed.

Results: Data from 498 participants (49% male, mean age 57±14 yrs, mean education 16±2 yrs) were analyzed; 299 (60%) were from kindreds with a known mutation and 198 (40%) were sporadic. The primary phenotypes were: clinically normal (234, 47%), mild behavioral and/or cognitive impairment (43, 9%), bvFTD (110, 22%), FTD/ALS (1, 0.2%), PPA (63, 13%), CBS (24, 5%), and PSP-RS (23, 5%). The global FTLD-CDR scores were: 0 (47%), 0.5 (15%), 1 (19%), >1 (19%), whereas the global MIR scores were: 0 (47%), 0.5 (11%), 1 (17%), >1 (25%). The global MIR > global FTLD-CDR scores in 43 (9%), which was largely driven by motor dysfunction. Six mutation carriers (2 C9orf72, 3 MAPT, 1 GRN) had global MIR > global FTLD-CDR scores, three of whom had motor dysfunction.

Conclusions: The MIR may provide greater utility than the FTLD-CDR for evaluating those with motor dysfunction, and may more optimally capture the full spectrum and functional impact of features in sporadic and familial FTLD.

O04.2

Understanding the role of somatic mutations in TARDBP in FTLD-TDP type C

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State of art: Somatic mutations in TARDBP were reported in FTLD-TDP type C cases using bulk exome sequencing. Systematic replication and validation of somatic TARDBP variants using single-cell methods, however, has not been performed.

Methodology: We performed single-nuclei targeted DNA sequencing of neurons derived from the superior temporal gyrus of sporadic FTLD-TDP type C cases (n=60) and controls (n=40) using the Mission Bio Tapestri platform. Samples were pooled in sets of 5. For each individual, we investigate the somatic variants in TARDBP and compare the burden of TARDBP variants in a case-control setting.

Results: We first developed a deconvolution strategy leveraging germline variants to assign neuronal nuclei to each individual. As a pilot study, we deconvoluted 4 pools resulting in ~10,300 nuclei derived from 11 cases and ~4400 nuclei from 9 controls. In the combined ~15,700 nuclei we identified 1203 different somatic TARDBP variants, each with very low frequency. Most nuclei (78%) had at least one TARDBP variant and 6% (n=74) of variants were found in a single nucleus. In cases, 30 somatic variants were found in >50 nuclei. Additionally, 15% of variants were exclusive to patients, with three variants appearing in >10 nuclei. One of these was a missense variant (p.L109S) with a CADD score of 29.

Conclusion: We detected a high level of very rare TARDBP somatic variants in neuronal nuclei in both cases and controls. The identification of variants unique to cases suggests their potential involvement in FTLD-TDP type C, however further analyses and validation is ongoing.

O13.2

New Insights into aFTLD-U through the brain transcriptomics analysis

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State of the art: FTLD-FET is a rare subgroup of FTLD. Among FTLD-FET subtypes, aFTLD-U is the most common. It is characterized by a clinical presentation of severe and progressive early onset bvFTD, often with psychiatric symptoms. More than a decade after its initial description, we only have a limited understanding of the etiology of this disease subtype, thus severely hampering translational research efforts.

Methodology: Short-read RNA sequencing data was generated from frontal cortex tissue of 21 aFTLD-U and 20 controls (HiSeq4000, Illumina), and differential gene expression (DESeq2), weighted gene co-expression network analyses (WGCNA), differential splicing analyses (Leafcutter), and pathway analyses (Enrichr) were performed. Results are adjusted for main cell types.

Results: Differential gene expression and co-expression analysis uncovered notable shifts in cell-type composition (a selective loss of excitatory neuronal markers and a strong increase in astrocytic markers), a decrease in the expression of mitochondrial function-related pathways, and an unexpected upregulation of the Sonic hedgehog (Shh) pathway, including the GLI1 transcription factor in aFTLD-U (log2FC= 1.90, Padj= 0.007). Differentially splicing analysis identified 308 distinctively spliced events distributed across 151 clusters corresponding to 136 unique genes (FDR < 0.05, ΔPSI > |0.1|), with enrichment for differentially spliced genes involved in neuron projection development and regulation of GTPase activity.

Conclusion: We identified the Shh signaling pathway and the GLI1 transcription factor as novel dysregulated pathways in aFTLD-U, possibly functionally related to a transportin (TNPO1) dysfunction already reported in these patients. Single-nuclei transcriptomics is underway to further characterize cell-type-specific expression and splicing changes.

O09.6

TMEM106B loss-of-function impairs the presynaptic protein machinery in human iPSC-derived cortical neurons

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State of the art
TMEM106B haplotypes have been found to modulate the risk for several neurodegenerative diseases such as Frontotemporal lobar degeneration with TDP-43 aggregates and were shown to impact healthy aging and neuronal reserve, suggesting that they determine neuronal vulnerability. These haplotypes are thought to regulate the expression levels of TMEM106B, a lysosomal type-II transmembrane protein, with a slight increase in expression associated with the risk haplotype. However, the mechanisms through which TMEM106B exerts its pathogenicity remain unclear.

Methodology
We generated TMEM106B knockout (TMEM106B-/-) iPSC-derived cortical neurons. We characterized the lines and performed whole cell mass spectrometry. We also analyzed lysosomal trafficking with live cell imaging and lysosomal enzymatic activity.

Results
We observed a downregulation of proteins involved in synaptic vesicular metabolism and transport (SYT1, GAD2, and ATP2B1) and an upregulation of proteins involved in actin cytoskeleton reorganization (TAGLN and PALLD). Moreover, we observed an upregulation of galectin-3, suggesting alterations of the endolysosomal pathway. We confirmed a significant loss of presynaptic markers (synaptophysin-1 and synaptotagmin-1) and increase of lysosomal markers (LAMP1 and GRN) by western blot. Moreover, functional characterization of endolysosomal fitness showed a reduced lysosomal trafficking and cathepsin D activity.

Conclusion
Our results show that loss-of-function of TMEM106B leads to a dysregulation of the presynaptic terminal and the endolysosomal system, suggesting a dysfunction in the recycling or docking of these vesicles. This would indicate a direct role of TMEM106B in the maintenance of healthy presynaptic compartments, and could explain how TMEM106B dysregulations affect neuronal vulnerability.

O13.3

Carboxy-terminal blockade of sortilin binding enhances progranulin gene therapy, a potential treatment for frontotemporal dementia

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State of the Art: Frontotemporal dementia is linked to loss-of-function progranulin gene mutations making AAV-progranulin gene therapy to boost progranulin levels a promising therapy. Previous studies demonstrate the effectiveness of AAV-progranulin tagged at the carboxy-terminus, disrupting interactions with sortilin. We hypothesize that transduction of progranulin lacking its carboxy-terminal sortilin-binding domain might be a more effective alternative to progranulin with intact sortilin binding.

Methods: This study determined whether blocking the carboxy terminal of progranulin improves or impairs progranulin gene therapy effectiveness. We compared treating progranulin knockout mice with carboxy-terminally blocked progranulin, progranulin with intact sortilin binding, or GFP control. We used outcome measures including immunohistochemistry, microdialysis, lipidomics, machine learning behavioral assays, and biomarker analysis to assess the impact of carboxy-terminal blockade.

Results: Carboxy-terminal blocked progranulin increased progranulin levels at the injection site through immunohistochemistry and microdialysis. While both progranulin vectors reduced neuronal lipofuscinosis, only the carboxy-terminal blocked variant improved microglial pathology, microglial lipofuscinosis, and pro-inflammatory microglial morphology. Additionally, both forms corrected BMP deficiency and ganglioside accumulation, with the carboxy-terminal blocked progranulin more effective in cerebellar BMP deficiency and cortical and thalamic ganglioside accumulation. Behavioral analysis revealed that mice treated with carboxy-terminally blocked progranulin resembled wild-type mice, while those with intact sortilin binding resembled progranulin knockout mice. Finally, only the carboxy-terminal blocked progranulin reduced plasma NfL, a neurodegeneration biomarker, in progranulin knockout mice.

Conclusions: These findings suggest that blocking the carboxy terminus of progranulin enhances the effectiveness of progranulin gene therapy. This modification should be considered in second-generation progranulin gene therapy programs.

O09.3

TDP-43 monomerization drives early pathological changes in FTD

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State-of-the-art

~45% of frontotemporal dementia (FTD) patients exhibit TDP-43 proteinopathy, characterized by the nuclear depletion and cytoplasmic aggregation of this RNA-binding protein. Since its discovery in 2006, our understanding of the consequences of TDP-43 pathology, namely the broad dysregulation of its RNA targets and direct neurotoxicity, has vastly increased. In contrast, the initial pathogenic events that drive TDP-43 out of the nucleus and into inclusions remain elusive. In this study, we identify TDP-43 monomerization as an early cause of TDP-43 dysregulation in FTD-TDP.

Methodology

We established a proximity ligation assay-based methodology to visualize TDP-43 dimers at single-cell resolution in post-mortem human brain tissue. The cellular pathways governing TDP-43 monomerization were dissected in iNets, our novel iPSC-derived human neural culture system with extraordinary longevity, optimal for the study of FTD-TDP (Hruska-Plochan et al Nature 2024; 626 1073-1083) and other age-related neurodegenerative disorders.

Results

Employing iNets and brain tissue of FTD-TDP patients and non-neurological controls, we show that physiological N-terminal domain-mediated TDP-43 oligomerization ensures nuclear retention and functionality, whereas monomerization drives nuclear clearance and inclusion formation. Additionally, we pinpoint the mechanisms tuning the TDP-43 monomer-to-oligomer ratio in cells, including post-translational modifications at specific TDP-43 epitopes.

Conclusion

Identification of early disease pathways is a key step towards rational and effective drug design to counteract the cause of TDP-43 dysregulation in TDP-43 proteinopathies. Our data reveal that monomerization fosters the pathological transition of TDP-43 in FTD-TDP and that promoting physiological TDP-43 oligomerization could counteract nuclear depletion and aggregation.

O01.6

Frontotemporal Dementia in India- Perspective and unique insights

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State of the art

Several well-characterized large genetic cohorts of Frontotemporal dementia (FTD) exist in Europe and North America, but such studies are uncommon in India. Here, we describe a large cohort of patients attending a memory clinic in South India and highlight several interesting and unique features.

Methodology

Mono and bilingual patients with FTD and subtypes were evaluated using a clinical protocol, pedigree analysis, neuroimaging, neuropsychological assessment, and language testing. Clinical features, age of onset in mono and bilinguals, and neuropsychological and linguistic features were analyzed with appropriate statistical tests.

Results

There were 255 patients: 158 behavioural variant FTD (bvFTD), 32 semantic dementia (SD), 24 progressive nonfluent aphasia (PNFA) and 41 FTD-overlap syndrome. Bilingual patients with FTD had ~ a 9-year delay in age of onset compared to monolinguals, which was not seen in other dementias. There was a substantial delay (median 30 months) in the diagnosis of FTD as compared to other dementias. There was a striking loss or severe impairment of L2 at presentation in bilingual patients with SD, which was not noted in other progressive aphasias. Parkinsonism and motor stereotypies were common and seen in ~65% of patients. Genetic characterization and a cross-cultural FTD study as part of the NIC-FTD initiative are underway, and results are expected in a few months.

Conclusion

Studying FTD from a diverse population provides a unique perspective, which is expected to improve our understanding of this complex disease. This will also allow Indian patients to participate in global clinical trial initiatives.

O08.2

Clinical Performance of Plasma Aβ1-42/Aβ1-40, p-tau217 and Neurofilament Light in Sporadic Frontotemporal Dementia Spectrum Disorders

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State of the art: The clinical utility of plasma Amyloid, Tau, and Neurodegeneration (ATN) biomarkers in frontotemporal dementia spectrum disorders (FTD) remains unexplored.
Methodology: 458 participants with available plasma biomarkers (45% female, median age 63 ± 4 years) were recruited through ALLFTD; 38 (median age 61 ± 9 years) had available autopsy data. Plasma Aβ1-42/Aβ1-40 was measured with immunoprecipitation-mass spectrometry, p-tau217 with electrochemiluminescence and NfL with Simoa. Biomarker concentrations were compared by phenotype disease severity, APOE genotype neuropathological diagnosis, and AD co-pathology stages (ADNC and Braak stage). Diagnostic performance was tested with Receiver Operating Characteristic (ROC) curves Relationships with measures of clinical severity and neuropathology were tested through linear regressions controlling for age, sex, and APOE genotype.
Results: Aβ1-42/Aβ1-40 did not differ between phenotypes and was not affected by clinical severity. P-tau217 was elevated in logopenic primary progressive aphasia (lvPPA) and amnestic dementia (AmD) cohorts, compared to other FTD groups. NfL was elevated in all symptomatic patients, compared to controls, and as a function of disease severity. P-tau217, but not Aβ1-42/Aβ1-40 nor NfL discriminated lvPPA and AmD combined from other phenotypes (AUC = 0.9 (95% CI 0.8 – 0.96, $p < 0.0001$, 68% sensitivity, 92% specificity). All markers showed baseline associations with cognitive, motor, and social behavior scores. Cases with more severe AD co-pathology had lower Aβ1-42/Aβ1-40 and higher p-tau217 than less severe AD-co-pathology.
Conclusion: When FTD is suspected, plasma AD biomarkers may identify individuals whose phenotypes are likely caused by primary AD pathology and those with more severe AD-co-pathology.

O04.4

Deciphering Distinct Genetic Risk Factors for FTLD-TDP Subtypes via Whole Genome Sequencing

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State of the art: Frontotemporal lobar degeneration with neuronal inclusions of the TAR DNA-binding protein 43 (FTLD-TDP) is a fatal neurodegenerative disorder with only limited number of risk loci identified. Importantly, most FTLD-TDP patients are not yet genetically explained.

Methodology: We conducted the largest genome-wide association study on FTLD-TDP including 985 patients and 3,153 controls. Common and rare variant association with disease status was performed using logistic regression and burden tests. Meta-analysis was performed using the DEMENTIA-SEQ dataset. Multiomics data integration and pathway analyses were conducted to nominate new genes and risk variants associated with FTLD-TDP.

Results: We confirmed UNC13A as an FTLD-TDP risk factor and identified TNIP1 as novel FTLD-TDP risk factor. In subgroup analyses, we further identify for the first-time 7 additional genome-wide significant loci specific to each of the three main FTLD-TDP subtypes: GRN, TINAG, MZT1 and FARP2 for FTLD-TDP type A, RCL1, PDS5B for FTLD-TDP type B and C19orf52 for FTLD-TDP type C. We highlight enrichment of risk loci in specific tissues and neuronal subtypes, suggesting distinct disease aetiologies in FTLD-TDP subtypes. Rare variant analysis confirmed TBK1 and nominated VIPR1, RBPJL, and L3MBTL1 as novel FTLD-TDP risk genes, highlighting the role of immunity and notch signaling pathway in FTLD-TDP.

Conclusion: In conclusion, we have confirmed 2 known genetic loci and identified 8 new genetic loci, and 3 new genes with rare variants associated with FTLD-TDP risk. By enriching in neuropathologically confirmed patients, we gained important knowledge of FTLD-TDP pathophysiology opening new disease modeling and therapeutic avenues.

O01.4

NEURODEVELOPMENTAL TRAJECTORIES TOWARDS NEURODEGENERATIVE DISEASE

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STATE OF THE ART: Previously, we observed an increased prevalence of non-right-handedness (nRH) in semantic dementia (SD) and posterior cortical atrophy (PCA) along with elevations of language-based and mathematical/visuospatial-based developmental disorders in logopenic variant primary progressive aphasia (lvPPA) and PCA, respectively. Theorizing these neurodevelopmental differences accounted for differential targeting of neurodegenerative disease, we sought to confirm these patterns in a 10-year follow-up study.

METHODS: Retrospective chart-based reviews across behavioral variant frontotemporal dementia (bvFTD) (n=336), corticobasal syndrome (CBS) (n=112), lvPPA (n=224), nonfluent PPA (nfvPPA) (n=168), PCA (n=115), progressive supranuclear palsy Richardson syndrome (n=111), SD (n=222), early onset Alzheimer's disease (AD) (n=549), and late onset AD (n=659) were compared for rates of nRH, developmental dyslexia, dyscalculia, stuttering, and ADHD.

RESULTS: nRH predicted SD [OR=1.64(95%CI:1.14-2.38)] and PCA [OR=1.90(95%CI:1.18-3.05)], dyslexia predicted lvPPA [OR=5.64(95%CI:3.76-8.46)], dyscalculia predicted PCA [OR=16.27(95%CI:9.16-28.92)], and stuttering predicted CBS presentations [OR=10.13(95%CI:4.70-21.86)]. Accordingly, nRH and dyslexia were twice, dyscalculia was three times, and stuttering, fourteen times greater in their respective conditions compared to the general population. Rates of dyslexia and stuttering were more similar across disorders whose epicenters were closer to themselves (e.g., following CBS, stuttering rates were highest in lvPPA and nfvPPA, while after lvPPA, dyslexia was highest in CBS, then nfvPPA). Dyslexia and dyscalculia cohorts possessed higher rates of nRH.

CONCLUSIONS: Neurodevelopmental differences present across frontotemporal lobar degenerative and AD syndromes with higher rates of nRH in select disorders and topographical correspondences between developmental disorders and neurodegenerative diseases, providing further evidence for our hypotheses that neurodevelopment informs susceptibility to neurodegenerative disease.

O08.5

Unbiased CSF proteomics reveals genotype-specific signatures of presymptomatic and symptomatic familial frontotemporal lobar degeneration

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State of the Art: Large-scale proteomics has accelerated fluid biomarker and therapeutic target discovery in Alzheimer's disease, yet remains underutilized in frontotemporal lobar degeneration (FTLD). We leveraged high-throughput cerebrospinal fluid (CSF) proteomics to identify individual proteins and pathways that change prior to symptom onset in autosomal dominant FTLD.

Methodology: 159 FTLD mutation carriers (73 C9orf72, 34 GRN, 52 MAPT) and 82 noncarrier controls from ALLFTD completed lumbar puncture and clinical assessment. Unbiased CSF proteomics on SOMAscan® v4.1 (7,289 proteins) were performed. Disease age estimates measuring predicted symptom onset were derived from a validated model incorporating genotype-specific clinical, neuroimaging, and plasma biomarker (NfL, GFAP) data. Mass linear regression models identified disease age 'thresholds' where individual proteins significantly diverged between each mutation carrier group and controls.

Results: Compared to controls, 290 proteins diverged (FDR-p<.05) in C9orf72, 189 in GRN, and 68 in MAPT. Proteins with increased abundance in mutation carriers tended to diverge at earlier thresholds (e.g., disease age: -30 to -15 years) and were enriched for RNA binding/splicing (C9orf72, GRN), calcium signaling (C9orf72), cytoskeletal organization (MAPT), and synaptic plasticity pathways (GRN, MAPT). Proteins with decreased abundance in mutation carriers tended to diverge closer to symptom onset (disease age: -15 to +5 years) and were enriched for neurodevelopmental/axonogenesis pathways in all gene groups.

Conclusion: Robust CSF protein changes are measurable in familial FTLD decades before predicted symptom onset, most prominently in RNA metabolism (FTLD-TDP) and cytoskeletal (FTLD-tau) networks. Replication and validation of top hits in other cohorts and tissues is warranted.

O09.4

AlphaFold2 Modeling of Mapt Mutation-derived Tau Conformations Plus Biochemical Data Support TauC3's Involvement in FTLD-tau

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State of the art: Frontotemporal lobar dementia due to tau (FTLD-tau) is a major type of FTLD. While FTLD-tau's molecular basis remains uncertain, evidence suggests involvement of tauC3, a highly noxious and aggregation-prone C-terminally truncated tau fragment produced by caspase-3 cleavage. Normal 4-repeat (4R) full-length tau (FLT) has a closed ("hairpin") conformation in which N- and C-termini closely overlap and the MTBR is partially buried. This conformation appears necessary for fast axonal transport, a normal tau function, and the MTBR's inaccessibility may restrict aggregation occurring in tauopathies. TauC3 cannot form the "hairpin," thus plausibly driving its toxicity and aggregation propensity.

Methodology: We used the AI-based modeling tool AlphaFold 2 (AF2) to predict the conformation of normal 3R and 4R FLT (with different insert numbers), tauC3, and tau encoded by several Mapt mutations, including P301 L/S substitutions that induce 4R tau pathology and the ΔK281 deletion recently reported to cause Pick's disease, a rare 3R FTLD-tau etiology. We also assessed tauC3's abundance in soluble oligomeric material from brains of P301S-bearing mice. Finally, we measured caspase-3 cleavage susceptibility for tau from several Mapt mutations vs. 4R FLT.

Results: AF2 modeling identified an open conformation for tauC3 and tau produced by several Mapt mutations, especially P301 L/S and the ΔK281 deletion, plus notable 3R/4R differences. We found substantial tauC3 in oligomeric material and increased caspase-3 cleavage for several mutations.

Conclusion: The open conformation produced by tauC3 and some Mapt mutations may underlie FTLD-tau pathology. AF2 and biochemical data align, supporting tauC3's involvement.

O06.1

Annexin A11 Proteinopathy in ANXA11 variant cases and FTLD-TDP Type C

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State of the Art:
Rare ANXA11 variants are associated with annexin A11 aggregates that variably colocalize with TDP-43 protein in genetic forms of amyotrophic lateral sclerosis (ALS). Annexinopathy has not been described in other sporadic or genetic forms of ALS, frontotemporal lobar degeneration (FTLD), or limbic predominant age related TDP-43 encephalopathy (LATE)

Methodology:
Genetic analysis was performed on 818 autopsy cases to identify cases with rare ANXA11 variants. Immunohistochemistry for annexin A11 aggregates was performed on 332 autopsy cases that represent a spectrum of TDP-43 proteinopathies and related neurodegenerative diseases. Double immunofluorescence was performed to determine the extent of colocalization between TDP-43 and annexin A11. Sequential extraction of frozen tissue was performed to assess for the presence of insoluble annexin A11 protein.

Results:
Annexinopathy was seen in 100% of FTLD-TDP type C, 7% of LATE-NC, 6% of FTLD-TDP type A, 3% of FTLD-TDP type B, and 3% of ALS cases. Immunofluorescence demonstrated strong colocalization of Annexin A11 and TDP-43 in FTLD-TDP and LATE-NC with variable colocalization in ALS. In addition, one novel ANXA11 variant case with a progressive supranuclear palsy-like frontotemporal dementia syndrome with striking striatal vacuolization exhibited a primary annexinopathy without TDP-43 proteinopathy. Annexinopathy was associated with the accumulation of insoluble, full-length and truncated annexin A11 protein.

Conclusion:
Annexinopathy is observed in both sporadic and genetic forms of TDP-43 proteinopathy including all cases of FTLD-TDP type C. Moreover, a case of primary annexinopathy due to a novel ANXA11 variant suggests that annexin A11 dysfunction is sufficient to cause neurodegeneration.

O13.4

Ultra-high resolution T2*-weighted ex vivo 7T MRI laminar patterns of pathology in FTLD

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State of the Art:
T2*-weighted(T2*w) MRI is sensitive to iron in healthy myelin and pathological gliosis. We developed ultrahigh resolution (160µm3) ex vivo whole-hemisphere T2*w 7T MRI imaging methods to study FTLD cellular pathology at high-throughput (Tisdall,et.al,Neuroimage Clin.,2022). Previous histology-validated work from our group and others suggests laminar-specific patterns of iron-rich gliosis and WM degeneration in molecular forms of FTLD and AD, but large-scale comparative studies are limited.

Methodology:
Ordinal ratings (0-3; none-mild-moderate-severe) were performed, blinded to clinical/pathologic diagnosis, for cortical layer hypointense-bands of iron-rich gliosis, hypointense-speckling for plaque, and hyperintense myelin-loss in WM from 66 available ex vivo 7T2*w MRIs (21=AD;26=FTLD-Tau;19=FTLD-TDP) compared to 2 control hemispheres in the coronal plane at the level of midfrontal (MFC;BA46), orbitofrontal (OFC;BA11) and anterior-inferior temporal cortex (AITC;BA20). Wilcoxon tests compared median scores between groups.

Results:
Mid-layer speckling, previously corresponding to amyloid-plaques, was evident in both AD and FTLD patients with mixed-medium/high AD co-pathology, with greater average scores across regions compared to pure FTLD ($p<0.02$). Deep-layer irregular hypointense bands, previously corresponding to iron-rich gliosis, was greater in FTLD-Tau overall compared to AD ($p<0.001$), and in AITC compared to both FTLD-TDP and AD ($p<0.02$). AITC WM hyperintensity, previously linked to myelin loss, was greater in FTLD-Tau than FTLD-TDP ($p<0.05$).

Conclusion:
Ultra-high resolution T2*w MRI visualizes microstructural degeneration and AD co-pathology in FTLD subtypes which are not readily apparent on conventional in vivo structural MRI. Future quantitative work with histology validation will elucidate whole-hemisphere patterns of FTLD cellular pathology and facilitate in vivo MRI biomarker development.

O09.2

Regulation of tau phosphorylation, secretion and splicing by variations in temperature during the sleep-wake cycle

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State of the art: Aggregates of hyperphosphorylated tau protein are a hallmark of Alzheimer's disease (AD) and other tauopathies. Sleep disturbances are common in AD patients, and insufficient sleep may be a risk factor for AD. Tau phosphorylation, secretion and mRNA splicing are dysregulated by sleep disturbances in mice and men. However, the physiological mechanisms of tau regulation during the sleep–wake cycle are currently unknown. We thus determined whether tau phosphorylation, secretion and splicing are regulated by circadian rhythms, inherently linked to the sleep-wake cycle and body temperature variations.

Methodology: We analyzed tau phosphorylation, secretion and splicing in the brains of awake, sleeping or sleep-deprived mice, while recording their temperature. We then exposed neuronal cells to the physiological temperatures observed during the different conditions to dissect the underlying mechanisms.

Results: We found that tau phosphorylation undergoes sleep-driven circadian variations, as it is hyperphosphorylated during sleep, when body temperature is lower. Similar changes in tau phosphorylation were reproduced in neuronal cells exposed to temperatures recorded during the sleep–wake cycle. In addition, we observed that the secretion of tau is temperature-dependant, as higher temperature increased total tau secretion. Similarly, tau splicing was dependent of temperature, with lower temperatures promoting exon 10 exclusion.

Conclusion: Taken together, these data suggest that tau phosphorylation, secretion and splicing follow a circadian rhythm driven mostly by body temperature and sleep. Since AD patients are prone to sleep disturbances and thermoregulation deficits, our study provides new knowledge on how tau pathology could develop and spread.