



Spatial Patterns of White Matter Hyperintensity: A Link Between Glymphatic Dysfunction and Alzheimer’s Disease Cognitive Trajectories

Lumin Leng ^a, Guoping Peng ^{a,*}

a Department of Neurology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China。 * Corresponding author

■ BACKGROUND

It remains unclear whether and how white matter hyperintensities (WMH) region-specifically mediates the relationship between glymphatic dysfunction and cognitive impairment along the Alzheimer's disease (AD) clinical spectrum.

■ METHODS

In a real-world cohort of 56 individuals with cognition unimpaired (CU), 89 mild cognitive impairment (MCI) and 80 AD, regional WMH volumes and the diffusion tensor image analysis along the perivascular space (DTI-ALPS) index features were compared and analyzed for cross-sectional associations. Then causal mediation analyses were performed in the longitudinal cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to quantify the mediating effect of regional WMH in the relationship between glymphatic dysfunction and cognitive decline. Finally, machine learning models integrating WMH topography and glymphatic function features were constructed to predict clinical transition to AD in CU/MCI populations and externally validated in the independent real-world cohort.

■ RESULTS

1. Group Differences in Glymphatic Function and Regional White Matter Hyperintensities

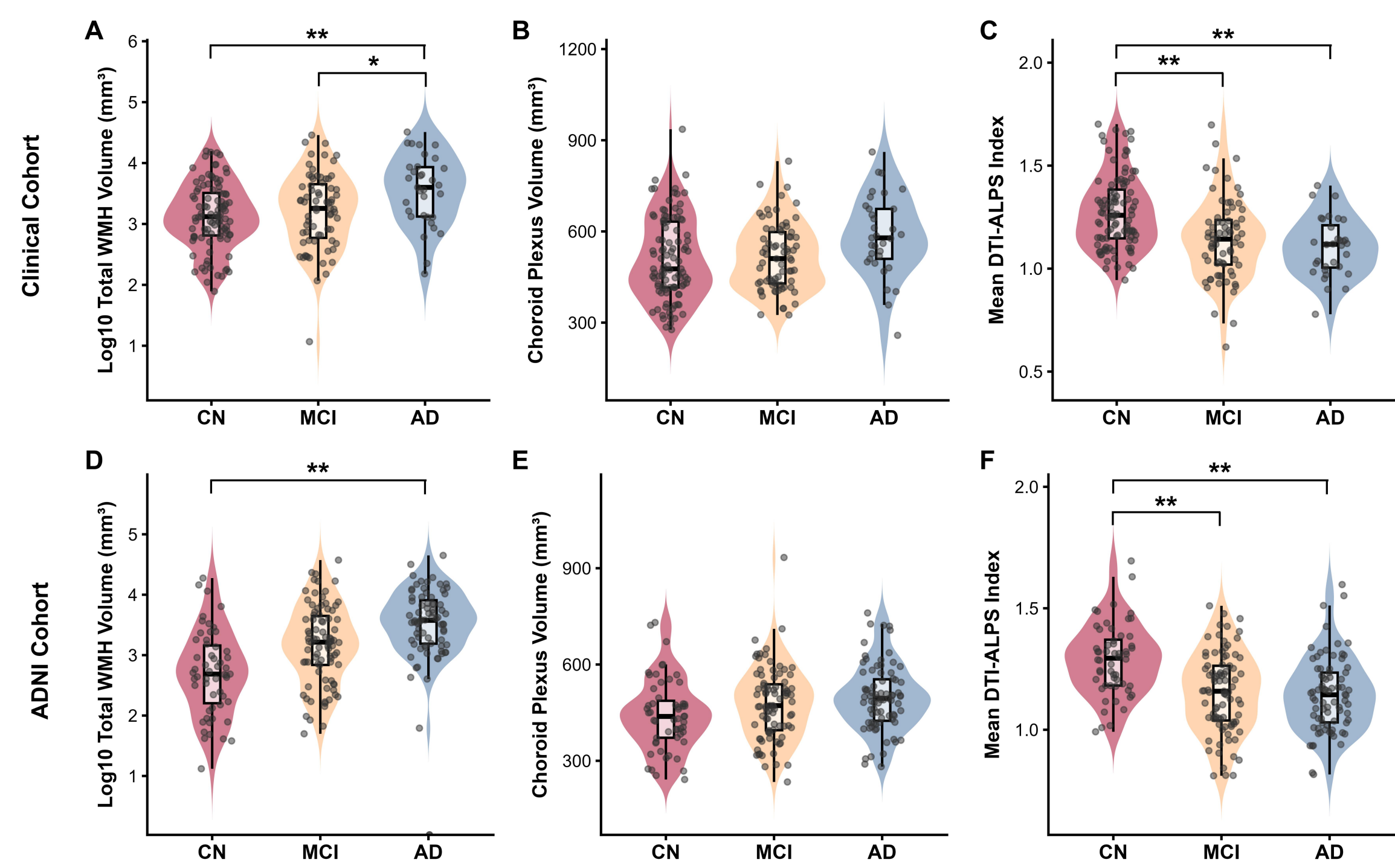


Figure1 Cross-sectional distributions of neuroimaging biomarkers across clinical diagnostic groups.

2. Associations of Regional WMH and Glymphatic Function with Cognitive Function

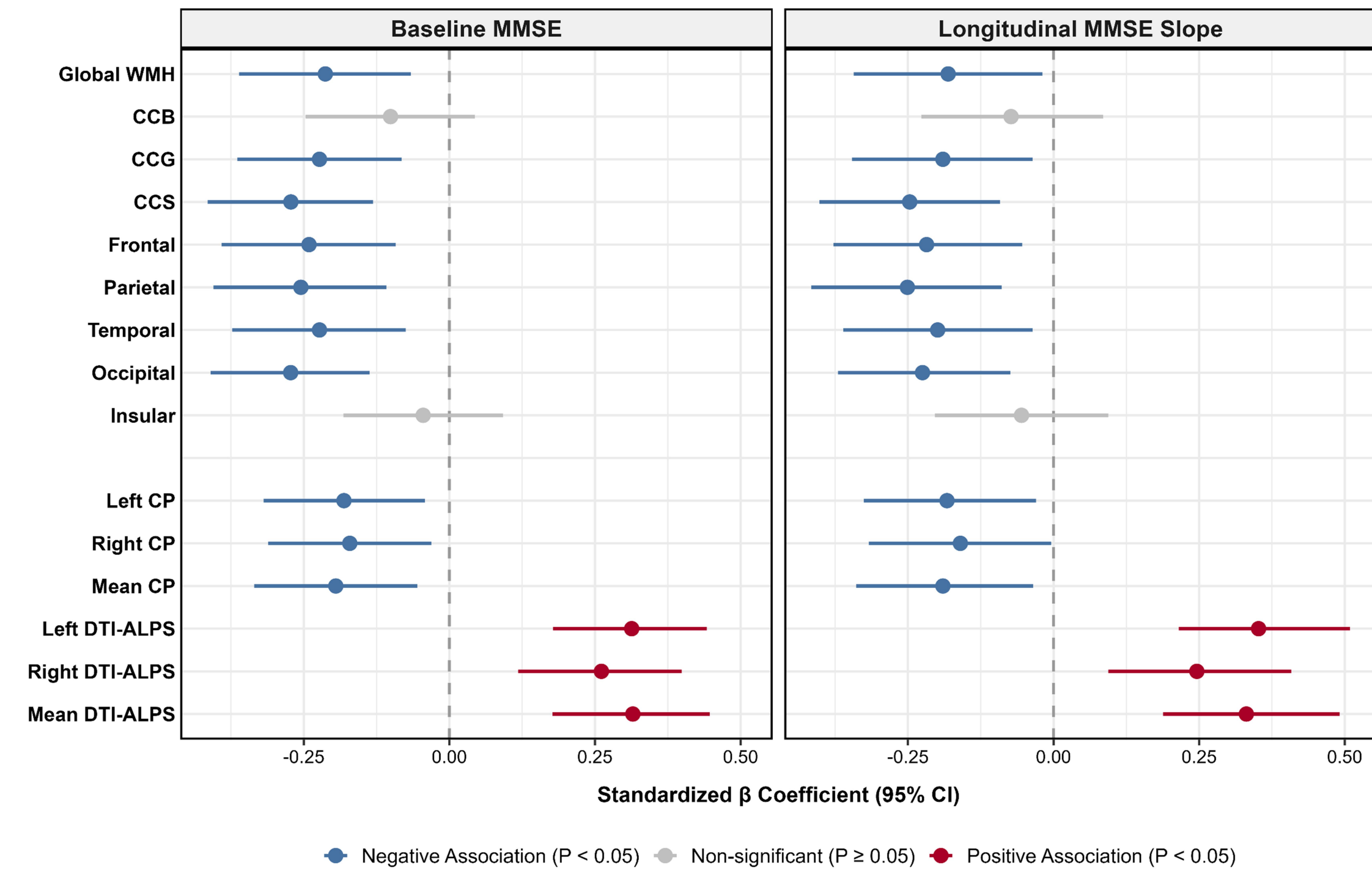


Figure 2. Forest plots showing the associations of neuroimaging biomarkers with cognitive performance

3. Mediation Analysis Of Regional WMH

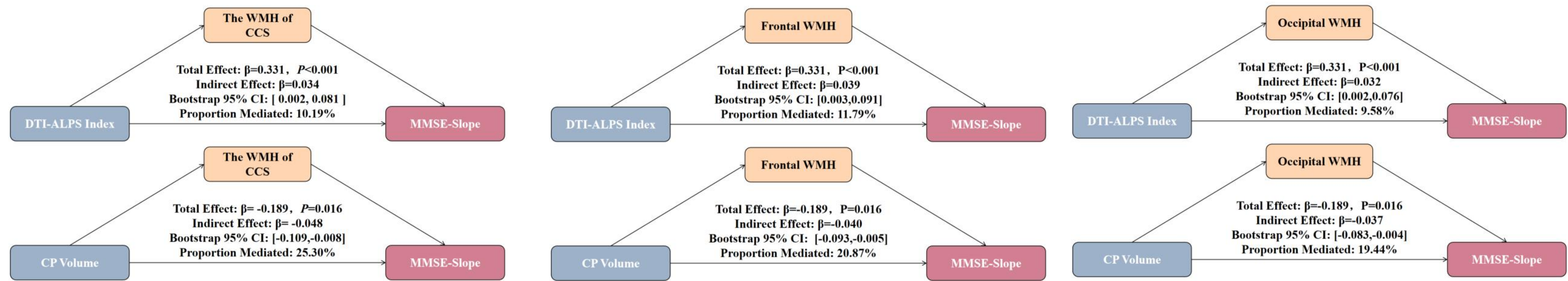


Figure 3. Mediating effects of regional WMH on cognitive decline.

4. Machine Learning For Predicting Cognitive Decline

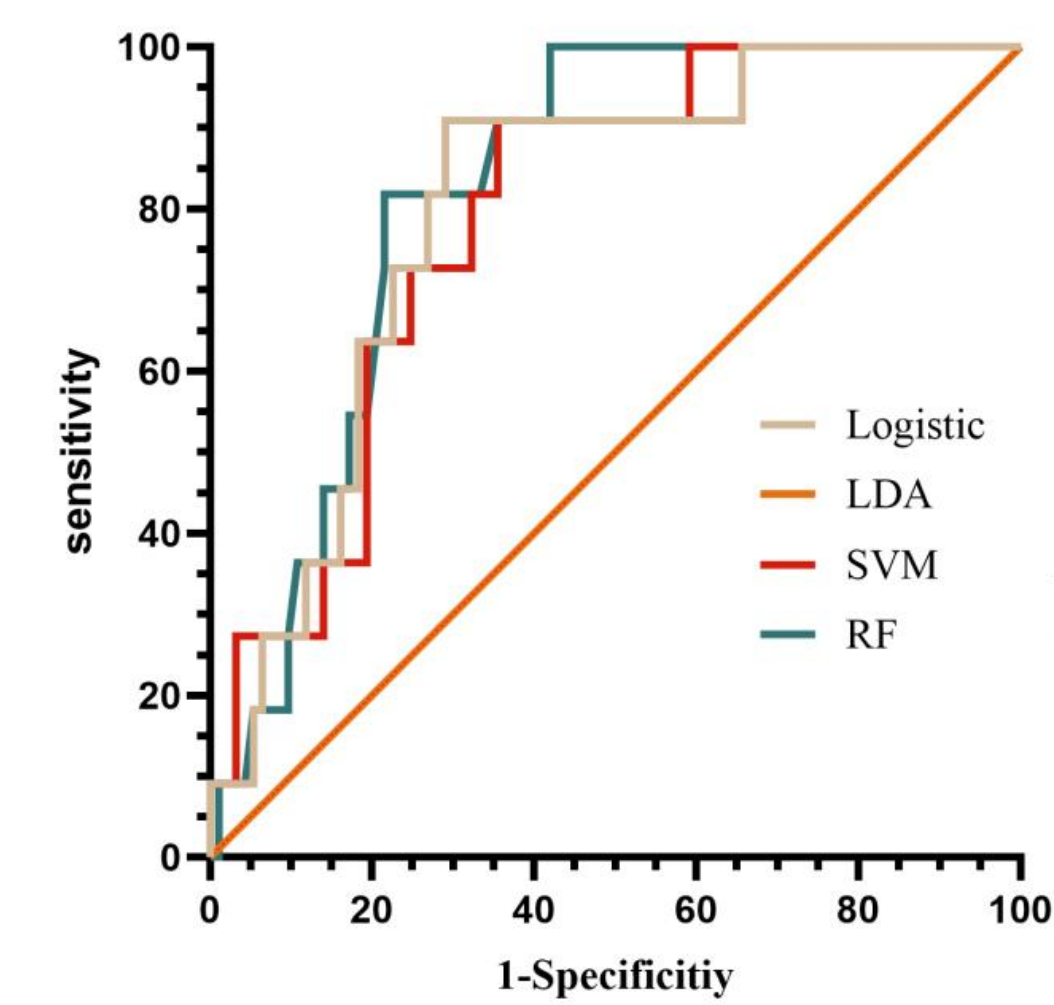


Figure 4. ROC curves for different machine learning prediction models.

■ CONCLUSIONS

Glymphatic impairment may precede WMH accumulation in the clinical AD continuum. The WMH region-specifically mediates the impact of glymphatic dysfunction on cognitive decline. A multi-modal neuroimaging prediction model integrating the WMH topography and glymphatic function demonstrates robust performance for AD progression.