

Longitudinal Segregation Of Heteromodal Networks As A Proximal Marker Of Cognitive Decline: Moderation By Amyloid Pathology

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Why longitudinal network change

- Predicting decline in MCI and early dementia is a major clinical challenge.
- Longitudinal evidence linking network change to decline comes mostly from cognitively unimpaired or genetically defined cohorts — not symptomatic, sporadic disease.
- Neurodegeneration blurs Mesulam's unimodal → heteromodal hierarchy (dedifferentiation; loss of segregation).

Objectives

Does longitudinal change in network segregation (1) track decline, (2) grade across the cortical hierarchy, and (3) depend on amyloid status?

Methods

- 111 patients with sporadic MCI or early dementia; single-center, integrated retrospective–prospective cohort.
- rs-fMRI + serial MMSE; mean follow-up 2.6 years.
- Modularity and system segregation (SysSeg):
 - whole-brain
 - unimodal (visual network [VN], somatomotor [SMN])
 - heteromodal (dorsal attention [DAN], ventral attention [VAN], frontoparietal [FPN], default-mode [DMN])
 - limbic excluded (low reliability).
- Covariate-adjusted partial correlations (age, sex, education, follow-up interval; $q = 4$).
- System contrast by Williams's test, corroborated by distribution-free and rank-based bootstraps (10,000), Zou (2007) CIs, leave-one-out, and a cluster-robust moderation model.
- Amyloid status by qualitative PET visual read (BAPL) in 82/111; used as a moderator.
- G*Power: minimum detectable partial $r \geq 0.26$ (80% power, two-sided $\alpha = 0.05$).

Framework: cortical hierarchy & segregation

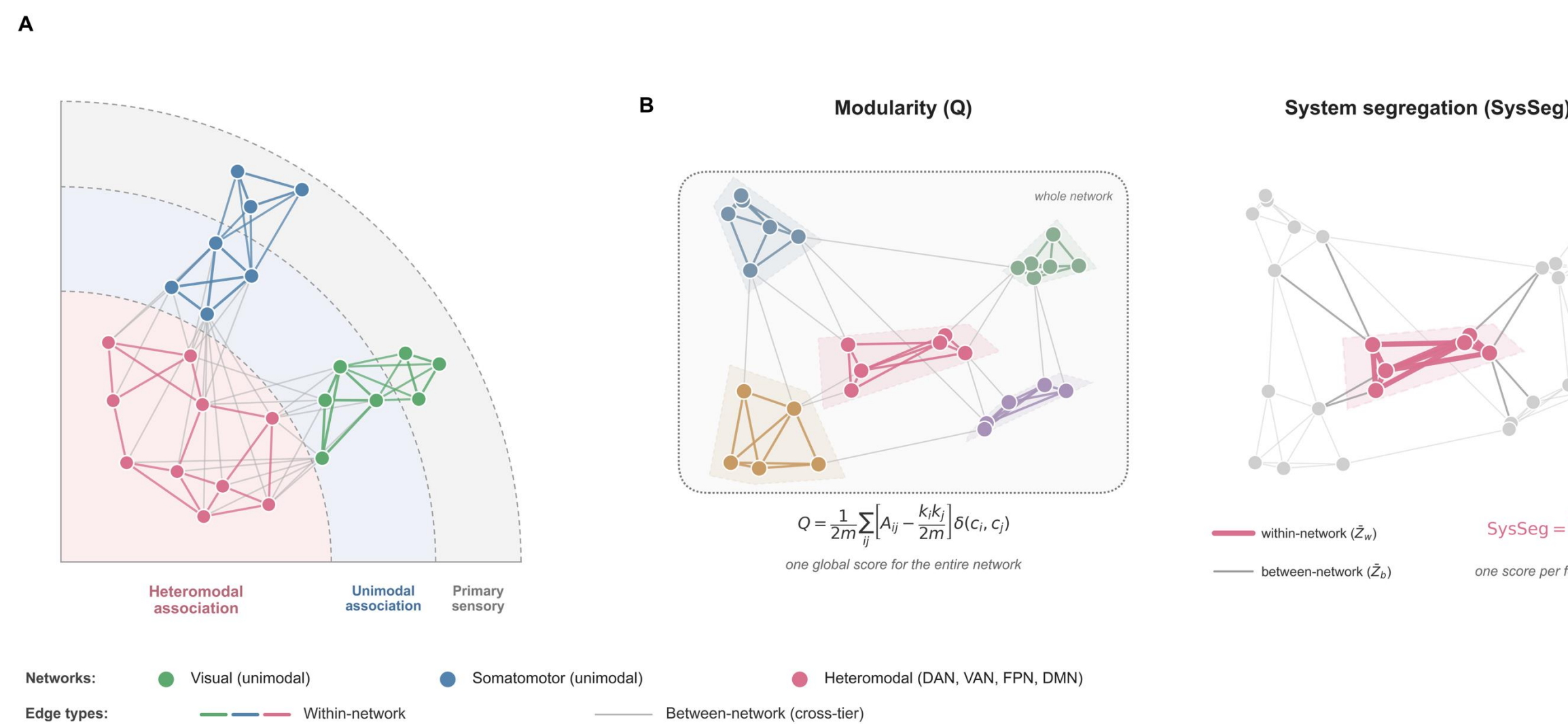


Figure 1. (A) Mesulam's unimodal → heteromodal cortical hierarchy. (B) Modularity (Q; one whole-network score) and system segregation (SysSeg; one score per focal network).

Longitudinal change, not baseline, tracks decline

- Baseline network measures: no association with cognitive outcomes.
- Higher follow-up modularity and SysSeg → better concurrent MMSE ($r = 0.25$ to 0.28 , $p \leq 0.009$).
- Loss of segregation over time → steeper decline (Δ modularity $r = 0.22$, $p = 0.02$; Δ SysSeg $r = 0.19$, $p = 0.05$).

Figure 2. Whole-brain modularity and system segregation vs cognition — baseline (n.s.), concurrent follow-up, and longitudinal change (Δ).

Graded across the cortical hierarchy

- Strongest in heteromodal systems (Δ SysSeg $r = 0.28$, $p = 0.004$), weakest in unimodal ($r = 0.17$, $p = 0.08$).
- Difference not significant (Williams's test $p \geq 0.32$; bootstraps and Zou CIs include zero).
- A graded, heteromodal-predominant gradient — not a heteromodal-only effect; driven by DAN, VAN, FPN.

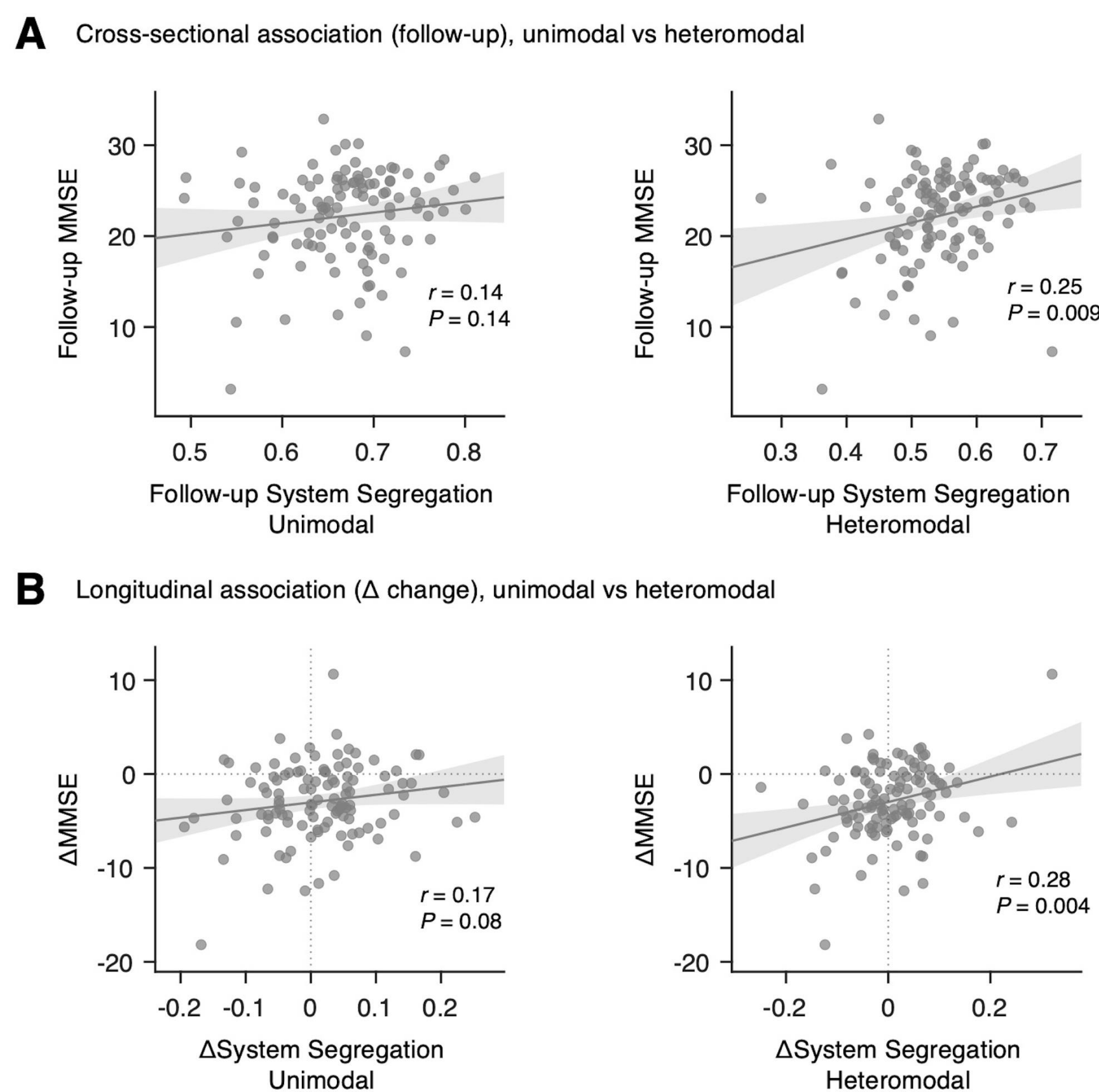
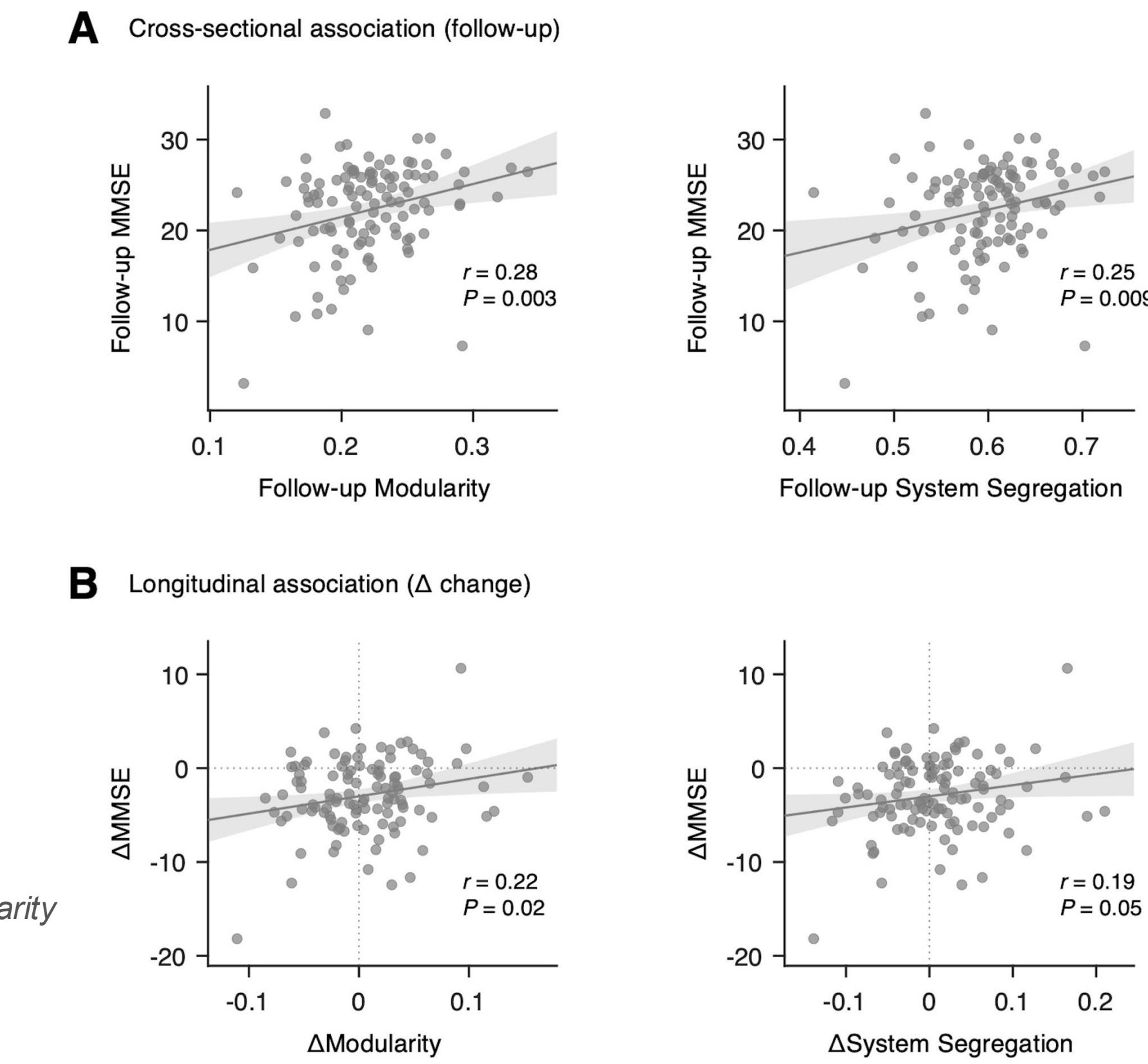


Figure 3. Unimodal vs heteromodal system segregation — a graded, heteromodal-predominant gradient (the study's novelty).

More evident in amyloid-negative

Exploratory · hypothesis-generating

PET in 82/111. Associations stronger in $A\beta^-$ than $A\beta^+$, but the network $\times$ amyloid interaction was not significant ($p \geq 0.09$).

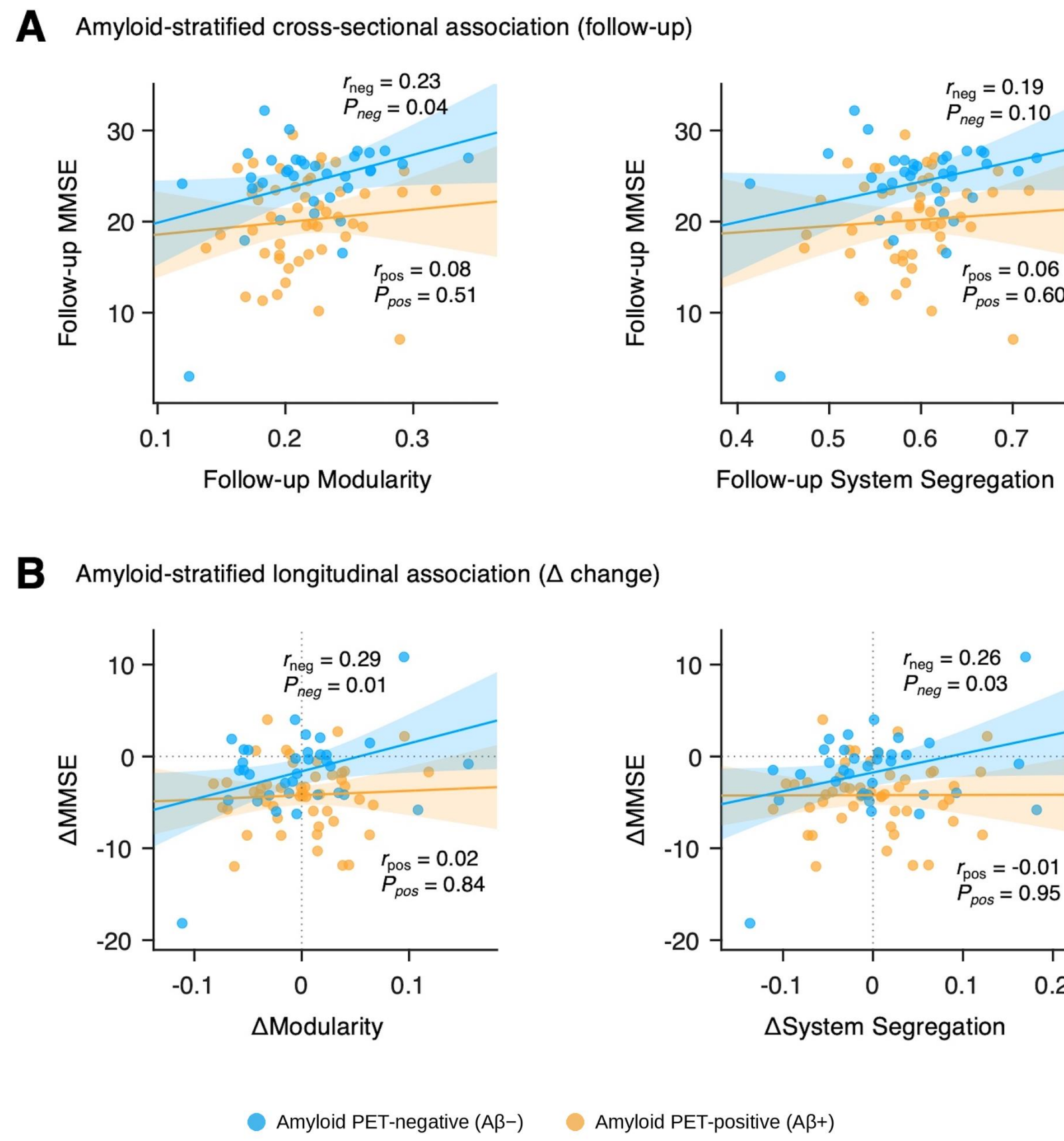


Figure 4. Modularity and system segregation vs cognition stratified by amyloid status ($A\beta^-$, blue; $A\beta^+$, orange; $n = 82$): cross-sectional (A) and longitudinal Δ (B)

Limitations

Single-center; modest sample ($N = 111$; amyloid $n = 82$) with qualitative amyloid; MMSE-based cognition; modest effects; no replication. Interpret cautiously; replication needed.

Conclusions

In MCI and early dementia, longitudinal preservation of network segregation — most evident in heteromodal systems — tracks cognitive preservation and exceeds baseline imaging as a marker of progression; a candidate marker for monitoring early neurodegeneration.

References

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