

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

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Abstract

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

Methods: From ADNI, we included 140 $A\beta$ -positive subjects across the AD spectrum plus 69 $A\beta$ -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 $A\beta$ and c-Fos, i.e. a marker of ante-mortem neuronal activity.

Results: In the AD spectrum cohort, we confirmed that $A\beta$ 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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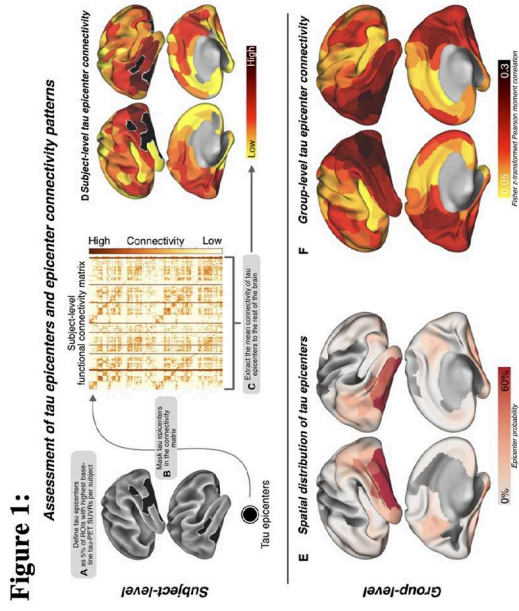
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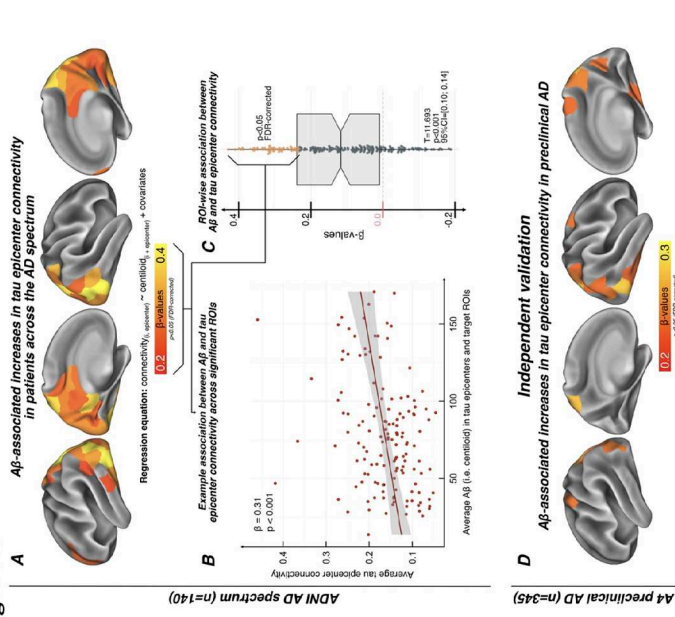
validation cohort of preclinical AD patients with low cortical tau-PET, suggesting that the emergence of A β -related hyperconnectivity precedes neocortical tau spreading (Figure 2D). Supporting that A β -associated fMRI-based hyperconnectivity may mirror neuronal hyperactivity, we found that neurons 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 A β -related connectivity increases of the tau epicenters to posterior brain regions mediated the effect of A β on tau accumulation and triggered faster tau spreading (Figure 4).

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



(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

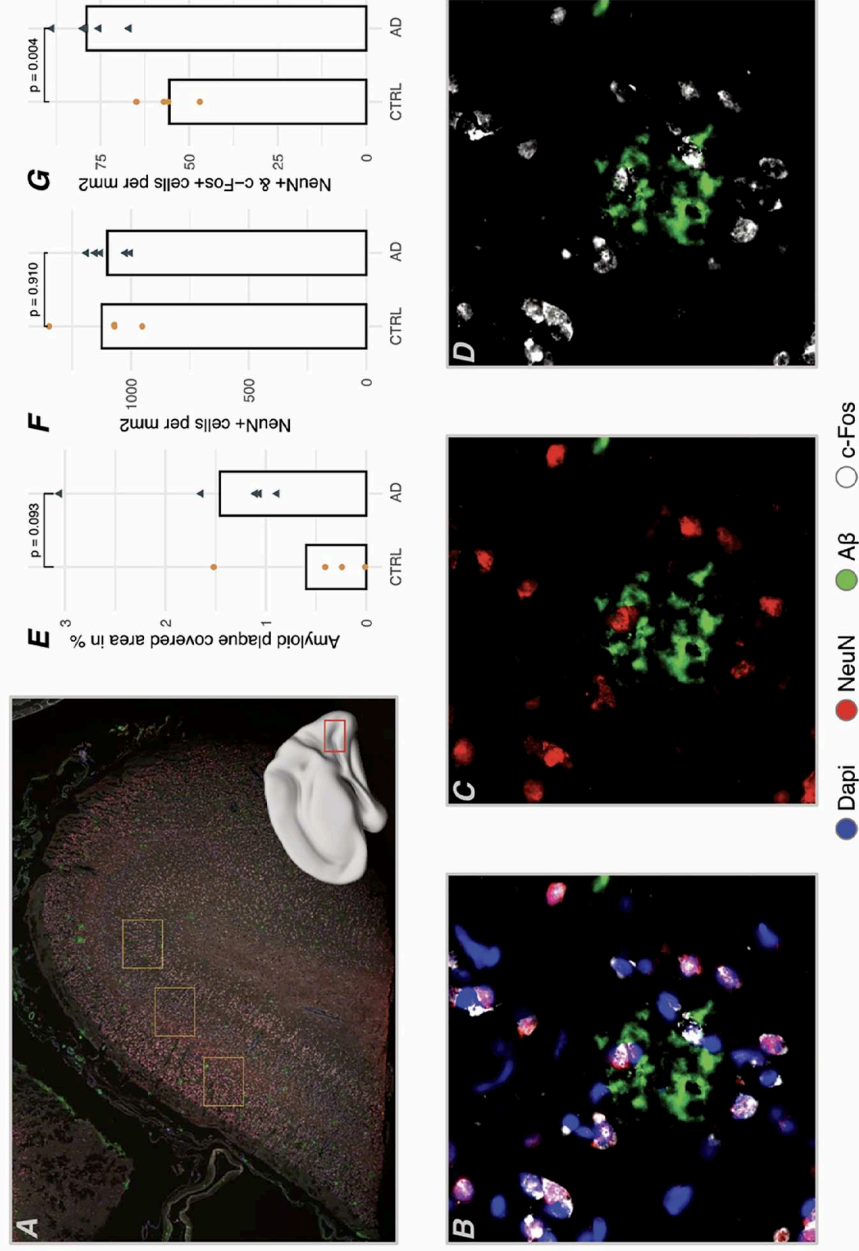
Figure 2:



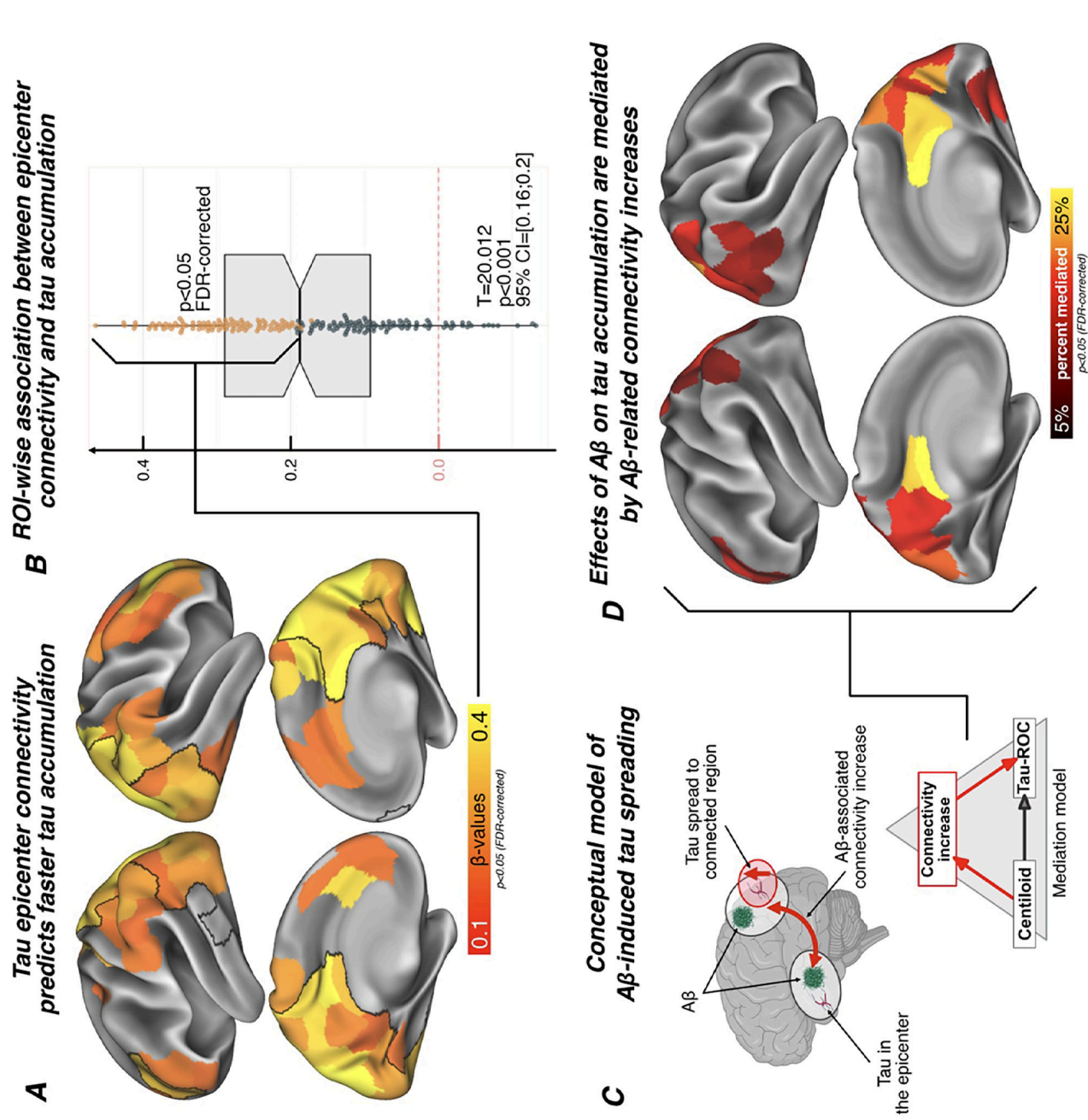
(A) Association between $A\beta$ and epicenter connectivity in ADNI. (B) average association between $A\beta$ and connectivity for significant ROIs displayed in panel (A). (C) Un-thresholded distribution of beta values displayed in panel (A) showing that beta-values are overall significantly larger than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

Figure 3:

Post-mortem assessment of neuronal hyperactivity in AD patients vs. controls



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) NeuN count (i.e. NeuN), and (G) the proportion of neurons with c-Fos positive signal.

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 A β -related tau spreading by increased epicenter connectivity.