



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



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Background

Alzheimer's Disease and Amyloid Pathology

- AD begins with amyloid- β (A β) deposition years before symptoms
- A β disrupts local synapses and large-scale brain networks, but mechanisms remain unclear

Brain Structure-Function Coupling

- Brain function (fMRI) is shaped by the underlying structural connectivity (DWI)
- Changes in coupling possibly reflects **network dysfunction** or **adaptation** in the early disease stages

Research Questions

- How is **A β burden** associated with brain structure-function relationships in cognitively unimpaired adults?
- What **network mechanisms** underlie A β -related changes in structure-function decoupling?
- How do these changes relate to **cognition** in the earliest stages of AD?

Methods

N = 460 cognitively unimpaired (CDR $\leq$ 0.5) older adults from the AMYPAD-PNHS study

- 88 individuals (19%) were A β +
- Mean age: 66.1 ± 7.4 years; 58% female
- 44% APOE $\epsilon 4$ carriers
- Cognitive scores: MMSE, Composite Memory scores (Immediate Recall, Delayed Recall, Visual)

Multimodal Neuroimaging

- A β -PET**: Global Centiloid (CL)
- DWI**: Structural connectome
- fMRI**: Timeseries signal, Functional connectome

Brain Network Metrics

- SDI (Structural-Decoupling Index)**: quantifies how much a region's fMRI signal deviates from its underlying structural embedding
- Functional Graph Properties**: clustering (segregation), betweenness (hubness), participation (integration)

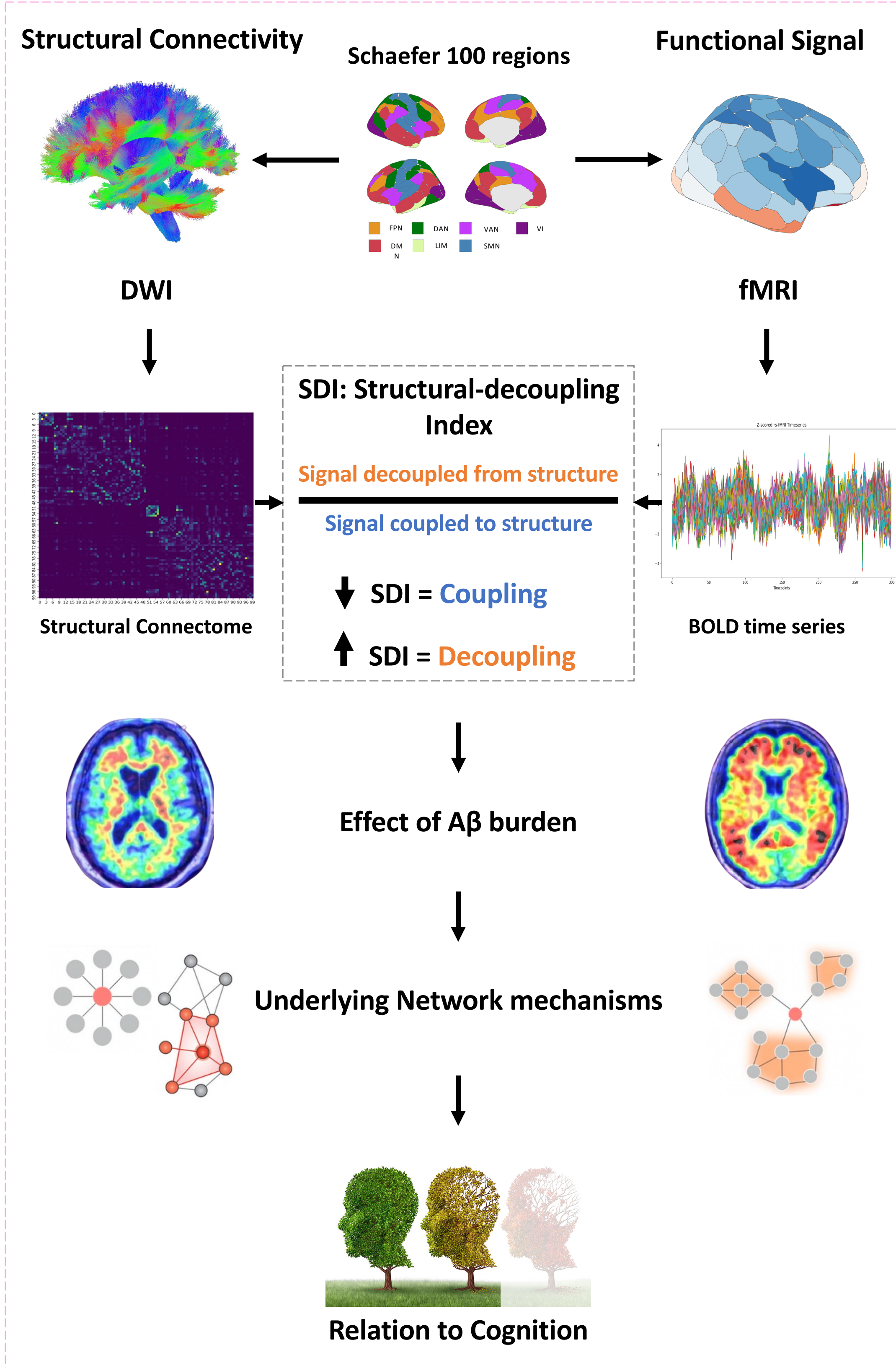
Statistical Models

Linear Models

- SDI (Global/Networks/Regional) $\sim$ A β -PET CL

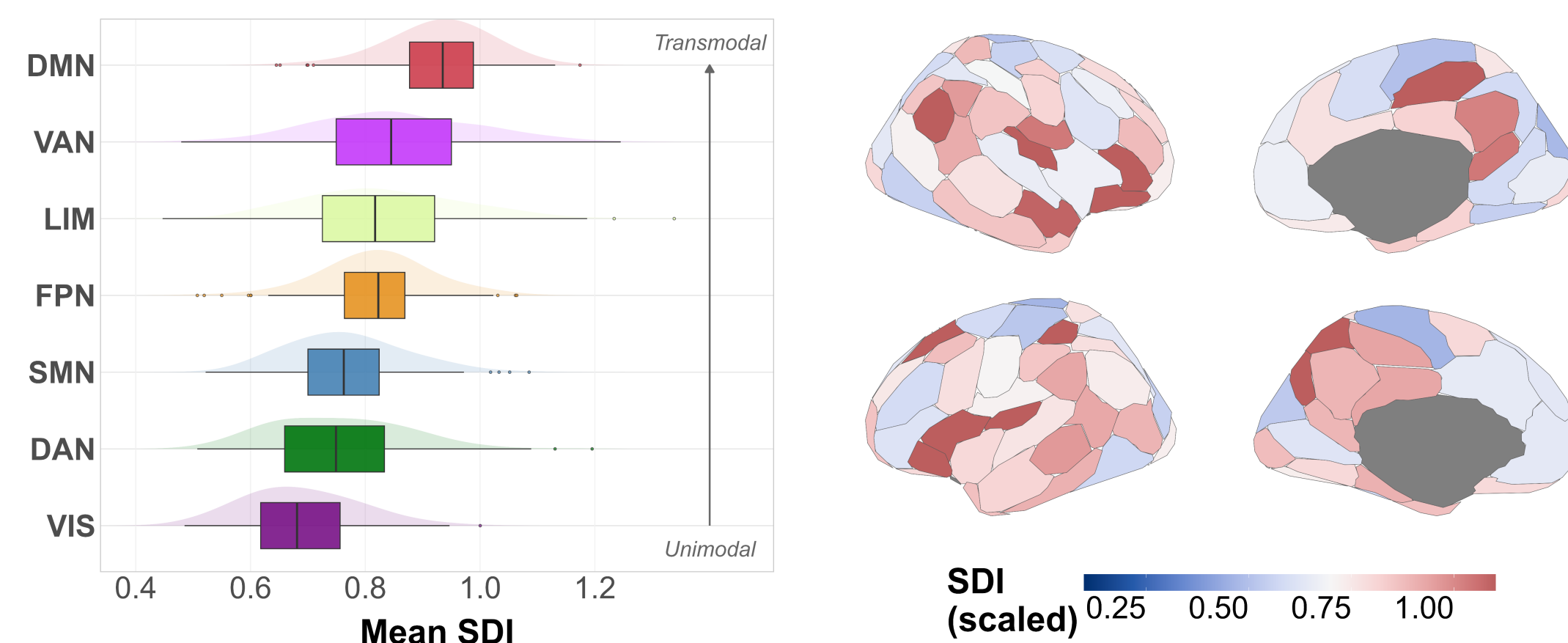
Mediation Models in A β subjects

- Model 1: Global A β -PET CL $\rightarrow$ Regional Graph Property $\rightarrow$ Regional SDI
- Model 2: Global A β -PET CL $\rightarrow$ SDI (Latent Factor) $\rightarrow$ Cognition (MMSE / Composite Memory scores)



Results

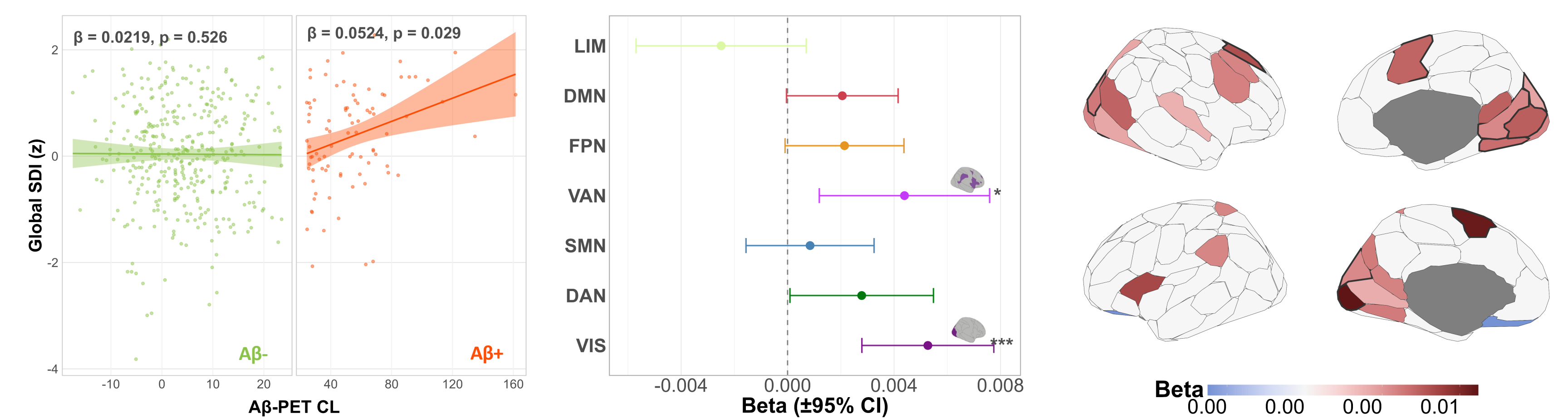
1. Increasing Spatial Gradient of Structure-Function Decoupling From Sensory-Motor to Higher-Order Cognitive Regions



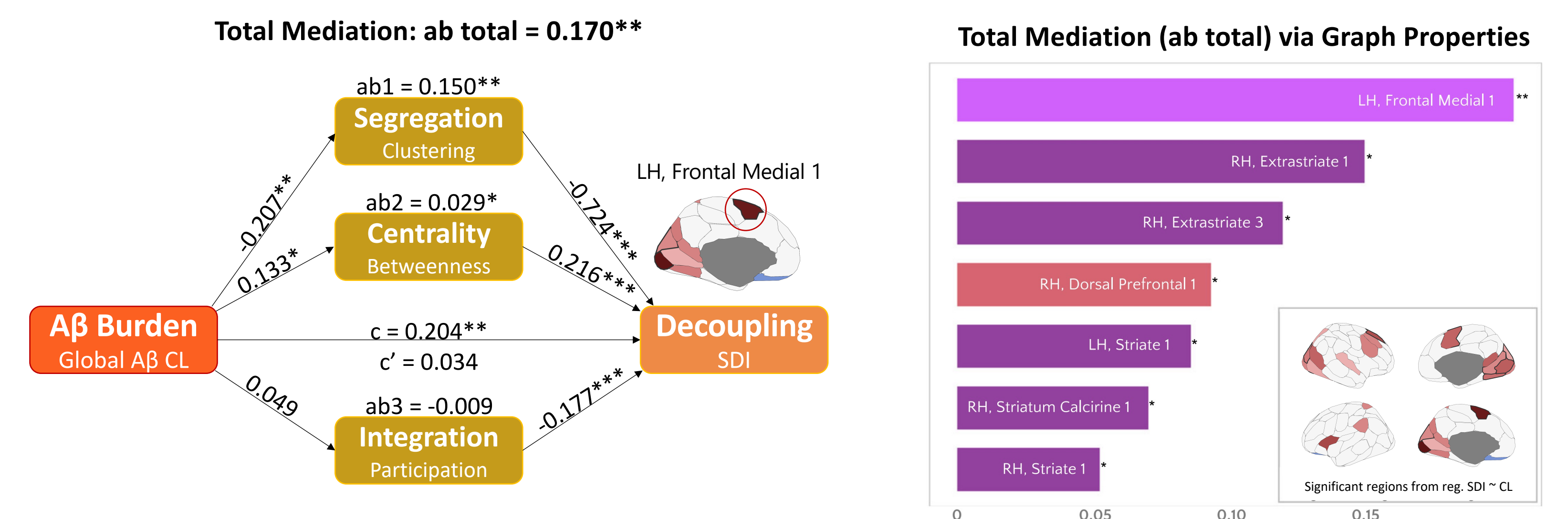
Take-home message

In cognitively unimpaired adults, early A β pathology is associated with a **decoupling of brain function from structure, primarily driven by the visual regions**. This decoupling is explained by **decrease in network segregation** and may reflect a **compensatory functional rerouting mechanism** that transiently **mitigates the impact of A β on cognition**

2. A β Burden Predicts lower Structure-Function Coupling Across Scales



3. Functional Network Rerouting via Less Constrained Pathways Explains A β -Related Decrease in Structure-Function Coupling



4. Decoupling Between Brain Structure and Function in the Early Stages Attenuates the Effect of A β on Cognition

