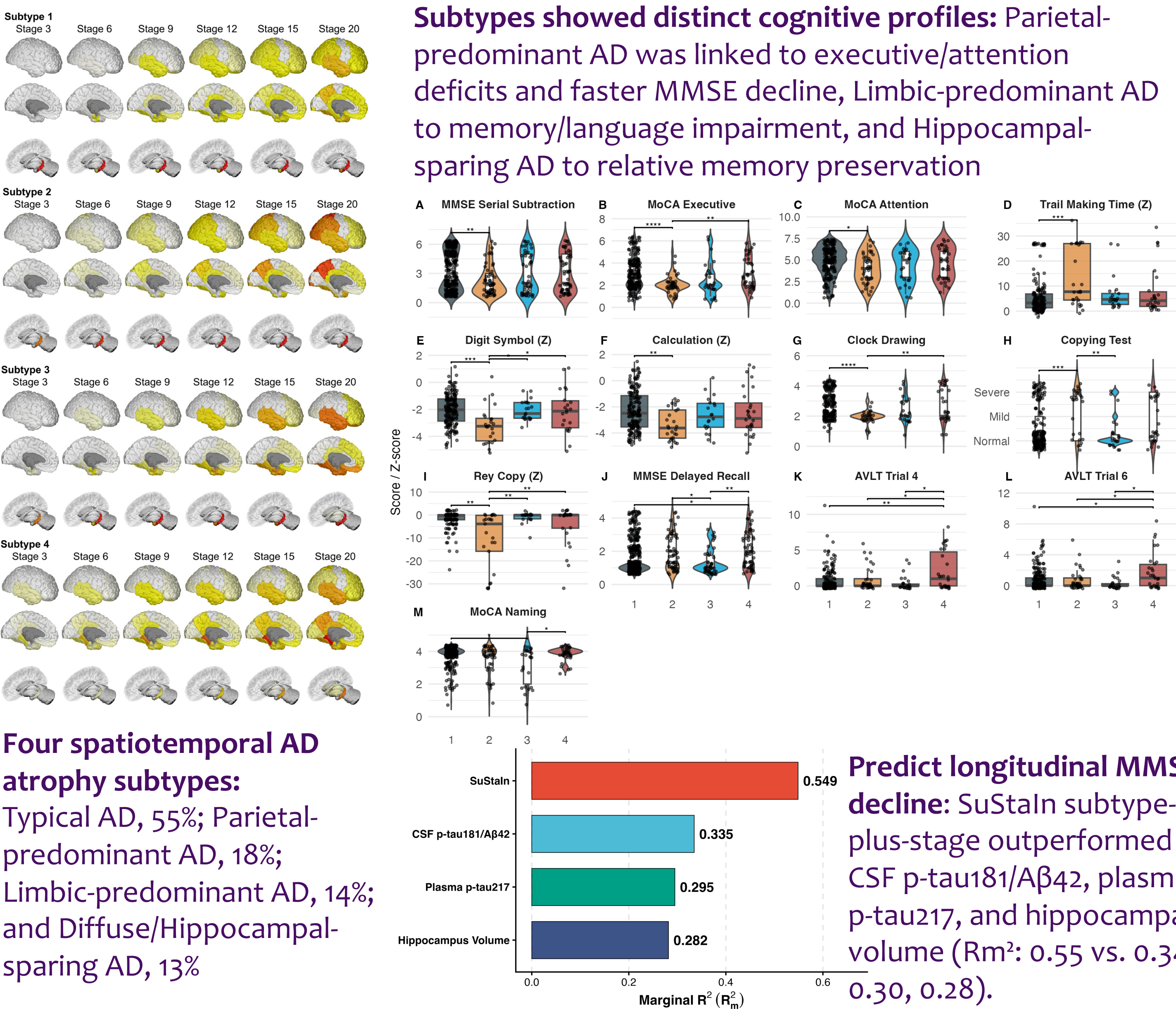
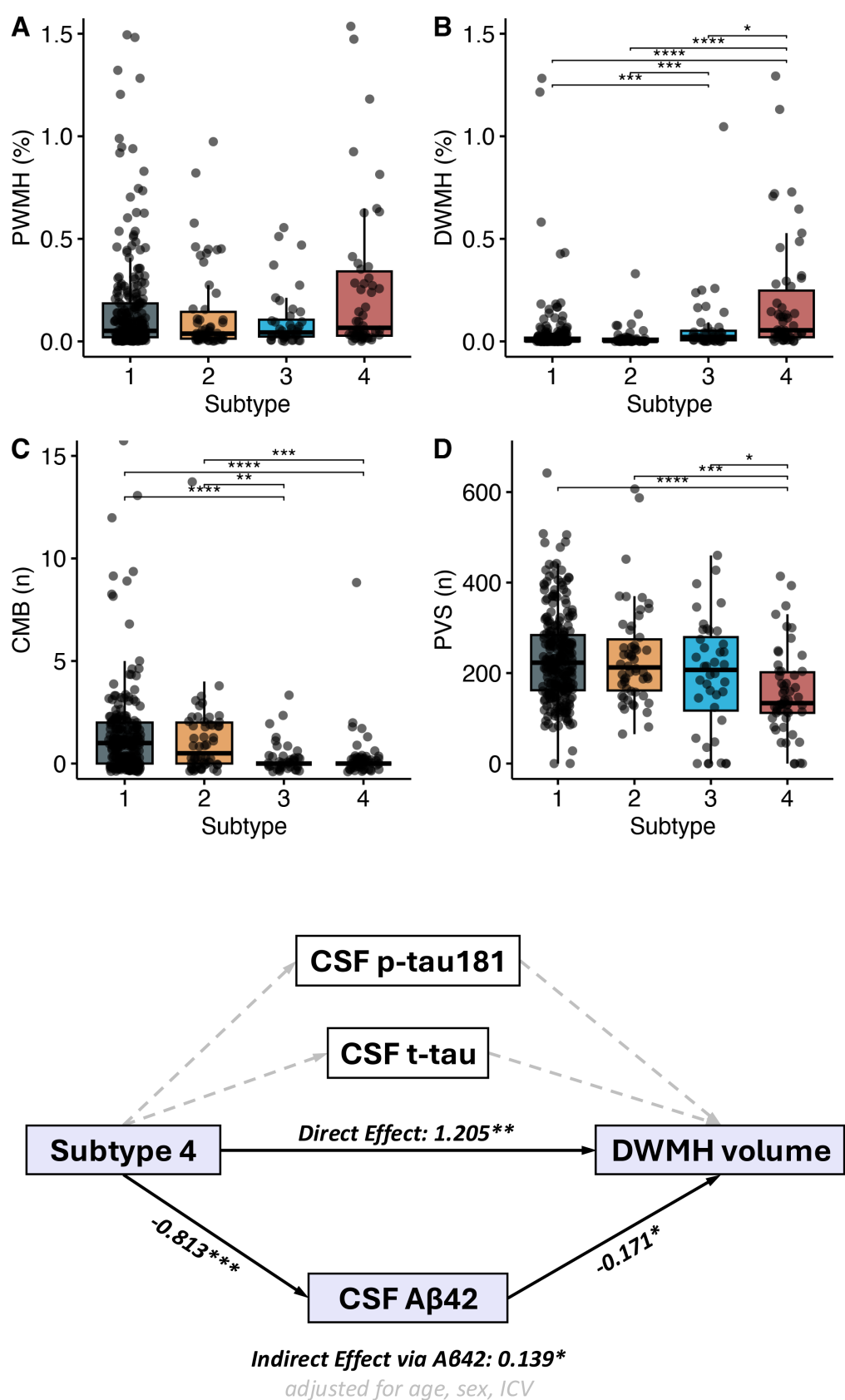


Spatiotemporal Atrophy Subtyping and Staging in AD: Neurodegeneration-Vascular Interplay and Prognostic Superiority

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INTRODUCTION: AD shows marked heterogeneity in atrophy patterns, cognitive symptoms, vascular burden, and clinical progression. Fluid biomarkers indicate whether AD pathology is present, but they do not capture where neurodegeneration begins or how it spreads. We applied SuStaln to biomarker-confirmed AD to map spatiotemporal atrophy trajectories, characterize subtype-specific cognitive and vascular profiles, and test prognostic performance against established biomarkers.

METHODS	RESULTS	CONCLUSIONS
- We included 484 amyloid-positive AD patients from the PUMCH dementia cohort after excluding major non-AD dementias and vascular dementia. - Structural MRI was processed into 17 composite regions, normalized to intracranial volume, and converted to control-based z-scores. SuStaln was used to infer atrophy subtypes and disease stages. - Subtypes were compared for cognition, cerebral small vessel disease markers, and longitudinal MMSE/ADL trajectories; prognostic performance was compared with CSF p-tau181/Aβ42, plasma p-tau217, and hippocampal volume.	Subtypes showed distinct cognitive profiles: Parietal-predominant AD was linked to executive/attention deficits and faster MMSE decline, Limbic-predominant AD to memory/language impairment, and Hippocampal-sparing AD to relative memory preservation  CSVD burden differed across subtypes. Hippocampal-sparing AD showed the highest deep WMH burden but the lowest PVS count, and CSF Aβ42 partially mediated this DWMH association  Four spatiotemporal AD atrophy subtypes: Typical AD, 55%; Parietal-predominant AD, 18%; Limbic-predominant AD, 14%; and Diffuse/Hippocampal-sparing AD, 13% Predict longitudinal MMSE decline: SuStaln subtype-plus-stage outperformed CSF p-tau181/Aβ42, plasma p-tau217, and hippocampal volume (R_m^2: 0.55 vs. 0.34, 0.30, 0.28).	- SuStaln identified 4 reproducible AD atrophy subtypes with distinct cognitive and vascular profiles. - In the Hippocampal-sparing subtype, CSF Aβ42 partially mediates the link between atrophy pattern and deep white matter hyperintensity burden, suggesting an AD-intrinsic vascular mechanism. - Spatiotemporal staging outperforms plasma p-tau217, CSF biomarkers, and hippocampal volume in predicting cognitive decline

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