

## Decreased amyloid-related structure–function coupling in preclinical Alzheimer's disease

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### Abstract:

**Background:** Structural pathways of the brain facilitate functional communication, and their disruption in preclinical Alzheimer's disease may reflect network vulnerability and compensatory brain maintenance. However, it remains unclear how early amyloid- $\beta$  affects structure-function alignment, whether effects are explained by functional network organisation, how they relate to cognition, and which biological processes contribute to their development.

**Methods:** We included 460 older adults without dementia from AMYPAD-PNHS with functional MRI, diffusion MRI, and amyloid- $\beta$  PET. Structure-function coupling was quantified using the structural-decoupling index (SDI) at global, sub-network, and regional scales. Linear models investigated the effect of amyloid- $\beta$  burden on SDI. Mediation analyses evaluated whether functional graph topology explained amyloid-associated SDI effects and whether SDI mediated the relationship between amyloid- $\beta$  burden and cognition. Regional gene expression data were integrated to assess transcriptomic determinants of amyloid-related structure-function coupling.

**Results:** Amyloid-positive individuals exhibit higher global SDI, driven by visual cortices. Mediation analyses demonstrate that amyloid-related SDI alterations are explained by reductions in local clustering, indicating less segregated processing. Despite higher SDI in amyloid-positive individuals, elevated SDI in visual regions mitigates the negative effect of amyloid- $\beta$  burden on cognition. Amyloid-related SDI changes correlate with genes associated with amyloid- $\beta$  metabolism, microglial activation, and synaptic remodelling.

**Conclusions:** Early amyloid- $\beta$  pathology is associated with decoupling of brain structure and function, primarily in visual cortices, mediated by network reconfiguration and shaped by regional molecular architecture. These findings suggest that lower structure-function coupling may represent a compensatory mechanism in preclinical Alzheimer's disease and highlight SDI as a biomarker for stratification and monitoring in prevention trial

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