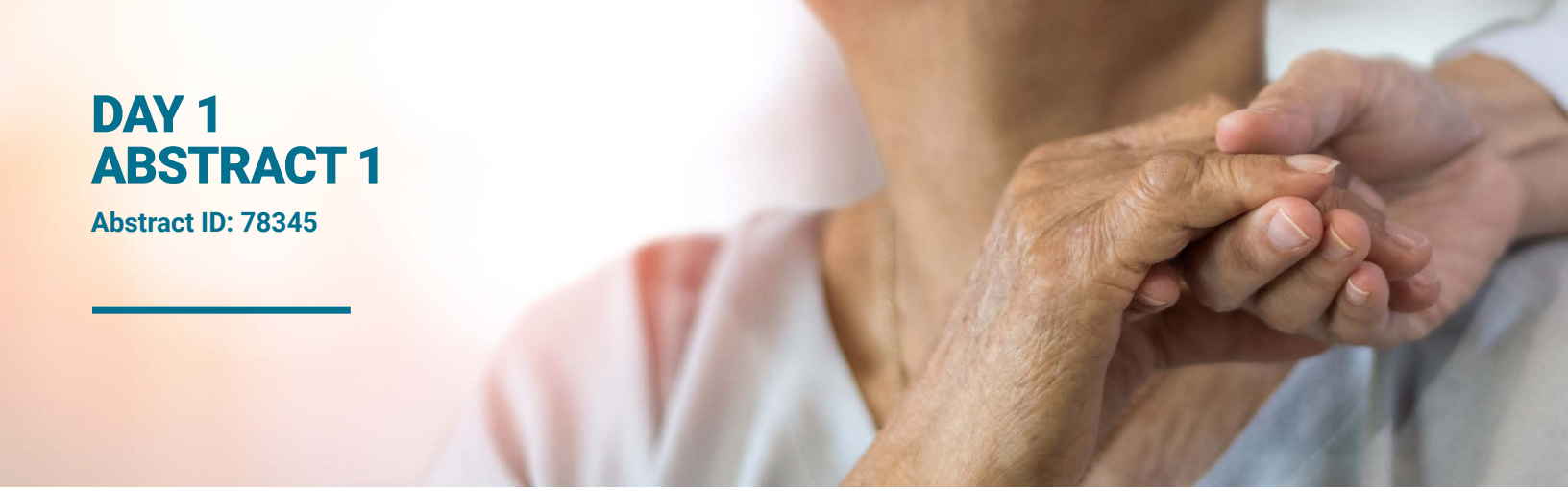

DAY 1
ABSTRACT 1

Abstract ID: 78345

Distinct associations between tau PET and cognitive impairment across brain regions and cognitive domains in Alzheimer's disease

Abstract:

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Background:

Compared with biofluid-biomarkers, tau-PET shows stronger association with cognitive impairment (Ossenkoppele,R-2021) and decline, and better detects Alzheimer's disease (AD) pathology (Coomans,EM-2022; Smith,R-2022). Conventionally, tau-cognition relationship has been evaluated between global cortical tau-PET and composite cognitive scores. However, tau-PET binding patterns are heterogenous, with regional binding showing strong correlations with domain-specific cognitive performance and decline. The goal of this study was to evaluate domain-specific patterns of tau-PET at baseline and in change-from-baseline (CFB) in symptomatic AD patients.

Method:

Amyloid-positive participants (n=172) with a clinical diagnosis of mild-cognitive-impairment (n=97) or dementia due to AD (n=76) and amyloid-negative healthy-controls (n=68) underwent a 18Flortaucipir tau-PET and neuropsychological testing (AV1451-A05:NCT02016560) at baseline and 18months. Observed cognitive scores in impaired patients were normalized to age-adjusted outcomes in healthy-controls at baseline and 18months (Ossenkoppele,R-2015). These scores were subsequently averaged within the episodic-memory, semantic-memory, language, visuospatial, and executive function cognitive domains (Malpetti,M-2022). Standardized uptake value ratio (SUVr) in automated-anatomical-labelling regions (Tzourio-Mazoyer,M-2002) and AD-specific region (MUBADA; Devous,M-2017) was calculated in reference to cerebellum-crus. The CFB (18months-baseline) in SUVr and domain-specific sub-scores were calculated for all participants. Correlations between global SUVr versus composite cognitive score and regional SUVr versus domain-specific scores at baseline and CFB were calculated.

Result:

Differential cross-sectional tau-PET patterns showed significant negative associations with domain-specific cognitive performance (Fig.1A). When evaluated longitudinally, higher global CFB in tau-PET SUVr showed no-to-modest correlation with cognitive decline (Fig.2: ADAS-Cog11=0.012, FAQ=-0.015, MMSE=-0.210, CDR-SB=0.014), however, heterogeneous associations were observed at the regional- and voxel-level (Fig.1B,Fig.3), ranging from maximum of r=-0.45 (p<0.001; frontal-inferior and visuospatial) to minimum of r=-0.002 (p<0.1; lingual and episodic). Increase in tau-PET signal was associated with greater cognitive decline (i.e. visuospatial function: predominantly frontal; executive function: parietal and prefrontal; semantic-memory: superior temporal region). An extensive and asymmetric tau-PET pattern (L>R) in frontal and occipital regions was related to language.

Conclusion:

We found associations between patterns of tau accumulation and domain-specific cognitive decline in MCI and AD dementia. After validations using larger datasets, these relationships can supplement widely used associations between global tau-PET and composite cognitive scores and, therefore, enhance tau PET-guided and patient-centered staging, prognosis, and response assessment.

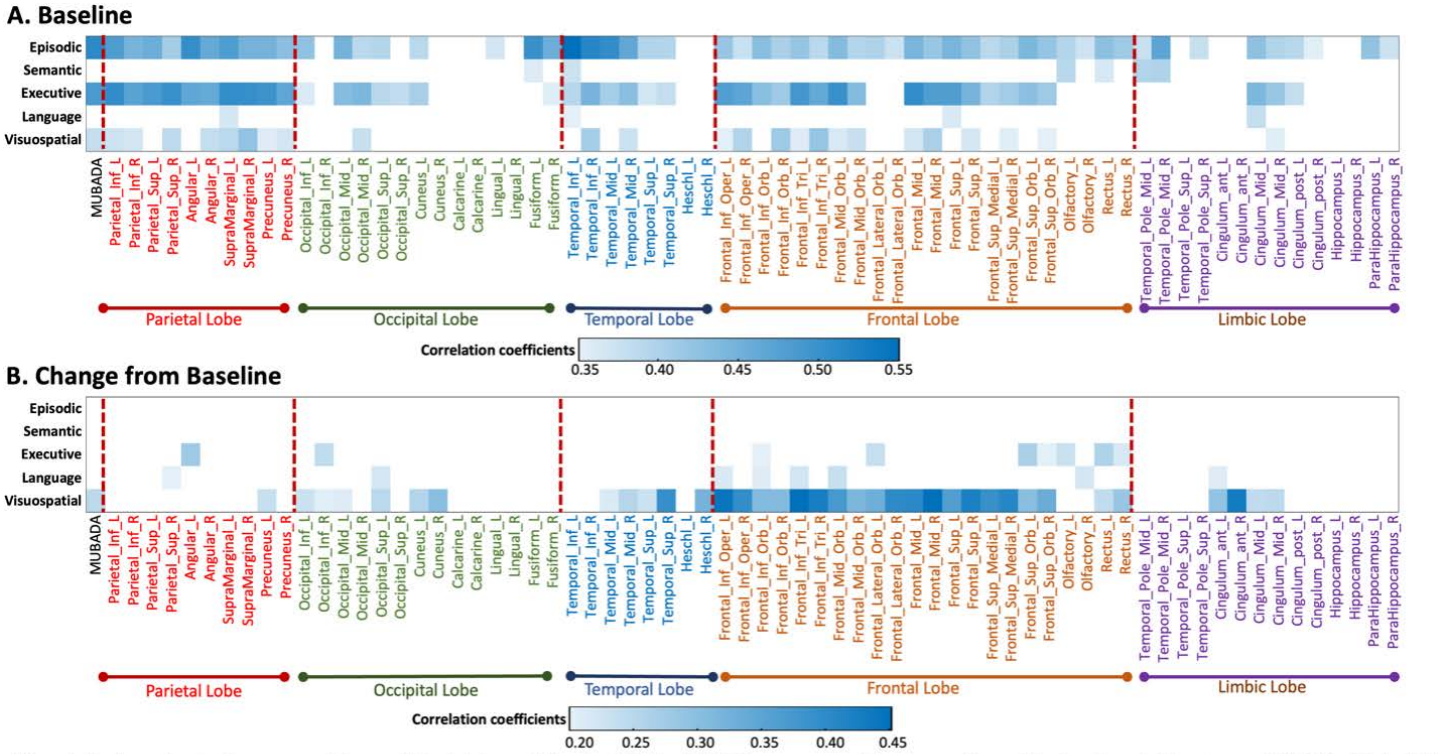

Figure 1: Heatmap showing Pearson correlation coefficients between (A) regional AAL tau-PET SUVr measures and domain-specific cognitive impairment at baseline, and (B) CFB in AAL tau-PET SUVr measures and domain-specific cognitive decline over a period of 18 months. Cerebellum crus1 was used as a reference region.

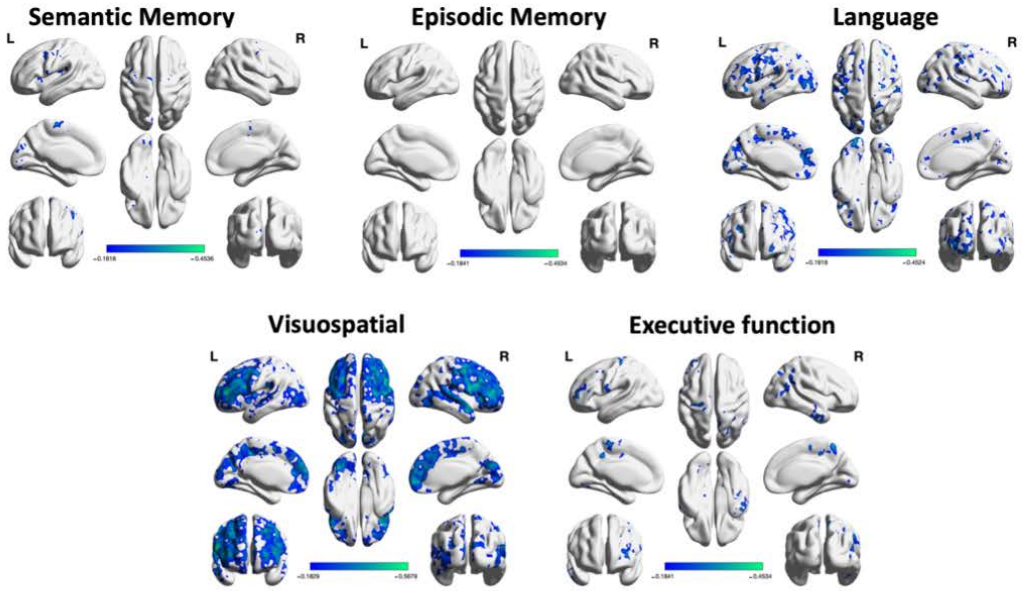

Figure 3: Voxel-wise multiple regression analysis showing the associations between CFB in tau PET SUVr and domain-specific sub-scores. All colored voxels are p<0.05 threshold. The negative values of CFB in domain-specific sub-scores indicate higher cognitive decline; therefore, correlations between increase in tau accumulation and higher cognitive decline over time are negative.

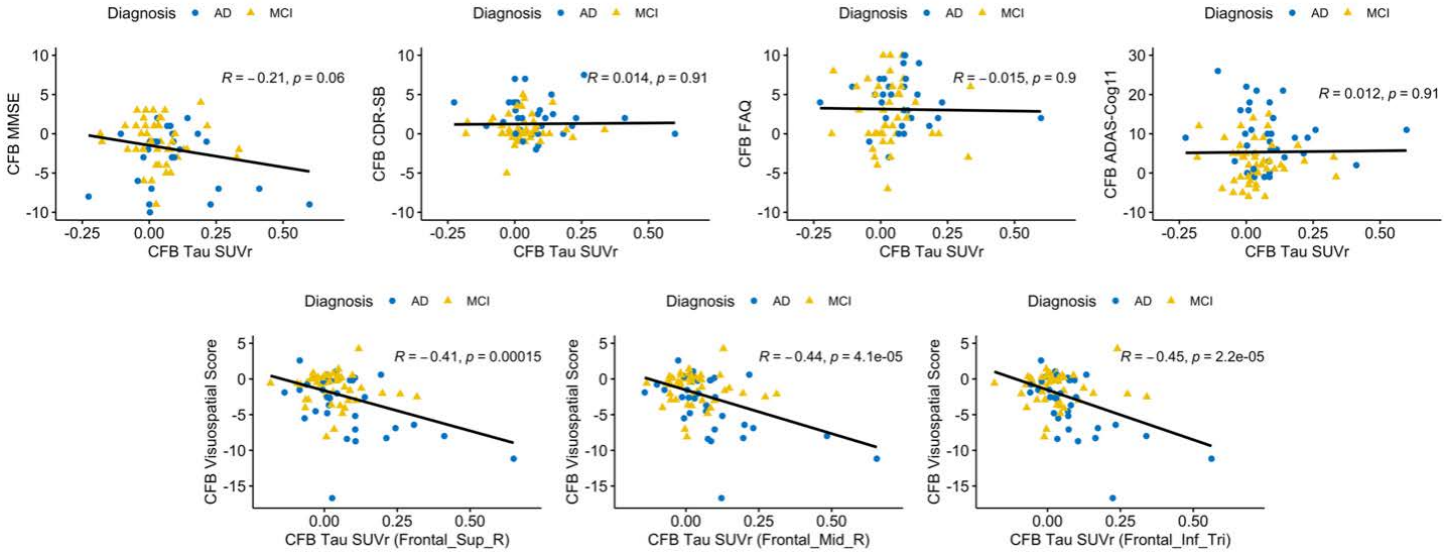

Figure 2: Top-row: Correlation plots between CFB in global cognitive scores (MMSE, CDR-SB, FAQ, ADAS-Cog11) and global cortical tau-PET SUVr (MUBADA). **Bottom-row:** Representative correlation plots between CFB in regional tau-PET SUVr measurements and domain-specific cognitive decline. Cerebellum crus1 was used as a reference region. CFB=Change from baseline, MMSE=Mini-Mental State Examination, ADAS-Cog11=Alzheimer's Disease Assessment Scale-Cognitive subscale, CDR-SB=Clinical Dementia Rating-Sum of Boxes, FAQ= Functional Activities Questionnaire.