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Plasma phospho-tau predicts differences in white matter microstructural complexity and cognition in non-demented older adults

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Abstract

Background: White matter (WM) measures from diffusion magnetic resonance imaging (dMRI) are sensitive to Alzheimer's disease (AD) pathology and cognitive impairment. Whereas most extant dMRI studies focused on uniformly-oriented WM fiber tracts, variations in crossing fiber regions also show sensitivity to mild cognitive impairment (MCI) and AD diagnoses. Such crossing fiber alterations may reflect differential disease effects on constituent fibers, suggesting that quantifying crossing fibers may provide unique markers of early WM changes and neurocognitive risk in AD and MCI. Although few methods exist for quantifying crossing fibers, recent findings show older age is associated with increased microstructural complexity (CX) a novel method to characterize in crossing fibers. The present study evaluated CX in relation to variation in plasma AD biomarkers and cognitive performance in older adults without dementia.

Method: Data from 48 participants included clinical evaluation, neuropsychological assessment, dMRI neuroimaging and venipuncture. SIMOA assays quantified the AD plasma biomarkers Aβ42, Aβ40, and tau phosphorylated at threonine181 (pTau-181). Participants were clinically characterized as cognitively normal (n=19) or with MCI (amnestic: n=18; non-amnestic: n=11). Diagnostic groups did not differ with respect to years of age and education, systolic and diastolic blood pressure, proportions of men and women, proportions of APOE ε4 allele carriers, or plasma biomarker levels. Processing of dMRI data followed the MRtrix fixel-based analysis (FBA) framework to estimate voxelwise CX data for all participants.

Result: Voxelwise regression of whole-brain CX on pTau-181 levels revealed a significant positive effect in the dorsal cingulum bundle and adjacent corpus callosum. Post hoc regression of mean CX sampled from significant voxels on pTau-181 showed greater pTau-181 level strongly predicts higher CX in this region (partial-R=0.579, p<0.001), even while controlling for age, education, and Montreal Cognitive Assessment (MoCA) score. Path analysis linking pTau-181 and cognition showed elevated

circulating pTau-181 levels strongly predict increased white matter complexity in mid-cingulum bundle, which in turn predicts reduced cognitive performance on measures of working memory, list learning, and semantic fluency.

Conclusion: Microstructural complexity in crossing fiber WM regions provides a sensitive marker of early WM alterations associated with elevated plasma phospho-tau and cognitive decrements in non-demented older adults.