

Non-linear Evolution of Glymphatic Function and Its Association with Plasma p-tau217 in Alzheimer’s Disease

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KEY TAKE AWAY: DTI-ALPS showed a biphasic trajectory across the Alzheimer’s disease continuum—paradoxically elevated and asymmetric in MCI but reduced in AD—and a multimodal model combining ALPS, MoCA, plasma p-tau217, and Aβ42/40 achieved excellent diagnostic performance (AUC up to 0.923).

INTRODUCTION

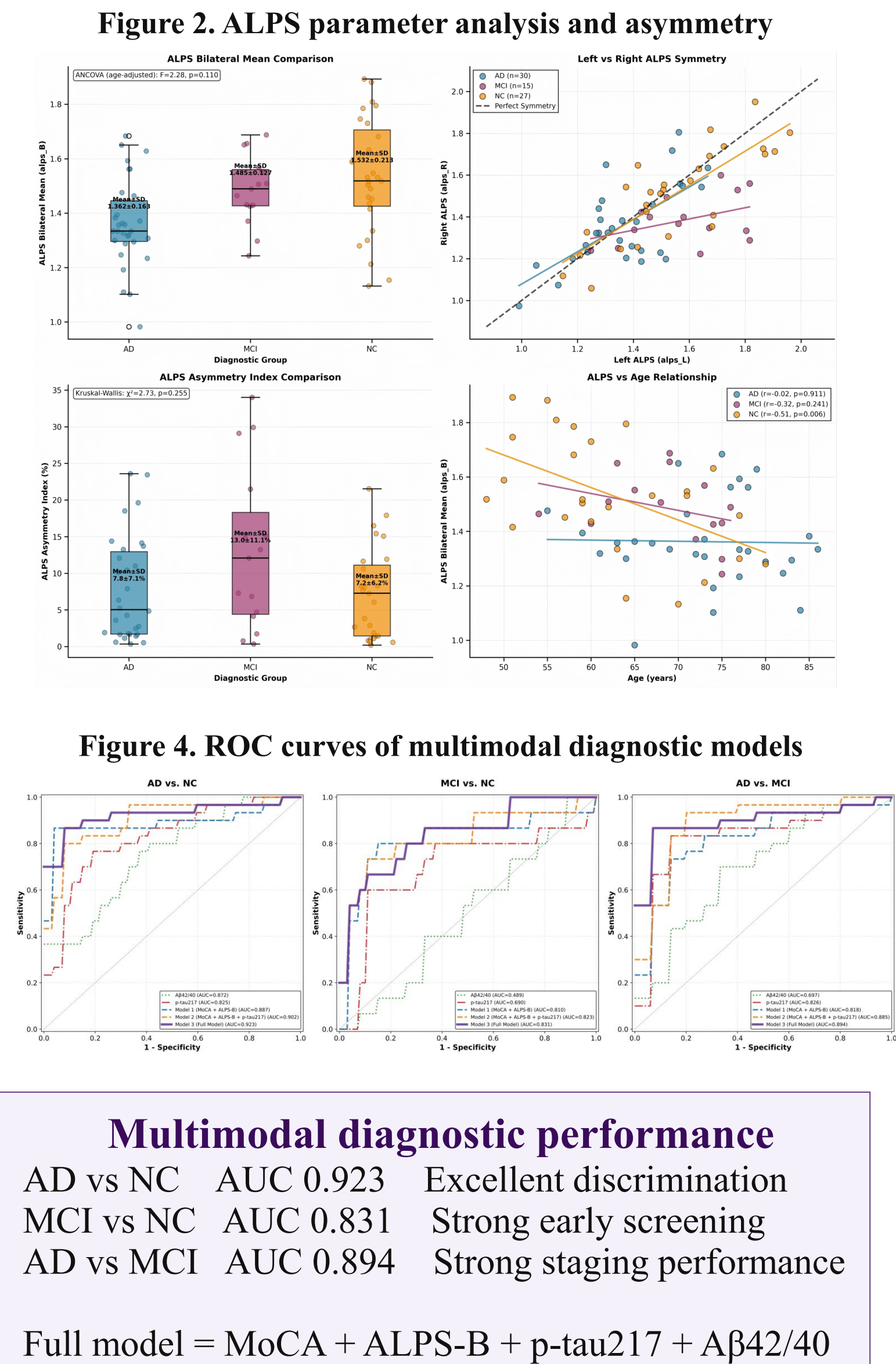
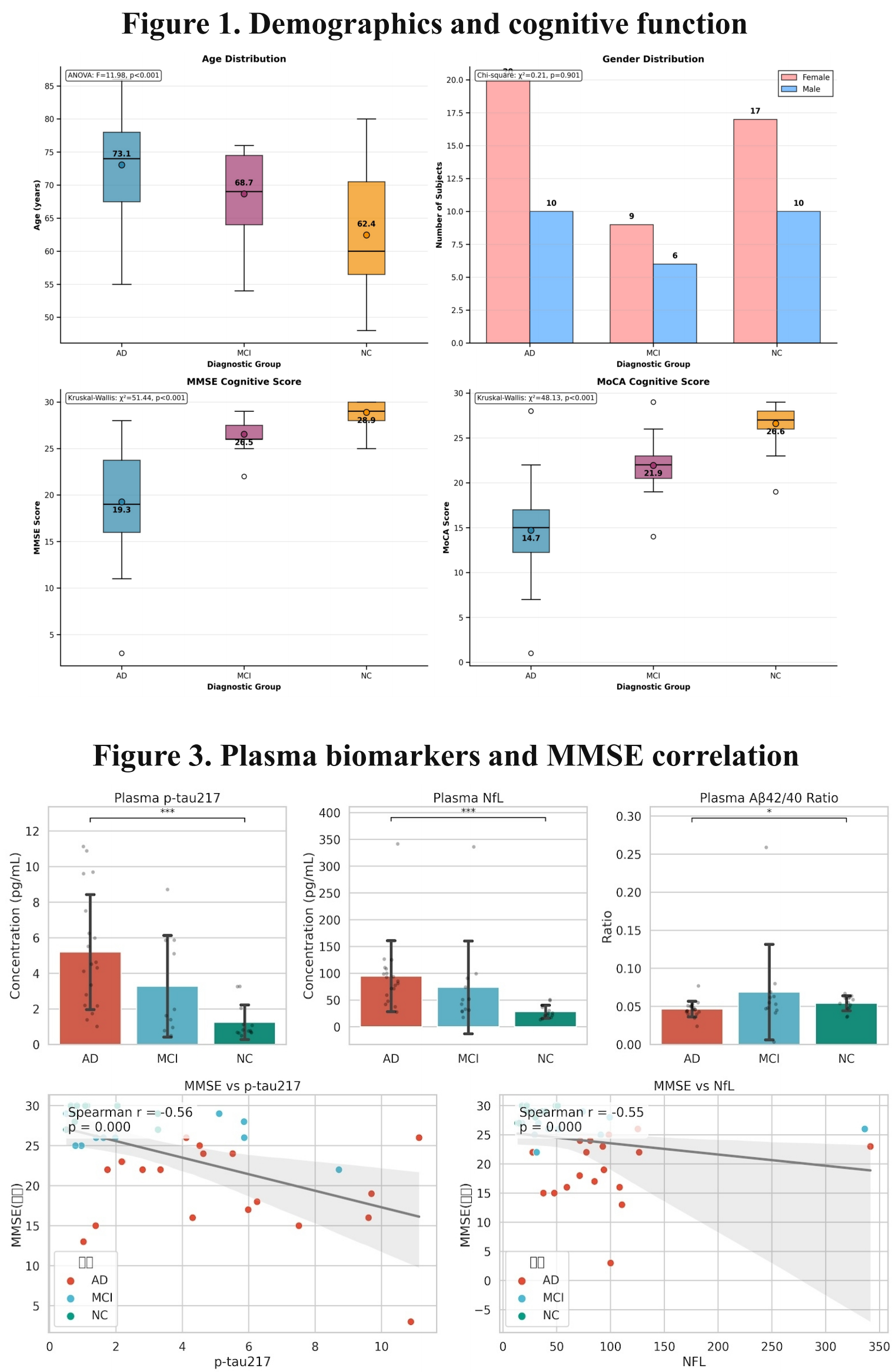
- Alzheimer’s disease (AD) diagnosis increasingly relies on multimodal biomarkers beyond symptoms alone.
- The glymphatic system is a brain-wide clearance pathway implicated in the removal of Aβ and tau.
- DTI-ALPS provides a noninvasive MRI surrogate of glymphatic function, but its dynamic pattern across NC → MCI → AD remains unclear.
- This study aimed to characterize ALPS changes across the AD continuum and evaluate its value when integrated with plasma biomarkers and cognitive assessment.

METHODS

- Single-center cross-sectional study including 72 participants: NC n=27, MCI n=15, AD n=30.
- All participants underwent 3.0T MRI with DTI-ALPS analysis, plasma biomarker testing (Aβ42/40, p-tau217, NfL, GFAP), and neuropsychological evaluation (MMSE, MoCA).
- ALPS indices were calculated bilaterally using ROIs in projection and association fibers at the lateral ventricular body level.
- Statistical analyses included ANOVA/Kruskal-Wallis tests, Spearman and age-adjusted partial correlations, and ROC analysis.
- Multimodal diagnostic models were constructed using logistic regression with feature selection.

ALPS index =
mean(Dproj) / mean(Dassoc)
at the lateral ventricular body level

RESULTS



CONCLUSIONS

- Glymphatic function appears to evolve non-linearly across the AD continuum rather than decline monotonically.
- MCI may represent a compensatory or dysregulated hyperdynamic stage, characterized by elevated left-sided ALPS and increased asymmetry.
- Established AD is associated with systemic glymphatic failure and worsening molecular pathology.
- Integrating imaging, plasma biomarkers, and cognitive assessment substantially improves discrimination across the AD continuum.
- Abnormally elevated left ALPS combined with p-tau positivity may be a promising early warning signal that warrants longitudinal validation.

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