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NEUROIMAGING

Amyloid-induced neuronal hyperactivity and -metabolism are associated with faster tau accumulation in Alzheimer's Disease

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Abstract

Background: The link between amyloid (Aβ) and tau accumulation in Alzheimer's disease (AD) is still unknown, hindering therapeutic efforts to attenuate the Aβ-tau axis. Preclinical studies demonstrated that Aβ promotes hyperexcitatory neuronal activity and that tau spreads trans-synaptically in an activity-dependent manner. We recently showed that tau spreads across connected brain regions, and that Aβ-related connectivity increases promote tau spreading (Roemer-Cassiano et al., 2024). Yet, it is unclear whether Aβ-related hyperconnectivity indeed represents hyperexcitatory neuronal activity. To test this, we combined resting-state fMRI, FDG-PET and post-mortem data, to determine whether Aβ promotes neuronal hyperactivity, thereby driving tau spread in AD.

Methods: We first assessed the effect Aβ on neuronal hyperactivity with a novel algorithm to estimate the excitatory to inhibitory (E/I) ratio applied to resting-state fMRI in 145 amyloid-negative controls and 441 amyloid-positive subjects across the AD spectrum, who also underwent amyloid-PET. Second, we used glucose metabolism (FDG-PET) as a marker of neuronal activity in 638 amyloid-positive AD spectrum patients, with a subset (n = 215) of them having tau-PET at a later timepoint. Lastly, we analysed post-mortem data of 5 AD patients and 4 controls stained for c-Fos as a marker of ante-mortem neuronal activity.

Results: Resting-state fMRI-based E/I-ratio assessment in Aβ- controls showed biologically plausible stronger inhibition in association cortices (Figure 1A). In AD,

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we found an association between higher amyloid-PET SUVRs and a higher E/I ratio, consistent across diagnostic groups (Figure 1B-D), indicative of Aβ-associated hyperexcitatory neuronal activity. Second, we found within individuals, that higher regional amyloid-PET was linked to higher FDG-PET ($correlation_{amyloid\text{-}PET\ vs.\ FDG\text{-}PET}$: 95% CI [0.37,0.40] p-value <0.001), suggesting higher neuronal activity in Aβ-harbouring regions (Figure 2A). Similarly, we found post-mortem elevated neuronal c-Fos expression in AD brain tissue vs. controls, indicating higher ante-mortem neuronal activity (Figure 3G). Finally, we found that amyloid-PET-based prediction of subject-level future tau accumulation is improved when including regional FDG-PET (Figure 2B) and that FDG-PET-assessed hypermetabolism mediates subject-level effects of Aβ on subsequent tau accumulation (Figure 2C).

Conclusions: Aβ promotes an hyper-excitatory shift in neuronal activity that manifests in glucose hypermetabolism which promotes Aβ-related tau accumulation. Thus, Aβ-associated neuronal hyper-excitability is a potential target for attenuating the Ab-tau axis in AD.

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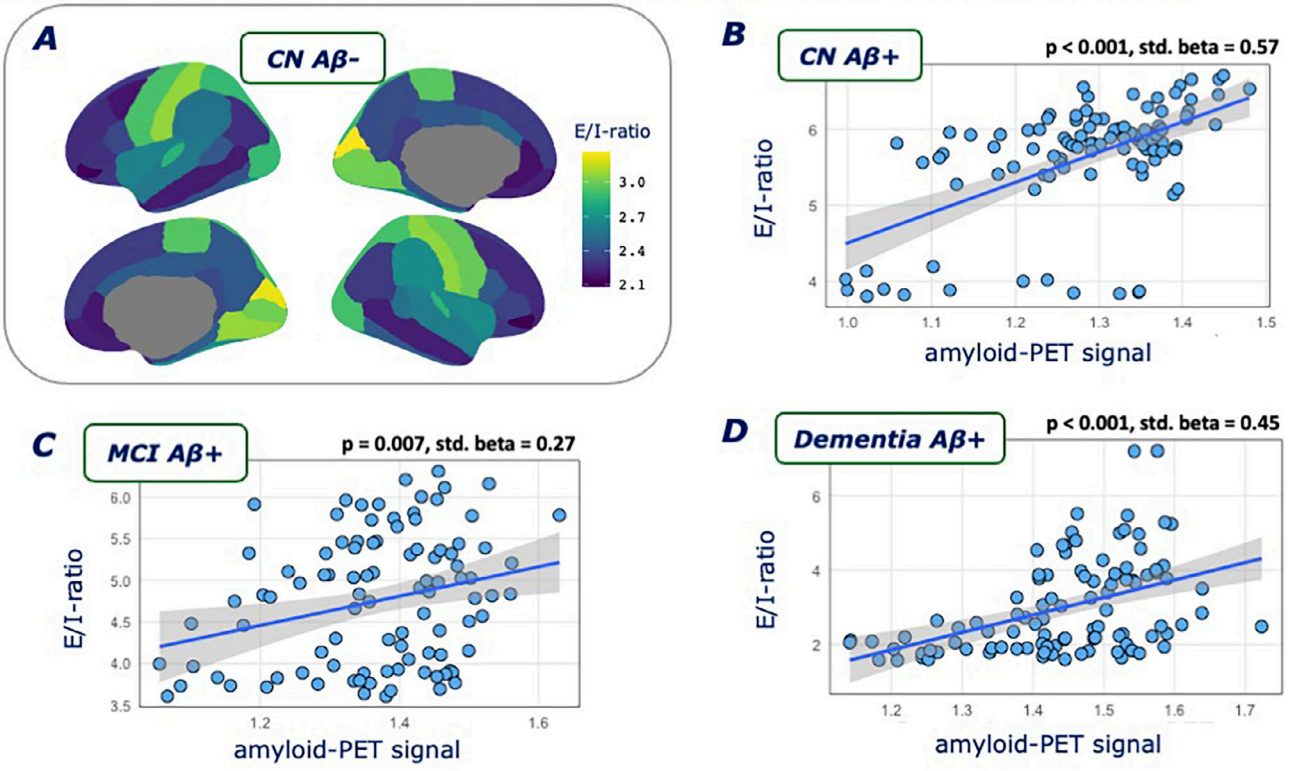
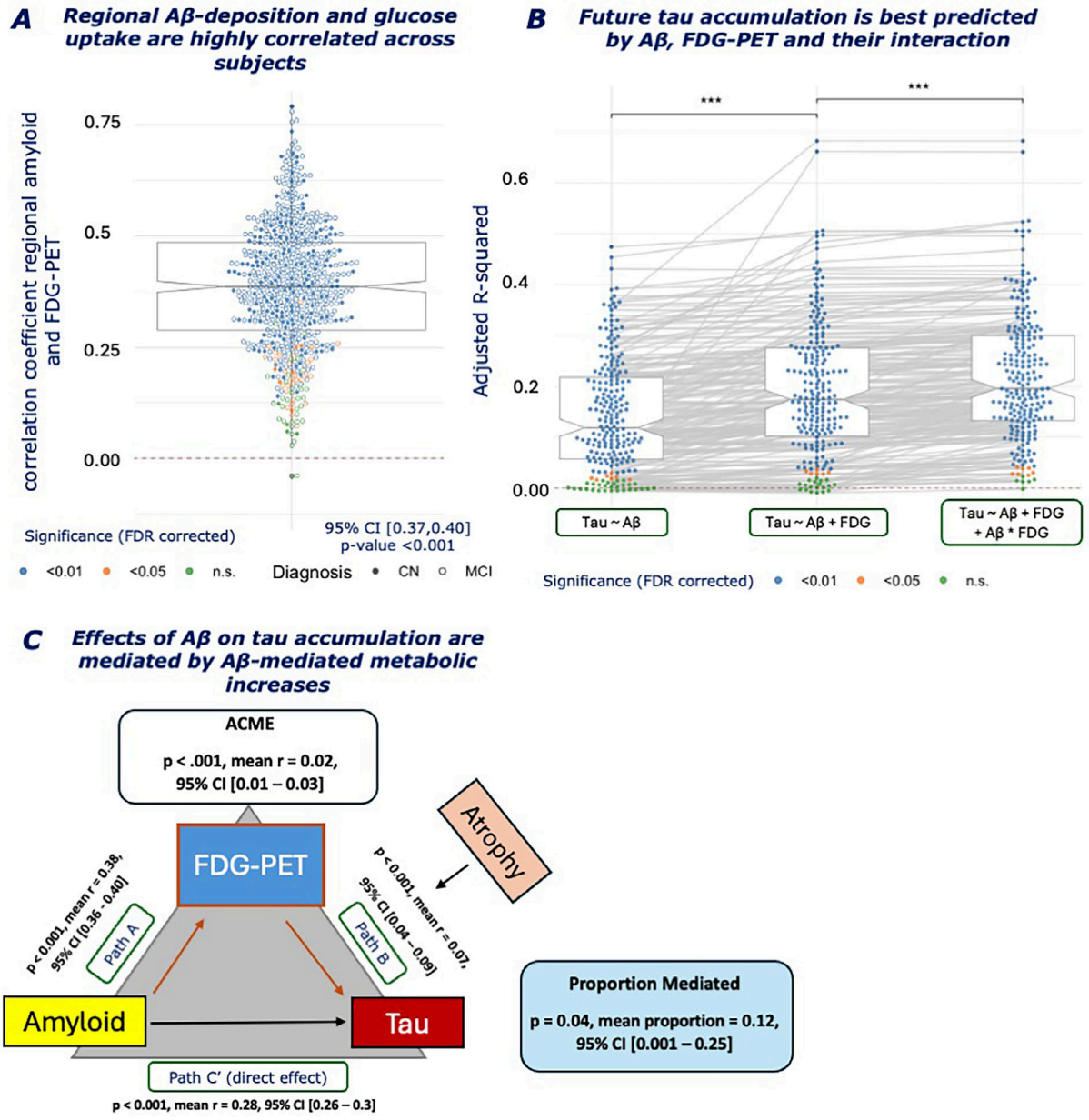
Figure 1

Regional Aβ-deposition and E/I-ratio are correlated across the AD spectrum



(A) *Surface rendering of the mean ROI-wise E/I-ratio estimation via the pFIC algorithm by Zhang et al., PNAS, 2024 in healthy controls; The distribution of the E/I-ratio in healthy controls matches biologically expected distributions (high in the occipital lobes, low in the frontal lobes), indicating biologically plausible E/I-ratio estimation by the pFIC algorithm;* ***(B-D)*** *Correlation analysis mean ROI-wise E/I-ratio estimation and regional amyloid- AV45-PET values across the Alzheimer's disease spectrum. Significantly positive correlations were found across all Aβ+ disease groups of the AD spectrum, indicating an excitatory shift in regions harbouring Aβ. E/I-ratio estimation and amyloid-PET data was parcellated to the Schaefer 100 homotopic atlas by Yan et al 2023.*

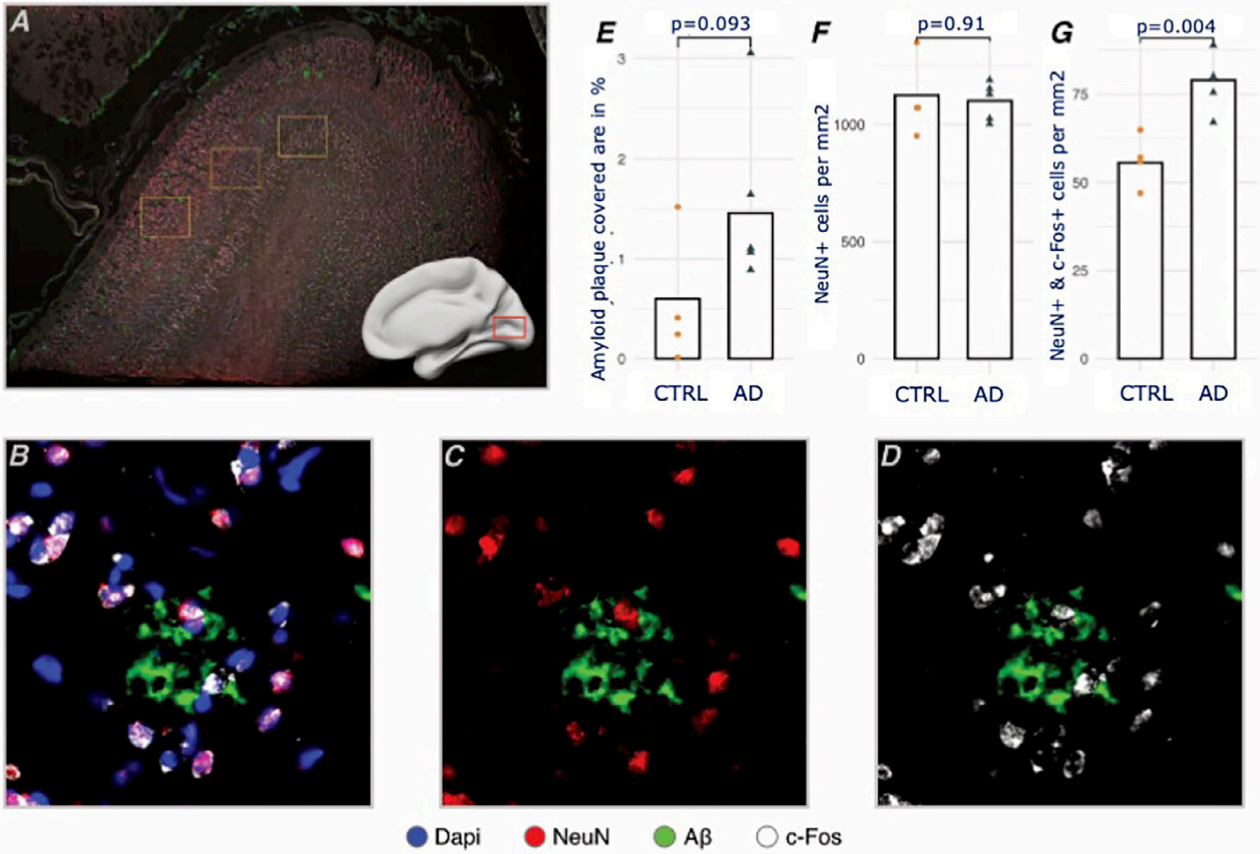
Figure 2



(A) Subject-wise correlation analysis of regional amyloid-PET signal in centiloid and regional FDG-PET signal. Overall, the correlation coefficients are significantly greater than zero (95% CI [0.37,0.40], p<0.001), indicating an overall positive correlation between Aβ-deposition and metabolism assessed via FDG-PET. **(B)** R-squared values of the model predicting future tau-PET signal based on centiloid, centiloid + FDG-PET and centiloid + FDG-PET + centiloid*FDG-PET, showing a significant better prediction for the last model. **(C)** Bootstrapped mediation analysis yielding the effect of Aβ on tau accumulation mediated by metabolism assessed via FDG-PET. The correlation of FDG-PET on tau is controlled for regional atrophy, based on MRI-assessed cortical thickness. The mean proportion mediated of the total effect of Aβ on tau accumulation is 12% (95% CI [0.001-0.25], p=0.04), indicating that the higher metabolism is a significant mediator of the influence of Aβ on tau. All analysis were corrected for multiple testing using the False Discovery Rate (FDR) method. Average Causal Mediated Effect (ACME); All PET data was parcellated to the Schaefer 200 atlas.

Figure 3

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



Post-mortem analyses of the occipital lobe of AD vs. control (CTRL) brains. ***(A)*** *Overview of tissue stainings.* ***(B)*** *Merged image of Dapi (cell nuclei), NeuN (Neurons), Aβ and c-Fos (marker of ante-mortem neuronal activity),* ***(C)*** *merged image of NeuN and Aβ stainings and* ***(D)*** *merged image of Aβ and c-Fos staining. Group differences in* ***(E)*** *Aβ-Plaque area, indicating a greater amount of Aβ pathology in the AD probes,* ***(F)*** *neuron count (i.e. NeuN), demonstrating the absence of significant neurodegeneration in the occipital lobe, and* ***(G)*** *the proportion of neurons with c-Fos positive signal. AD patients showed a significantly greater number of c-Fos positive neurons, indicating a higher ante-mortem neuronal activity in AD patients in the occipital lobes, where Aβ is the dominant pathology.*