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BIOMARKERS

PODIUM PRESENTATION

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NEUROIMAGING

Amyloid-associated hyperconnectivity drives tau spreading across connected brain regions in Alzheimer's disease

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Abstract

Background: In Alzheimer's disease, Aβ triggers tau spreading which drives neurodegeneration and cognitive decline. However, the mechanistic link between Aβ and tau remains unclear, which hinders therapeutic efforts to attenuate Aβ-related tau accumulation. Preclinical research could show that tau spreads across connected neurons in an activity-dependent manner, and Aβ was shown to trigger neuronal hyperactivity and hyperconnectivity. Therefore, we hypothesized that Aβ induces neuronal hyperactivity and hyperconnectivity, thereby promoting tau spreading from initial epicenters across connected brain regions.

Methods: From ADNI, we included 140 Aβ-positive subjects across the AD spectrum plus 69 Aβ-negative controls, all with baseline amyloid-PET, 3T resting-state fMRI and longitudinal Flortaucipir tau-PET data. For validation, we included cross-sectional tau-PET, amyloid-PET and resting-state fMRI data of 345 preclinical AD patients from A4. PET and fMRI data were parceled into 200 cortical ROIs, ROI-wise longitudinal tau-PET change rates were computed using linear mixed models. Resting-state fMRI connectivity was computed across the 200 ROIs. Subject-specific tau epicenters were defined as 5% of ROIs with highest baseline tau-PET. Further, we included post-mortem brain tissue from 5 AD patients vs. 4 controls stained for Aβ and c-Fos, i.e. a marker of ante-mortem neuronal activity.

Results: In the AD spectrum cohort, we confirmed that Aβ induces hyperconnectivity of temporal lobe tau epicenters (Figure 1) to posterior brain regions that are highly vulnerable to tau accumulation in AD (Figure 2A-C). This was fully replicated in the

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validation cohort of preclinical AD patients with low cortical tau-PET, suggesting that the emergence of Aβ-related hyperconnectivity precedes neocortical tau spreading (Figure 2D). Supporting that Aβ-associated fMRI-based hyperconnectivity may mirror neuronal hyperactivity, we found that neurons in AD post-mortem tissue expressed higher levels of c-Fos compared to controls, i.e. a Calcium-sensitive marker of ante-mortem neuronal activity (Figure 3). Lastly, using longitudinal tau-PET, we confirmed that Aβ-related connectivity increases of the tau epicenters to posterior brain regions mediated the effect of Aβ on tau accumulation and triggered faster tau spreading (Figure 4).

Conclusions: Our translational results suggest that Aβ promotes tau spreading via increasing neuronal activity and connectivity. Therefore, Aβ-associated neuronal hyperexcitability may be a promising target for attenuating tau spreading in AD.

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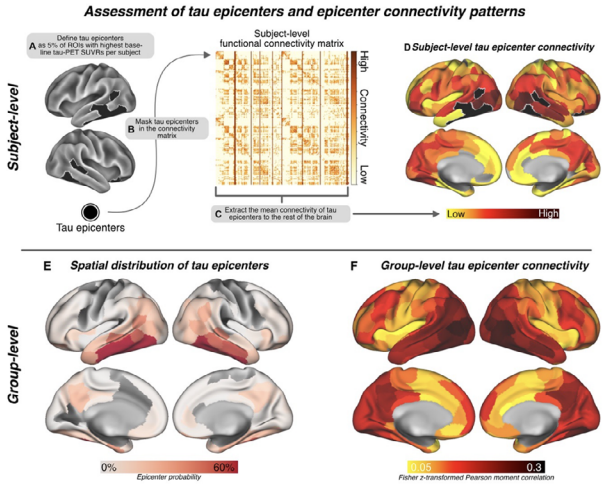
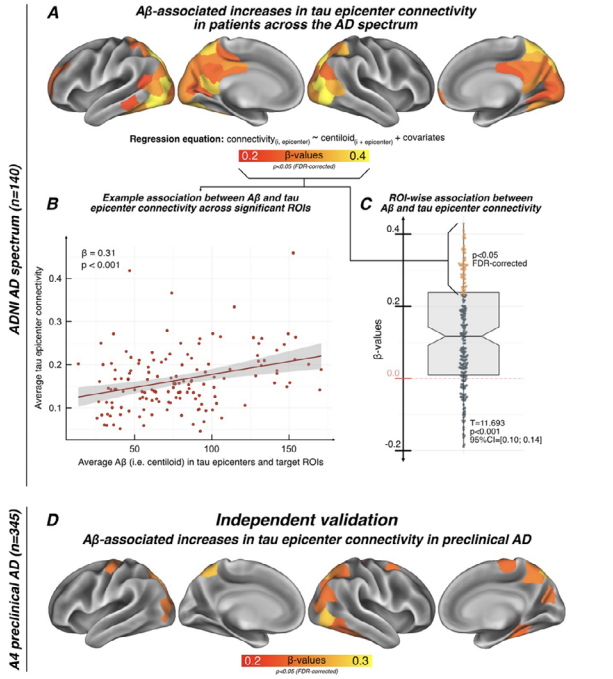
Figure 1:



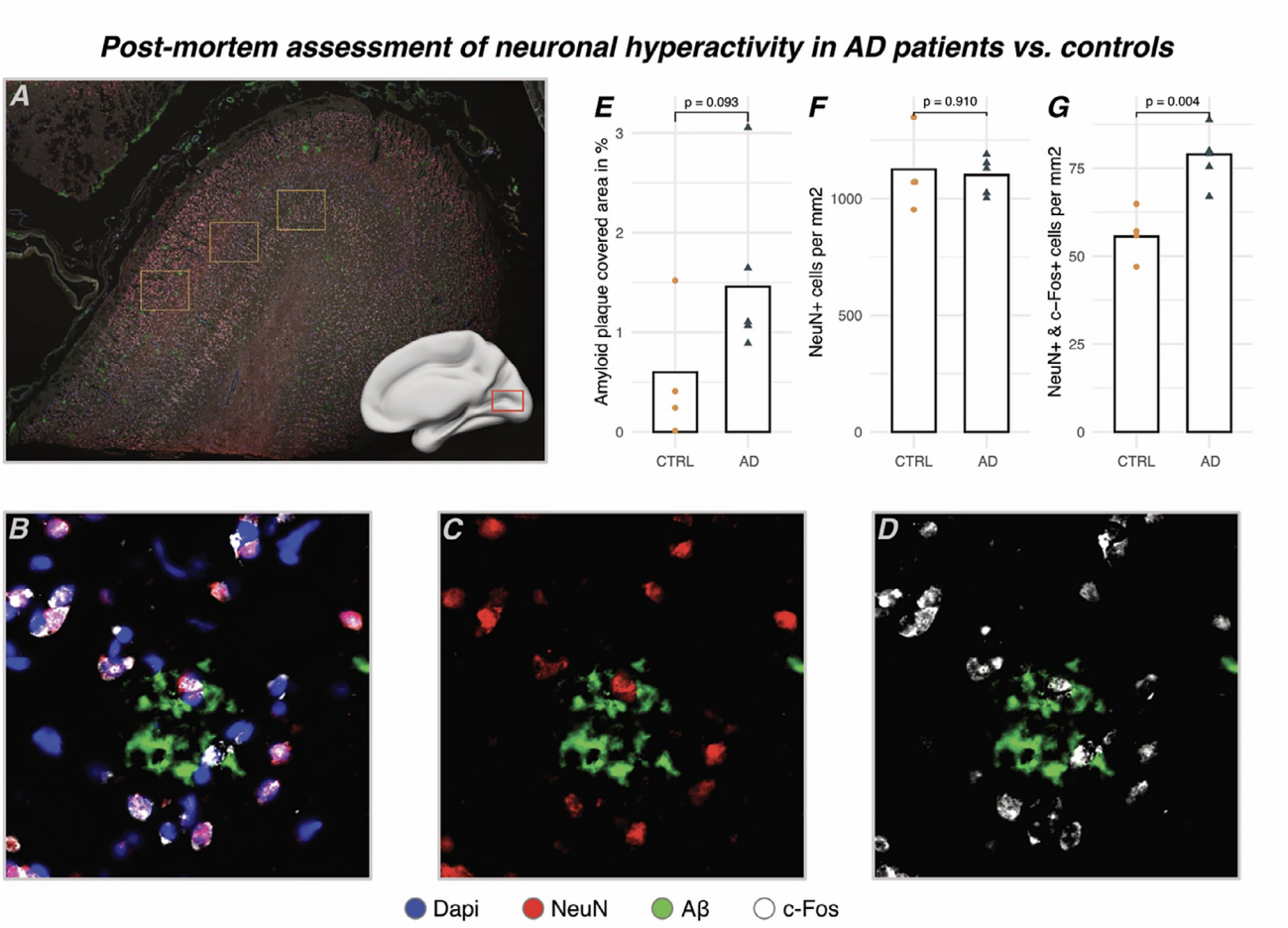
(A) For each participant 5% of brain regions with the highest baseline Tau-PET SUVRs were defined as tau epicenters. (B) Epicenters were applied to (C) subject-level connectivity matrices to (D) extract epicenter connectivity patterns. (E) Mapping of group-level epicenter probability and (F) epicenter connectivity

Figure 2:



(A) Association between Aβ and epicenter connectivity in ADNI. (B) average association between Aβ and connectivity for significant ROIs displayed in panel (A). (C) Un-thresholded distribution of beta values displayed in panel (A) showing that beta-values are overall significantly larger than zero. (D) Validation of the association between Ab and epicenter connectivity in A4.

Figure 3:



Post-mortem analyses of AD vs. control (CTRL) brains. (A) Overview of tissue stainings. (B) Merged image of Dapi (cell nuclei), NeuN (Neurons), Aβ (amyloid) and c-Fos (marker of ante-mortem neuronal activity), (C) merged image of NeuN and amyloid stainings and (D) merged image of Aβ and c-Fos staining. Group differences in (E) Amyloid-Plaque area, (F) neuron count (i.e. NeuN), and (G) the proportion of neurons with c-Fos positive signal.

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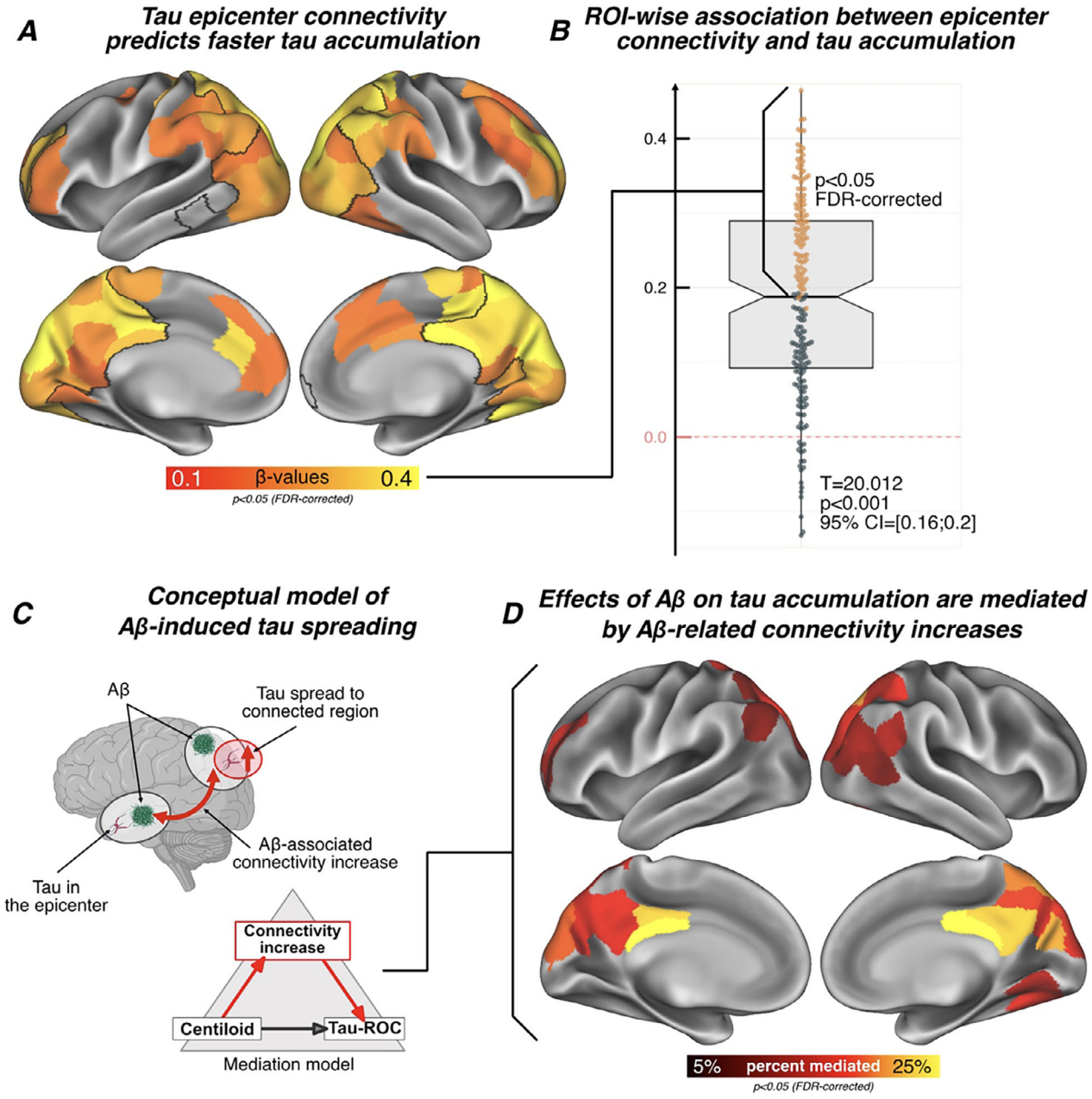
Figure 4:



(A) Association between stronger epicenter connectivity and faster tau accumulation in ADNI, including (B) the un-thresholded distribution of beta-values, showing an overall positive association between epicenter connectivity and faster tau accumulation. (C) Conceptual model of Ab-related tau spreading and (D) bootstrapped mediation showing that effects of Ab on tau accumulation are mediated by increased epicenter connectivity.