

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 (A β) and tau accumulation in Alzheimer's disease (AD) is still unknown, hindering therapeutic efforts to attenuate the A β -tau axis. Preclinical studies demonstrated that A β 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 A β -related connectivity increases promote tau spreading (Roemer-Cassiano et al., 2024). Yet, it is unclear whether A β -related hyperconnectivity indeed represents hyperexcitatory neuronal activity. To test this, we combined resting-state fMRI, FDG-PET and post-mortem data, to determine whether A β promotes neuronal hyperactivity, thereby driving tau spread in AD.

Methods: We first assessed the effect A β 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 A β - controls showed biologically plausible stronger inhibition in association cortices (Figure 1A). In AD,

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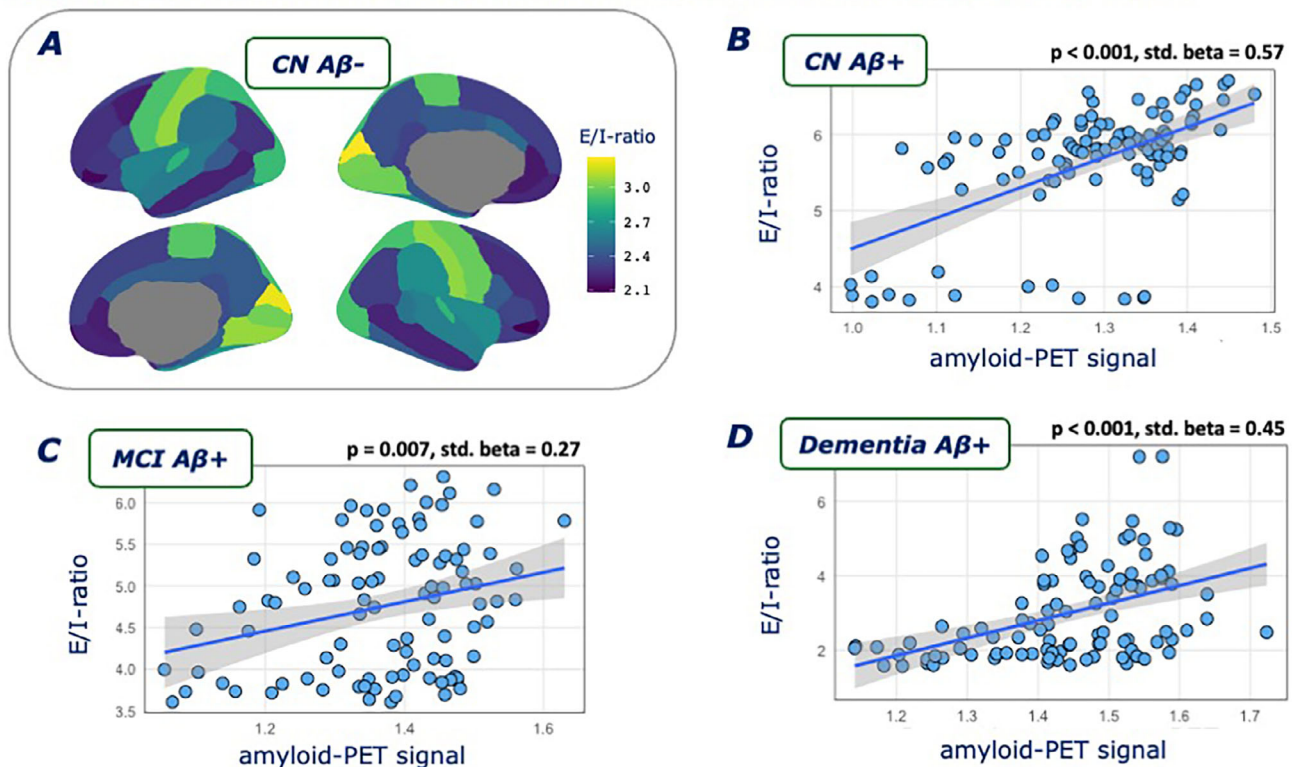
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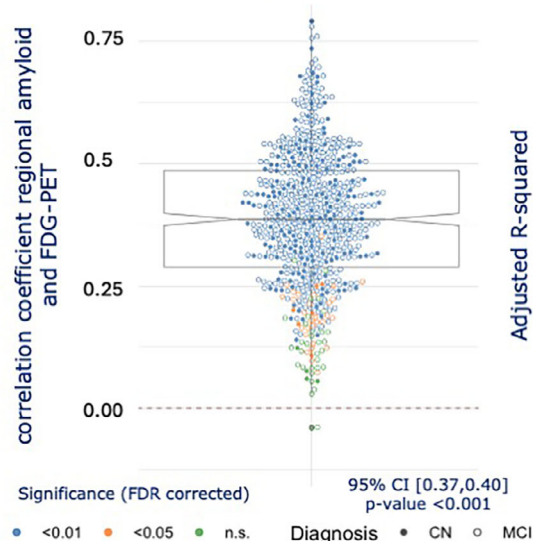
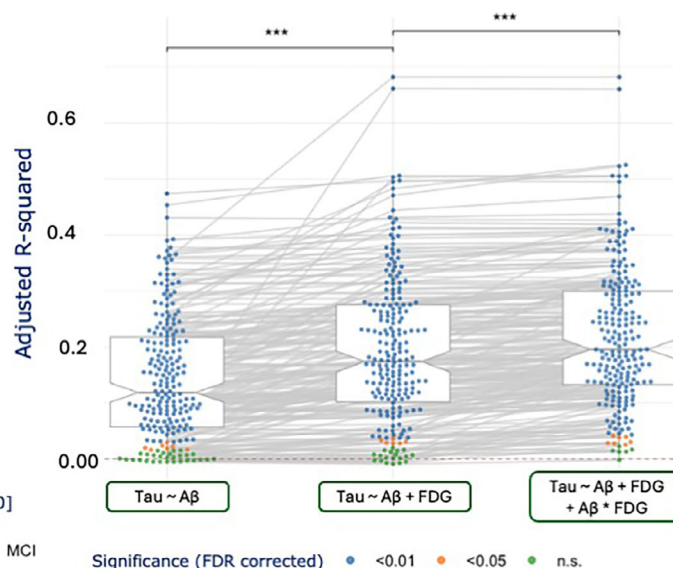
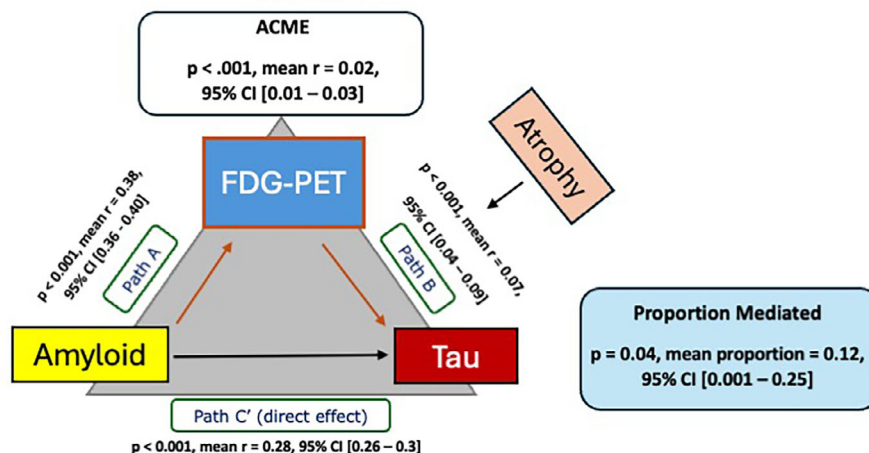
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we found an association between higher amyloid-PET SUVRs and a higher E/I ratio, consistent across diagnostic groups (Figure 1B-D), indicative of A β -associated hyperexcitatory neuronal activity. Second, we found within individuals, that higher regional amyloid-PET was linked to higher FDG-PET (correlation_{amyloid-PET vs. FDG-PET}: 95% CI [0.37,0.40] *p*-value <0.001), suggesting higher neuronal activity in A β -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 A β on subsequent tau accumulation (Figure 2C).

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

Figure 1**Regional A β -deposition and E/I-ratio are correlated across the AD spectrum**

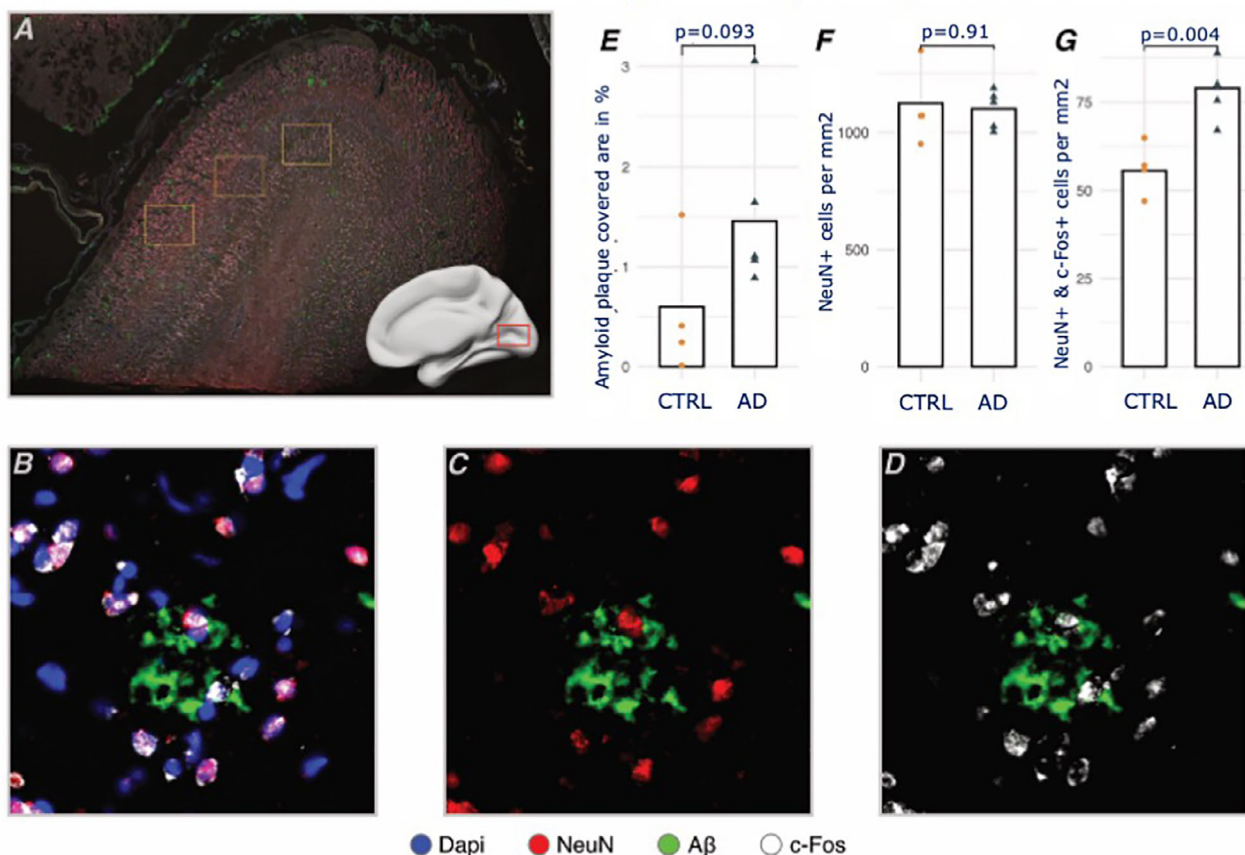
(A) Surface rendering of the mean ROI-wise E/I-ratio estimation via the pFIC algorithm by Zhang et al., PNAS, 2024 in healthy controls; The distribution of the E/I-ratio in healthy controls matches biologically expected distributions (high in the occipital lobes, low in the frontal lobes), indicating 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 A β + disease groups of the AD spectrum, indicating an excitatory shift in regions harbouring A β . E/I-ratio estimation and amyloid-PET data was parcellated to the Schaefer 100 homotopic atlas by Yan et al 2023.

Figure 2**A** *Regional A β -deposition and glucose uptake are highly correlated across subjects***B** *Future tau accumulation is best predicted by A β , FDG-PET and their interaction***C** *Effects of A β on tau accumulation are mediated by A β -mediated metabolic increases*

(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 A β -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 A β 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 A β 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 A β 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), A β and c-Fos (marker of ante-mortem neuronal activity), **(C)** merged image of NeuN and A β stainings and **(D)** merged image of A β and c-Fos staining. Group differences in **(E)** A β -Plaque area, indicating a greater amount of A β 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 A β is the dominant pathology.