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POSTER PRESENTATION

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NEUROIMAGING

Connector Hubs Accelerate the Spread of Tau Pathology in Alzheimer's Disease

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Abstract

Background: Tau accumulation drives neurodegeneration and cognitive decline in Alzheimer's Disease (AD) and preclinical research suggests that tau spreads transsynaptically across connected neurons. We translated tau spreading models to human neuroimaging data, showing that tau pathology spreads from circumscribed epicenters to connected regions in AD, following the architecture of functional brain networks. To further determine whether the topology of brain networks influences tau spreading dynamics, we investigated whether functional hubs (i.e. regions with strong inter-regional connections) accelerate tau spread in AD. Specifically, we hypothesized that more efficient communication from tau epicenters towards hubs that cross-link large-scale brain networks (connector hubs) rather than hubs that interconnect neighboring regions (local hubs) accelerates amyloid-related tau accumulation and cognitive decline (Figure 1).

Method: Longitudinal tau/amyloid-PET and cognitive data from two independent cohorts covering the AD spectrum (ADNI/A4 $n = 325/220$) were analyzed to examine amyloid-driven spatiotemporal tau accumulation patterns and cognitive decline. Structural- and functional-connectivity templates from healthy controls were used to model the connectional efficiency of subject-level tau epicenters (i.e. 10% of brain regions with highest baseline tau-PET) towards connector/local hubs (Figure 2). Using robust regression, we then tested whether more efficient communication of subject-level tau epicenters to connector vs. local hubs accelerated global tau accumulation, cognitive decline, and tau dissemination across networks.

Result: Supporting our hypotheses, we found that the effect of higher baseline amyloid-PET on faster global tau-PET increases was moderated by more efficient

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communication of tau epicenters towards connector relative to local hubs (ADNI/A4: β = 0.31/0.40, p<0.001/0.03), such that subjects with stronger epicenter communication to connector hubs showed an amplified effect of amyloid on global tau accumulation rates (Figure 3A). The same interaction models also predicted faster cognitive decline (ADNI/A4: β = -0.49/-0.34, p<0.001/0.04, Figure 3B), and larger extents of tau dissemination across functional networks (ADNI/A4: β = 0.6/0.36, p<0.001/0.04). All p-values were FDR-corrected.

Conclusion: Brain network topology shapes spatiotemporal tau accumulation rates and cognitive trajectories in AD. Specifically, stronger communication of tau epicenters with connector hubs that are characterized by widespread cross-network connections amplifies amyloid-related tau accumulation. This suggests that brain network architecture has a profound modulating impact on tau aggregation and disease progression in AD.

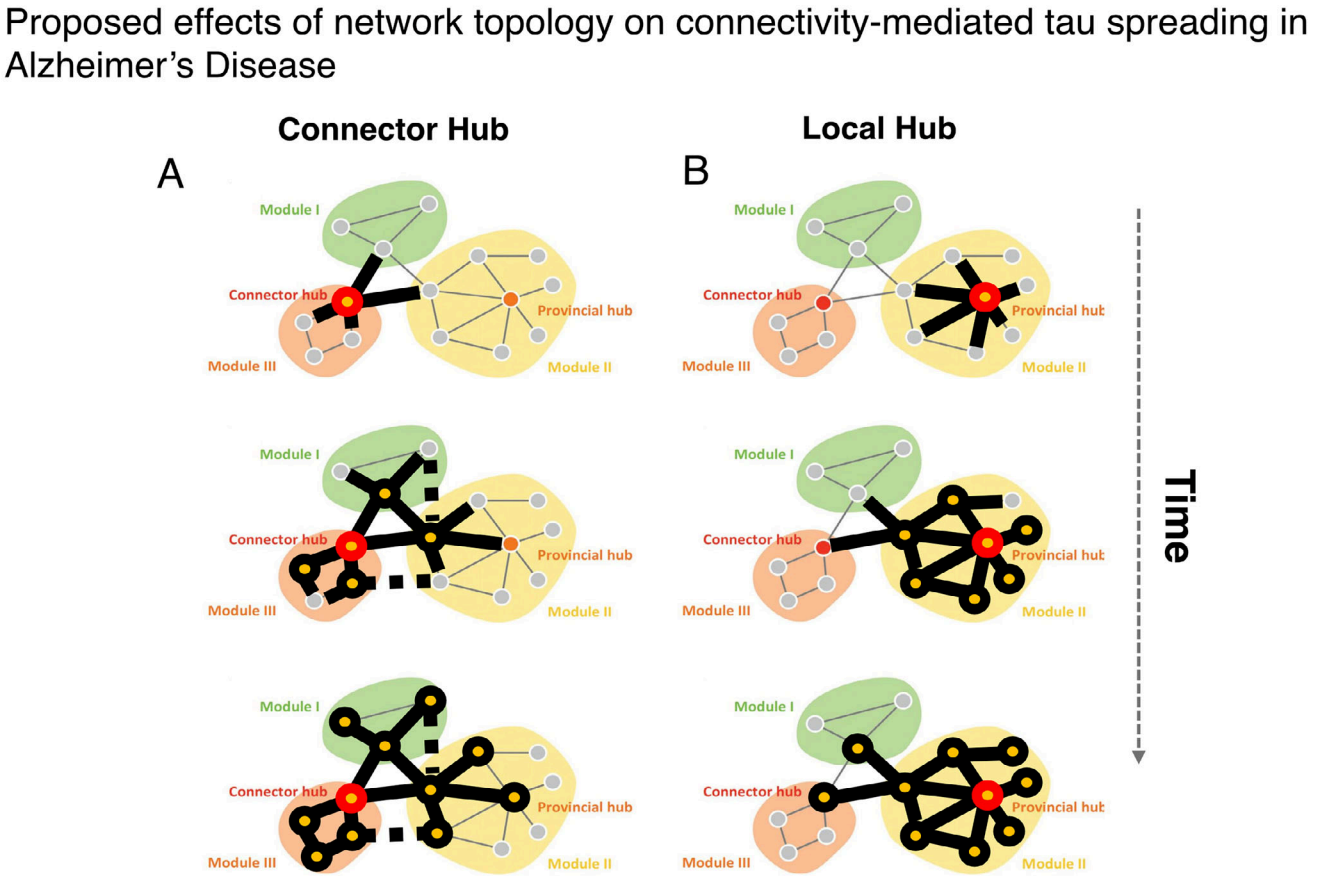

Figure 1. Proposed effects of network topology on connectivity-mediated tau spreading in Alzheimer's Disease, starting from initial tau epicenters (red circles). Dark yellow nodes are "infected", and black edges denote active tau dissemination. **(A):** Connector Hub mediated tau spreading is associated with more widely distributed tau pathology, followed by cascading effects and cross-module spreading (dotted black edges). **(B):** Local Hub mediated tau spreading is associated with more localized tau pathology and lower rates of tau accumulation.

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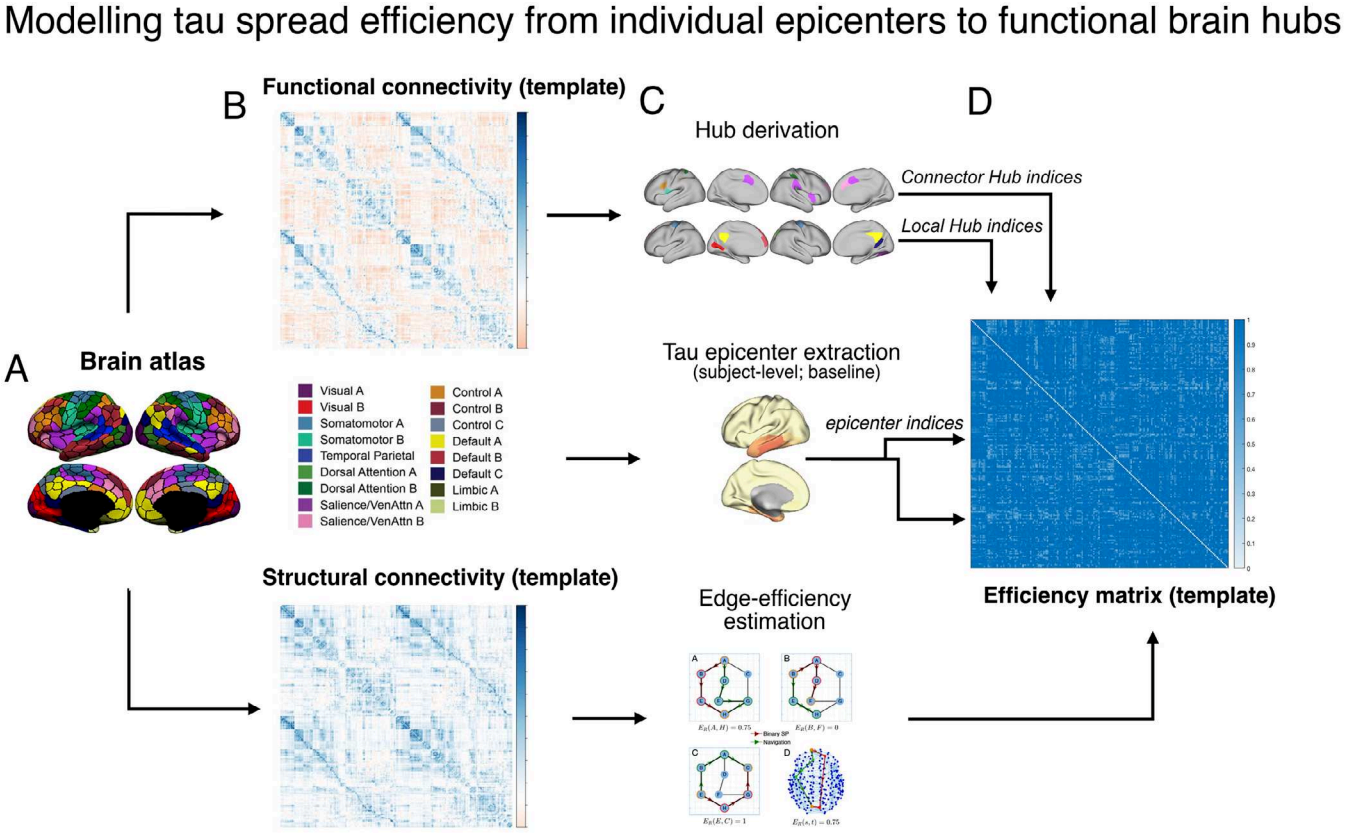

Figure 2. Network-based modelling of tau spread efficiency**. (A)***:* The Schaefer brain-atlas defines brain regions and their network membership. (**B):** Connectivity templates (functional and structural) capture network topology. **(C):** Hubs are derived from the functional templates (top); tau epicenters *(*10% of brain regions with highest baseline tau-PET) are defined in individual subjects (middle); the efficiency of communication amongst all pairs of brain regions is calculated based on structural connections (bottom). (**D):** The resulting efficiency matrix is indexed to derive communication efficiencies from individual epicenters towards hubs for further analyses.

Network topology moderates the relationship between global amyloid levels and disease progression in Alzheimer's Disease

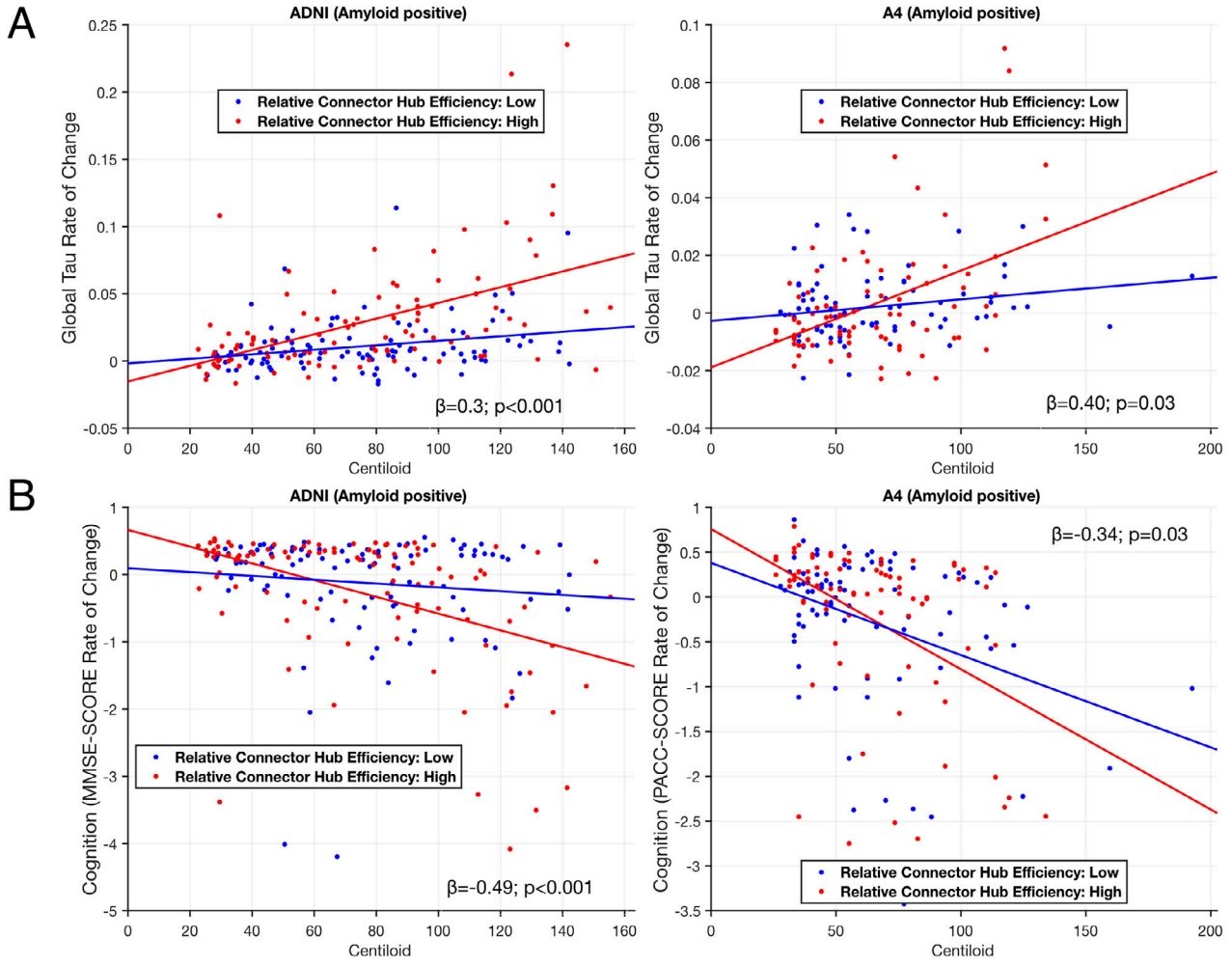

Figure 3. Across independent AD spectrum cohorts (ADNI/A4), relative connector hub efficiency moderates the impact of baseline amyloid levels (Centiloid; x-axis) on **(A):** Global tau accumulation rates and **(B):** Cognitive decline (ADNI: MMSE-Score; A4: PACC-Score). Linear regression lines represent group trends in amyloid-positive individuals. Displayed beta- and p-values indicate strength and significance of the interaction between amyloid-levels and relative connector hub efficiency. MMSE=Mini Mental Status Examination; PACC=Preclinical Alzheimer Cognitive Composite.