



Disentangling the effects of amyloid- β and tau on synaptic biomarkers across the Alzheimer's continuum

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Background

Synaptic dysfunction is a hallmark of neurodegenerative diseases, including Alzheimer's disease, and is the biological basis of cognitive impairment. Previous research indicates that amyloid and tau pathology interact to cause synaptic damage, but their independent effect remains poorly understood.

Methods

We included 109 cognitively unimpaired and impaired individuals (mild cognitive impairment or dementia) from the Geneva Memory Center, with available CSF measurements of synaptic biomarkers (neurogranin, SNAP-25, and GAP-43). Participants were classified according to amyloid and tau status based on available Alzheimer's disease biomarkers (PET or CSF). Group differences, associations between synaptic biomarkers and Alzheimer's disease biomarkers, and the independent contributions of amyloid and tau to synaptic damage were assessed. Mediation analyses explored whether tau mediated the association between amyloid burden and synaptic biomarkers. All findings were replicated in the Alzheimer's Disease Neuroimaging Initiative cohort ($n = 787$).

Results

CSF p-tau181 showed the strongest correlations with synaptic markers ($P < 0.001$, Fig. 1A). Synaptic biomarker concentrations were significantly higher in A+/T+ ($n=27$) individuals compared to A-/T- ($n=52$) and A+/T- ($n=30$) groups ($P < 0.001$, Fig. 1B). GAP43 levels were positively associated with CSF A β 42 ($\beta=0.31$, 95%CI 0.23 to 0.40, $P < 0.001$; partial $R^2=0.321$) and p-tau181 ($\beta=0.94$, 95%CI 0.84 to 1.04, $P < 0.001$; partial $R^2=0.809$). Lower Centiloid ($\beta=-0.31$, 95%CI -0.46 to -0.16 , $P < 0.001$; partial $R^2=0.225$) and higher CSF p-tau181 ($\beta=0.94$, 95%CI 0.84 to 1.04, $P < 0.001$; partial $R^2=0.758$) predicted higher GAP43 levels (Fig. 2). Similar findings were obtained for neurogranin and SNAP25 ($P < 0.001$). In mediation analyses, the direct relationship between amyloid burden and GAP43 shifted from a positive to a negative predictor, once tau was accounted for as the mediator (Fig. 3). All results from the ADNI cohort were consistent.

Figure 1. Correlations (A) and group differences (B) of synaptic biomarkers in relation to amyloid and tau pathology (GMC).

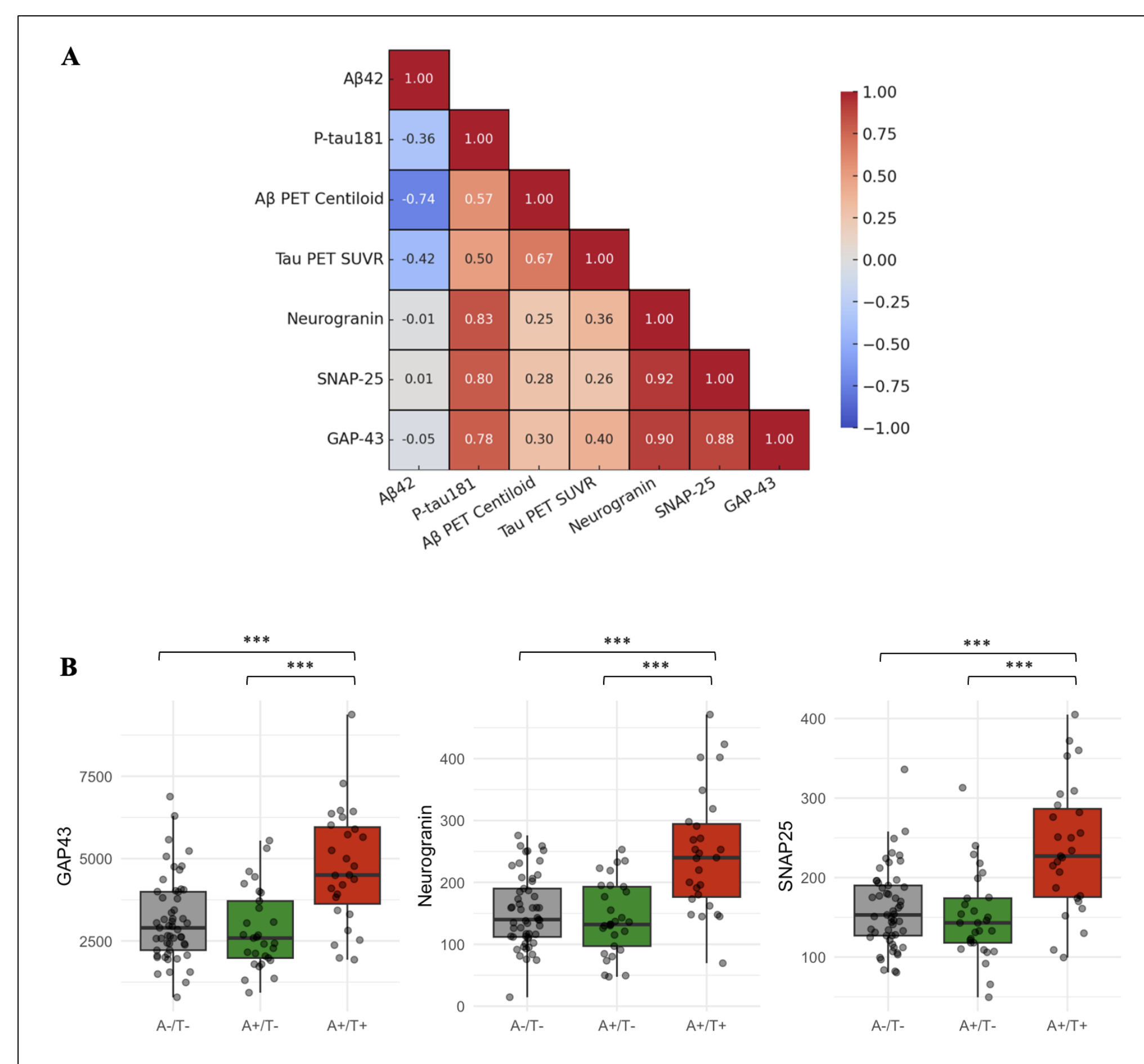


Figure 2. Associations of A β PET and p-tau181 with GAP43 (A, GMC; B, ADNI)

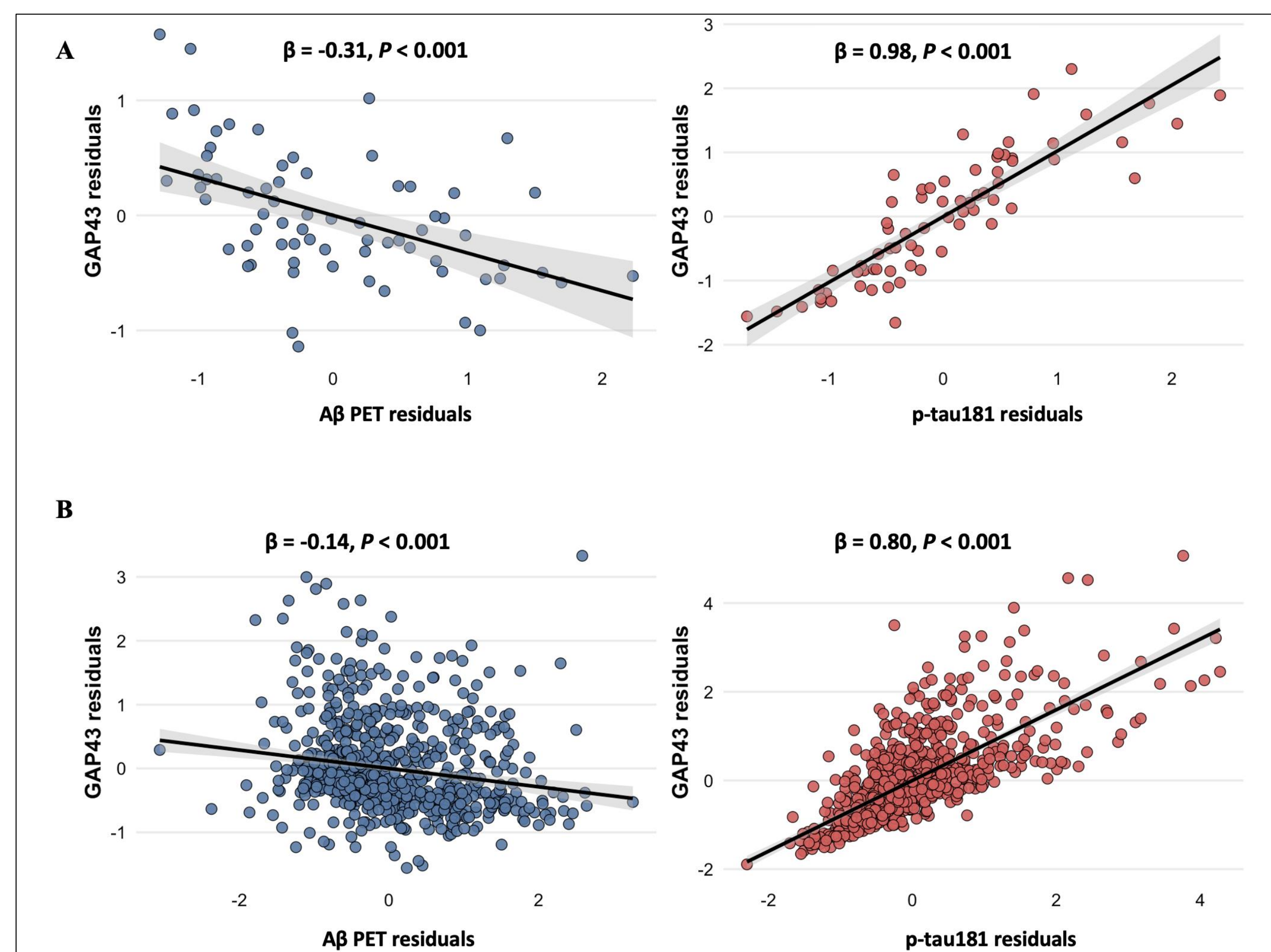
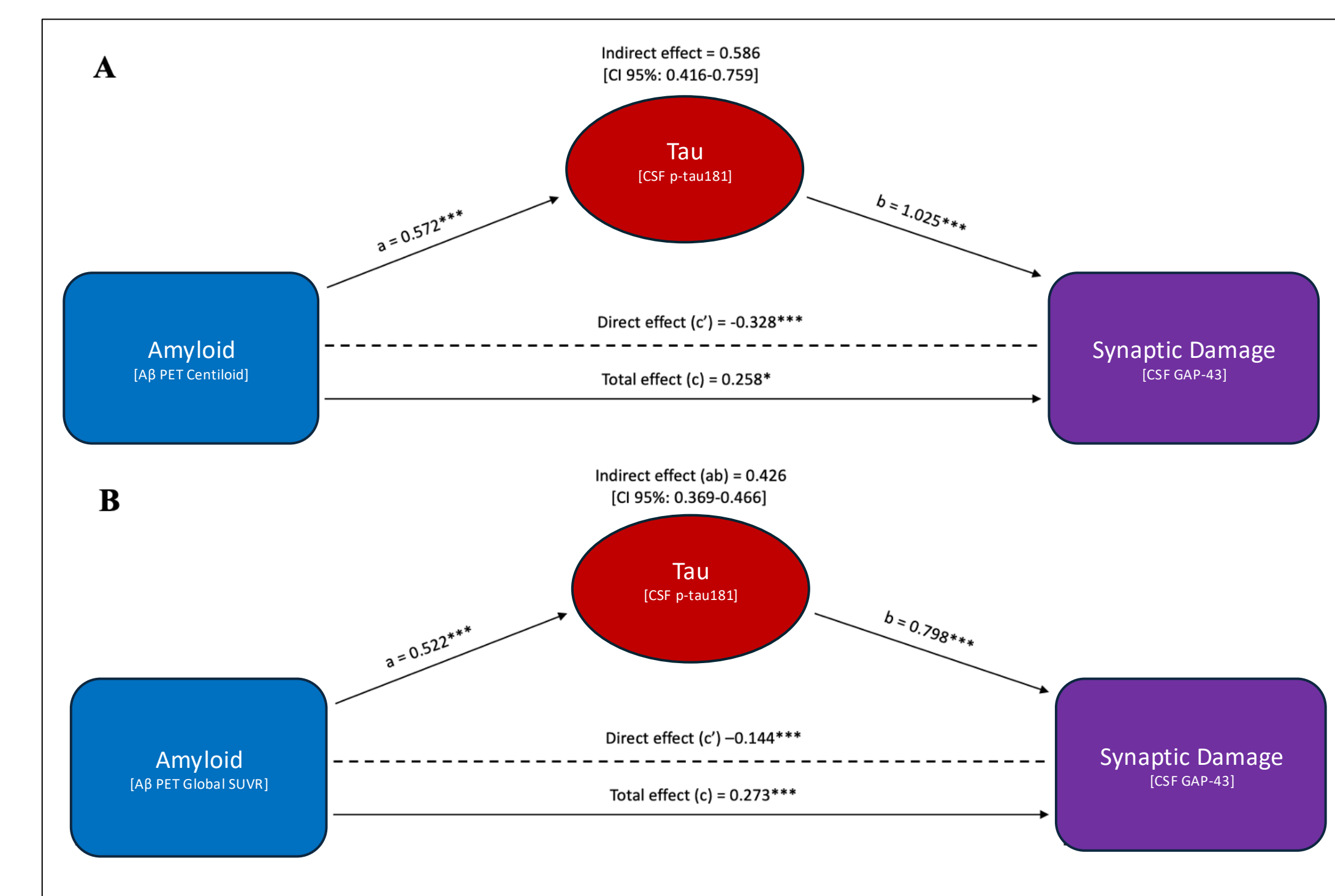


Figure 3. Amyloid association to synaptic damage is mediated by tauopathy (A: GMC; B: ADNI)



Discussion and conclusion

These findings suggest that synaptic biomarkers primarily reflect tau-related synaptic pathology in vivo. They support a model in which synaptic injury occurs downstream of tau-related processes and indicate that amyloid- β contributes to synaptic alterations predominantly through its relationship with tau rather than through a direct effect.

