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BIOMARKERS

POSTER PRESENTATION

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NEUROIMAGING

Connectivity as a universal predictor of tau spreading in typical and atypical Alzheimer's disease

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Abstract

Background: There is a strong link between tau and progression of Alzheimer's disease (AD), necessitating an understanding of tau spreading mechanisms. Prior research,

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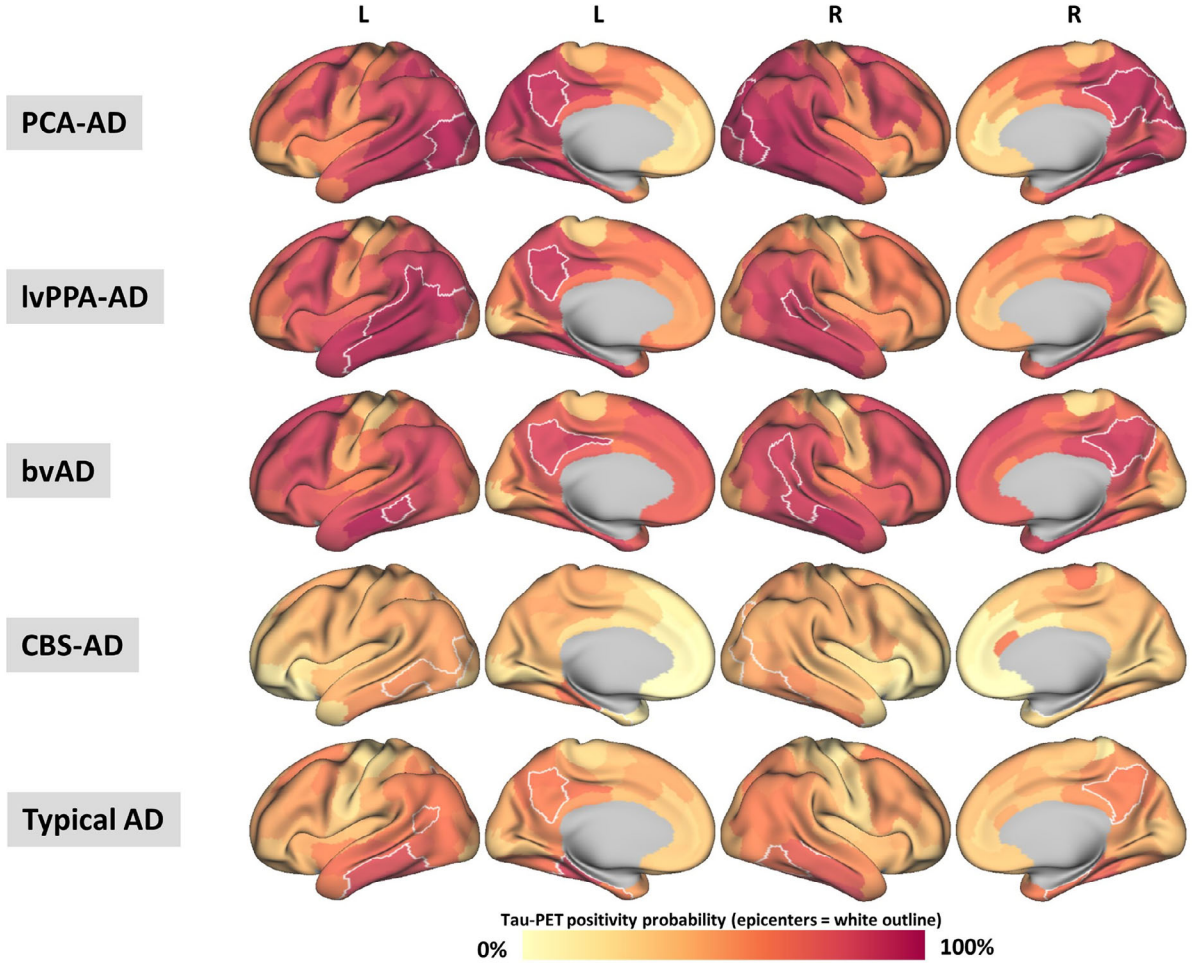
predominantly in typical AD, suggested that tau propagates from epicenters (regions with earliest tau) to functionally connected regions. However, given the constrained spatial heterogeneity of tau in typical AD, validating this connectivity-based tau spreading model in AD variants with distinct tau deposition patterns is crucial.

Method: We included 269 amyloid-β-positive (PET/CSF) individuals with clinically diagnosed atypical AD (113 posterior cortical atrophy, PCA-AD; 83 logopenic variant primary progressive aphasia, lvPPA-AD; 33 behavioural variant AD, bvAD; 40 corticobasal syndrome, CBS-AD) and 68 with typical AD from 12 international cohorts, who underwent tau-PET (54% [^{18}F]AV1451/[^{18}F]flortaucipir/Tauvid, 27% [^{18}F]MK6240, 19% [^{18}F]PI2620). Using Gaussian mixture modeling including amyloid-β-negative controls, cross-sectional tau-PET standardized uptake value ratios within Schaefer-200 atlas regions were transformed to tau positivity probabilities. Tau epicenters were defined as the 5% regions with highest tau positivity probabilities. For each variant, the association between functional connectivity-based distance (using the 30% strongest positive region-to-region connections of a group-average connectivity matrix from ADNI elderly controls) and tau-PET covariance (group-average correlation per region pair) was assessed through linear regression, adjusting for age, sex, site, and Euclidean distance. Regions were categorized based on functional proximity to the epicenter (quartiles 1-4) and tau positivity probabilities were assessed accordingly.

Result: Tau positivity probabilities matched clinical variants, with a posterior pattern in PCA-AD, left-hemispheric dominant pattern in lvPPA-AD, widespread pattern in bvAD, sensorimotor cortex involvement in CBS-AD, and temporo-parietal predominance in typical AD (Figure 1). In line with this, tau epicenters were highly heterogeneous across variants (Figure 1). In all variants, greater tau-PET covariance was associated with shorter functional connectivity-based distance (Figure 2). We observed that regions in closer functional proximity to the epicenter exhibited higher tau positivity probabilities than regions functionally further away ($p<0.05$, Figure 3).

Conclusion: This multi-center study shows that the brain's functional architecture serves as a universal predictor of tau spreading in AD. Since tau is a key driver of neurodegeneration and cognitive decline in AD, this finding holds potential for personalized medicine and defining participant-specific endpoints in clinical trials.

Figure 1: Tau-PET positivity probabilities and epicenters across AD variants



Group-average tau-PET positivity probability mapping showed a posterior tau-PET pattern in PCA-AD, left-hemispheric dominant pattern in lvPPA-AD, widespread pattern in bvAD, lack of sparing of the sensorimotor cortex in CBS-AD, and temporo-parietal predominance in typical AD. Tau epicenters (white outline; only epicenter probabilities ≥20% are shown) generally matched those regions with the highest tau positivity probabilities. Tau epicenters were defined as the 5% regions with highest tau positivity probabilities. Abbreviations: AD = Alzheimer's disease; bvAD = behavioural variant Alzheimer's disease; CBS = corticobasal syndrome; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography.

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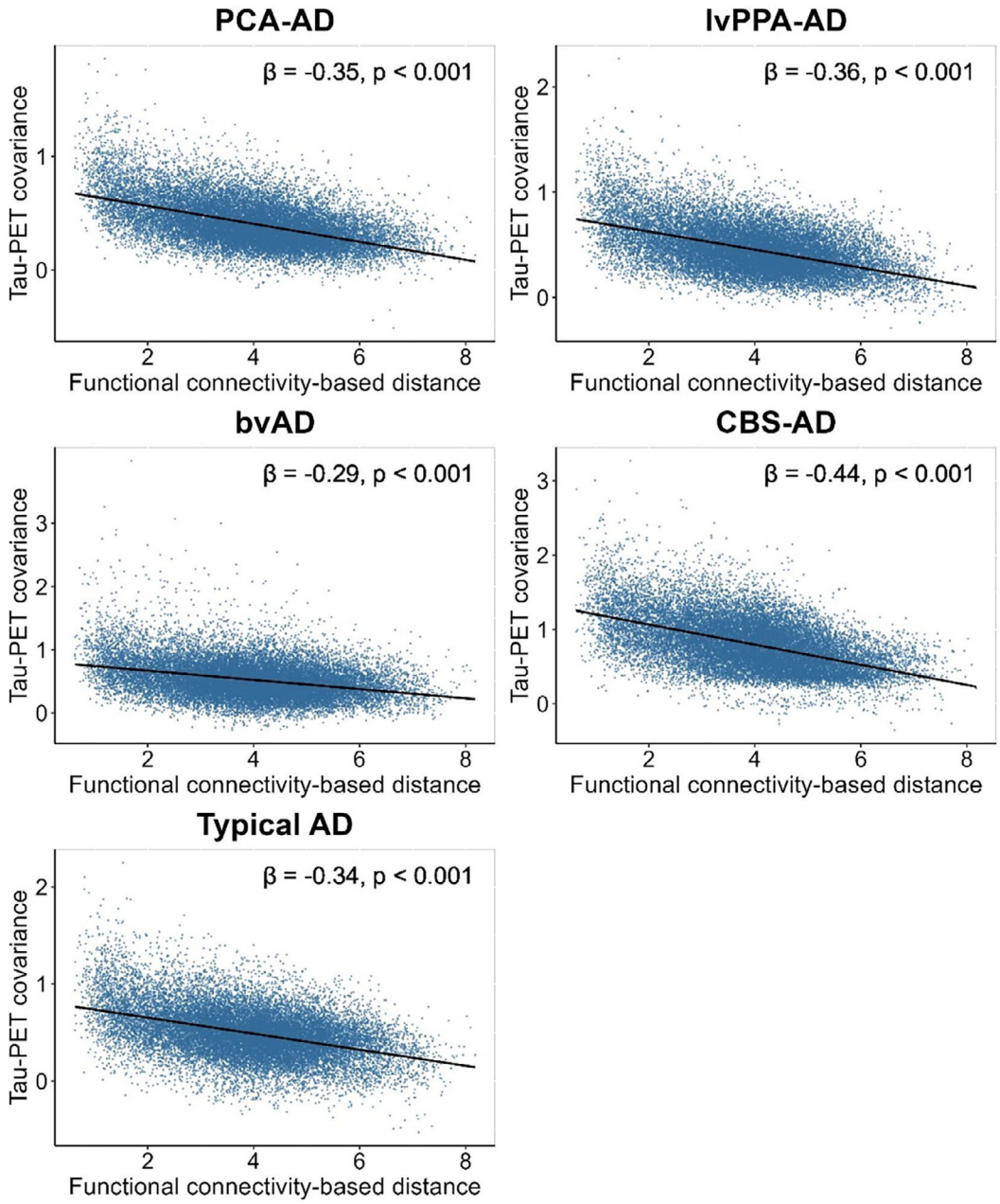
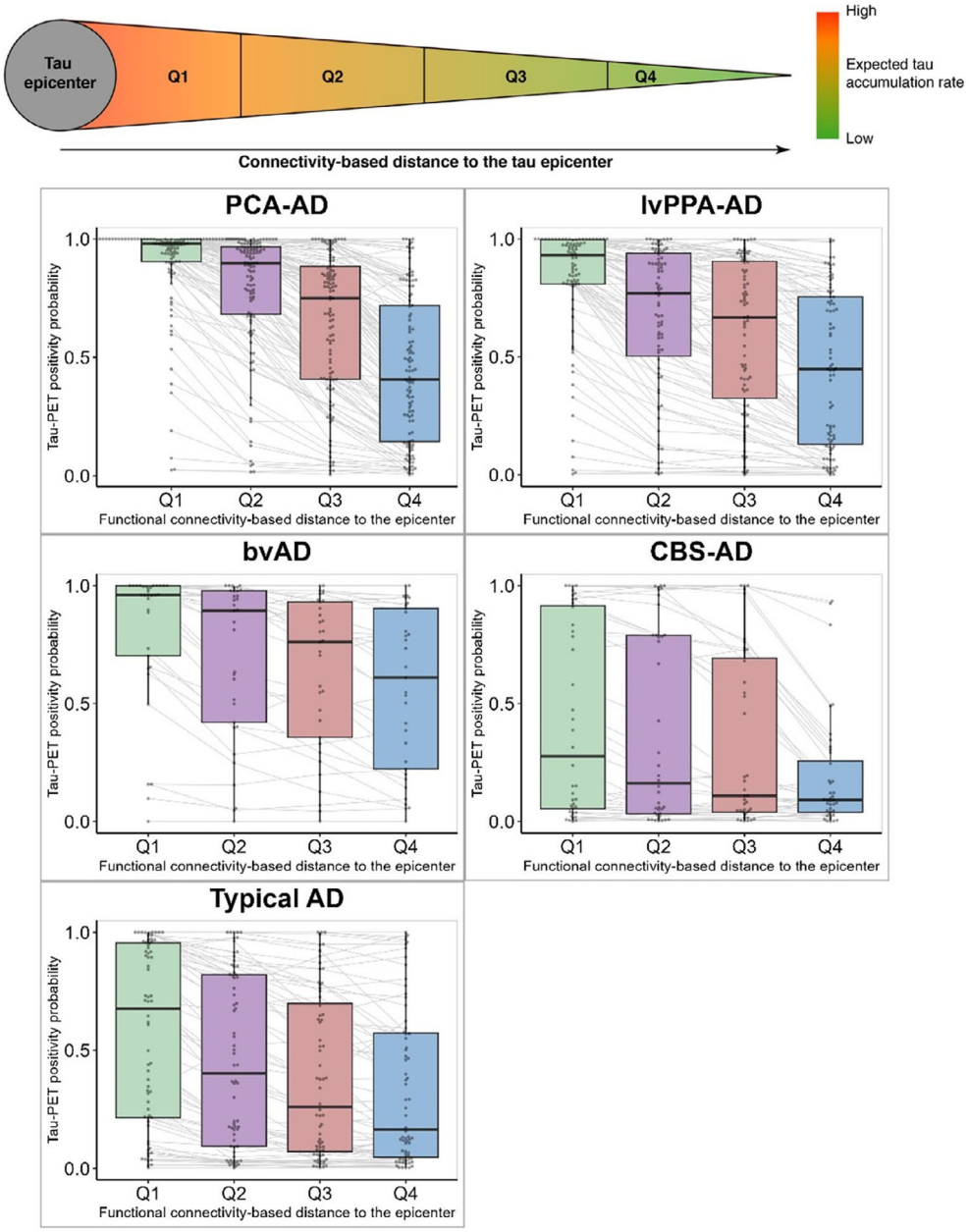
Figure 2: The relationship between functional connectivity and tau-PET covariance in AD



Linear regression analyses showed that, in all AD variants, greater tau-PET covariance was associated with shorter functional connectivity-based distance. Functional connectivity was defined as Fisher z-transformed Pearson correlations between fluctuations in the blood oxygen level-dependent (BOLD) signal of all possible region of interest (ROI) pairs. The 200 x 200 ROI functional connectivity matrix was density thresholded at 30% (i.e., 30% of the strongest positive connections were retained) and transformed to distance (strongly connected regions are 'close', while weakly or indirectly connected regions are 'distant'). Tau-PET covariance was defined as group-average Fisher z-transformed partial correlations between tau positivity probabilities of all possible ROI pairs, while adjusting for age, sex, site, and Euclidean distance. Abbreviations: AD = Alzheimer's disease; bvAD = behavioural variant Alzheimer's disease; CBS = corticobasal syndrome; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography.

Figure 3: Tau-PET positivity probabilities across regions of interest in AD



Paired Wilcoxon signed-rank tests between all quartiles showed that, in both atypical and typical AD, brain regions in closer functional proximity to the epicenter exhibited higher tau-PET positivity probabilities compared to brain regions functionally further away (all comparisons p<0.05). Functional connectivity was defined as Fisher z-transformed Pearson correlations between fluctuations in the blood oxygen level-dependent (BOLD) signal of all possible region of interest (ROI) pairs. The 200 x 200 ROI functional connectivity matrix was density thresholded at 30% (i.e., 30% of the strongest positive connections were retained) and transformed to distance (strongly connected regions are 'close', while weakly or indirectly connected regions are 'distant'). Regions were categorized into quartiles based on functional connectivity-based distance to the epicenter (Q1 = closest, Q4 = furthest). Abbreviations: AD = Alzheimer's disease; bvAD = behavioural variant Alzheimer's disease; CBS = corticobasal syndrome; lvPPA = logopenic variant primary progressive aphasia; PCA = posterior cortical atrophy; PET = positron emission tomography; Q = quartile.