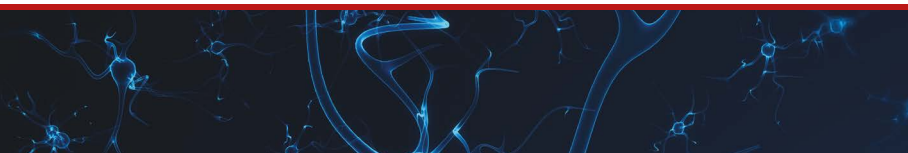
Parallel Session 6: Cognitive

Fri 8 May, 11:30 - 12:30

Hall 5

1. Plasma Alzheimer's biomarker p-tau217: appropriateness of test requests and impact on patient management: **Ashvini Keshavan**
2. EEG slowing predicts future dementia: A population-based cohort study: **Abidemi Otaiku**
3. A new drug target in Huntington's disease: **Tom Massey**
4. NULISA identifies VILIP-1 as a novel diagnostic and prognostic blood biomarker for sporadic CJD: **Leah Holm-Mercer**
5. Trontinemab: Brainshuttle™ AD proof-of-concept to pivotal TRONTIER 1 and 2 studies in early symptomatic AD: **Catherine Mummery**
6. Outcomes of referrals to a regional NPH MDT in 2024 and comparison with previous years: **Jacob Roelofs**



Plasma Alzheimer's biomarker p-tau217: appropriateness of test requests and impact on patient management

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Plasma phosphorylated tau 217 (p-tau217) became clinically available in the NHNN lab in January 2025. We assessed appropriateness of p-tau217 requests at NHNN according to presence of objective progressive cognitive impairment (as per the Alzheimer's Association's clinical practice guideline 2025; documented by the diagnosing clinician's impression) and examined the impact of testing on working diagnosis, referral to CSF/amyloid PET, starting or stopping symptomatic Alzheimer's medication, and consideration of amyloid lowering therapy. We reviewed medical records for 111 of 228 patients who had plasma p-tau217 testing over January-May 2025 (cognitive service n=86, other clinicians n=25). Objective cognitive impairment was documented in 86% of cognitive clinic patients and 32% of patients attended by other clinicians. Impact was ascertained post-testing in 77 individuals with follow-up. Working diagnoses changed in 25% (13% toward and 6% away from Alzheimer's/mixed Alzheimer's); 12% were referred for CSF/amyloid PET (mostly those with indeterminate-range p-tau217 results), 30% started but none stopped symptomatic AD medication, and 3% were counselled about amyloid lowering therapy. A full audit through December 2025 will be presented; findings will provide support for business cases for other NHS trusts to adopt the test. We will re-audit after clinician education utilizing the newly developed DART educational module.

EEG slowing predicts future dementia: A population-based cohort study

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Background: Electroencephalogram (EEG) slowing is commonly seen in dementia. However, it is unclear whether EEG slowing in the absence of cognitive impairment is predictive of future dementia.

Methods: 2,800 cognitively unimpaired older adults from the Osteoporotic Fractures in Men Study (MrOS) and the Study of Osteoporotic Fractures (SOF) underwent in-home polysomnography (PSG) at baseline and returned for follow-up during the subsequent 12 years. Theta-to-alpha ratio (TAR) was calculated using power spectral analysis of the EEG. Incident all-cause dementia at follow-up was based on doctor-diagnosis. Multivariable Poisson regression was used to estimate Incidence rate ratios (IRR) for incident dementia according to categories of baseline TAR (Low [≤ mean], Moderate [<2 SD above mean], High [>2 SD above mean]).

Results: Compared with participants with a low TAR, those with a high TAR had a 3.6-fold risk of developing dementia in the pooled cohort (P<0.001). Furthermore, a higher TAR at baseline, and greater increase in TAR over time, were associated with greater genetic risk for dementia, faster cognitive decline, faster epigenetic ageing (measured by GrimAge and PhenoAge), and increased risk of all-cause mortality (P's<0·05).

Discussion: EEG slowing predicts future dementia and accelerated ageing in cognitively unimpaired men and women in the general population.

A new drug target in Huntington's disease

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Huntington's disease is a central neurodegenerative condition characterised by progressive worsening of movement control and mental health, culminating in dementia and premature death. There is no disease-modifying treatment. HD is caused by a single repeat expansion of at least 36 CAGs in the HTT gene, with symptoms typically starting in adulthood. Recent insights suggest that 'somatic expansion' of the repeat tract beyond its inherited length in susceptible striatal neurons is a key driver of HD pathology. Once a repeat tract exceeds ~150 CAGs in a striatal neuron, that cell will degenerate. As such, if we can inhibit or slow somatic expansion we could slow progression of HD.

We have used human genetic data to identify modifiers of HD progression in patients. Many of these modifiers are DNA repair genes that impact rates of somatic expansion. One novel modifier is PMS1, an accessory factor in mismatch repair. We have shown that PMS1 knockout ablates somatic expansion in an induced pluripotent stem cell model of HD. Furthermore, purified PMS1 protein has ATPase activity and this activity is needed for somatic expansion in our cell model. Thus, PMS1 ATPase activity represents a novel therapeutic target in HD and other related repeat expansion disorders.

NULISA identifies VILIP-1 as a novel diagnostic and prognostic blood biomarker for sporadic CJD

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Blood-based biomarkers such as neurofilament light chain (NfL) offer scalable tools for early detection of neurodegenerative disease. However, NfL is non-specific and sporadic Creutzfeldt–Jakob disease (sCJD) progresses rapidly, creating a need for blood biomarkers that improve discrimination of sCJD from similar non-prion syndromes.

We used a high-sensitivity multiplex plasma immunoassay (NULISA) to measure a panel of proteins in baseline samples from 48 individuals with sCJD, 29 age-matched controls, and 26 patients with non-prion conditions referred as suspected sCJD (mimics). Diagnostic performance was assessed by ROC analysis. Prognostic associations were examined using penalised regression and survival modelling.

NfL showed excellent discrimination between sCJD and controls (AUC 0.99) and between mimics and controls (AUC 0.96). In the clinically relevant comparison of sCJD versus mimics, VILIP-1 provided the strongest discrimination (AUC 0.83), with mean higher levels in sCJD (NPQ 13.33+/-1.0 versus 12.25+/-0.9). In penalised regression, VILIP-1 was consistently selected as the strongest predictor of clinical progression. In survival analysis for every one NPQ increase in VILIP-1 the hazard of death increased by 25% (HR 1.25, 95% CI 1.10–1.41).

Plasma VILIP-1 is a promising diagnostic and prognostic biomarker for sCJD that may support earlier clinical decision-making and risk stratification in therapeutic studies.

Trontinemab: Brainshuttle™ AD proof-of-concept to pivotal TRONTIER 1 and 2 studies in early symptomatic AD

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Background: Trontinemab is a novel bispecific 2+1 Brainshuttle™ amyloid β-targeting monoclonal antibody (mAb) engineered for transferrin receptor 1-mediated transcytosis across the blood-brain barrier. The Brainshuttle™ active transport mechanism improves mAb bioavailability and target engagement in the brain.

Methods: Brainshuttle™ AD is an ongoing Phase Ib/IIa study (NCT04639050) assessing the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of trontinemab in individuals with mild cognitive impairment or mild-to-moderate Alzheimer's disease (AD).

The primary endpoints are incidence of adverse events and amyloid plaque burden reduction, measured using amyloid positron emission tomography (PET) imaging (positivity threshold: ≤24 Centiloids).

Results: Interim data show dose-dependent lowering of amyloid plaques with trontinemab 3.6 mg/kg; in participants with available PET scans, 92% (n=54/59) reached amyloid removal below the positivity threshold after 28 weeks (mean reduction: 99 Centiloids from baseline). Early, pronounced effects on downstream cerebrospinal fluid and plasma biomarkers were observed. The safety and tolerability profile of trontinemab was favourable, with low incidence of amyloid-related imaging abnormalities.

Conclusion: Trontinemab demonstrated rapid and robust amyloid plaque reduction in participants with AD, supporting initiation of two identical Phase III TRONTIER 1 and 2 studies evaluating efficacy and safety in early symptomatic AD; TRONTIER study designs are detailed herein.

Outcomes of referrals to a regional NPH MDT in 2024 and comparison with previous years

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Idiopathic Normal Pressure Hydrocephalus (iNPH) is a syndrome of enlarged ventricles with symptoms affecting gait, cognition, and urinary function(1). Diagnosis can be challenging as the symptoms overlap with other neurodegenerative disorders. The primary treatment is shunt insertion(2), but correct diagnosis is crucial.

We reviewed NPH referrals to a regional MDT in 2024 and compare the management of the referred patients to the 2021 Japanese NPH guidelines(1). We compare the findings with data from 2022, and from 2017-2019 prior to the NPH MDT being introduced.

More patients were referred in 2024 than in 2022 and in 2017-2019 (131 vs 89 and 87). Only 66% of patients in 2024 met the criteria for possible iNPH compared to 87% in 2022 and 80% in 2017-2019, but with improvements in documentation. 64% had a positive response to LP in 2024 and 2022, and 59% in 2017-2019.

The rate of patients referred for shunt insertion was 17/yr in 2017-2019, 14/yr in 2022 and 20/yr in 2024, with better shunt outcomes reported in 2022 and 2024, and fewer returns to theatre compared to 2017-2019. RAD scores were lower in patients who responded to shunting. We have deviated from the 2021 guidelines at points with increased experience.