

Association of plasma p-tau217-white matter hyperintensity network pattern with memory in older adults at risk for Alzheimer’s dementia

Madeline Ally¹, Pradyumna K. Bharadwaj¹, Rachel N. Schade², Andrew O’Shea², Sruti Rayaprolu³, Katie Rodriguez², Joshua Gertler², Isabella Nelson¹, Sreeshanth Katta¹, Zhiguang Huo⁴, Christian G. Habeck⁵, Steven T. DeKosky³, Adam J. Woods⁶, Dawn Bowers², Gene E. Alexander¹

¹Department of Psychology, University of Arizona, Tucson, AZ, ²Department of Psychology, University of Florida, Gainesville, FL, ³Department of Neurology, University of Florida, Gainesville, FL, ⁴Department of Biostatistics, University of Florida, Gainesville, FL, ⁵Department of Neurology, Columbia University, New York, NY, ⁶School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, TX



Introduction

Plasma phosphorylated tau 217 (p-tau217) is increasingly recognized as a sensitive blood-based biomarker of Alzheimer’s disease (AD) pathology that has demonstrated utility in identifying early AD-related changes.^{1,2} Recent research has begun to examine its relationship with additional markers of neurodegenerative and cerebrovascular brain aging.

White matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) reflect small vessel cerebrovascular disease and are prevalent in healthy aging.³ Greater WMH burden has been associated with cognitive decline,⁴ increased dementia risk,^{4,5} and, more recently, elevated plasma p-tau217.⁶⁻⁷ However, WMHs are not uniformly distributed throughout the brain,⁸ and it remains unclear whether plasma p-tau217 is associated with a specific regional pattern of white matter lesion load. Examining such patterns may provide insight into the cerebrovascular changes associated with early AD pathology and their relationship with cognitive functioning.

Objectives

- To identify a regional WMH volume (rWMHV) pattern related to plasma p-tau217 in healthy older adults with elevated dementia risk.
- To examine its relationship with demographics, clinical characteristics, and cognition.

Participant Characteristics

n = 154	
Age (years)	70.93 ± 4.82
Female	95 (61.69%)
White, non-Hispanic	132 (85.71%)
Bachelor’s degree or greater	108 (70.13%)
APOE ε4 carrier	58 (37.66%)
Hypertension	56 (36.36%)
Mean plasma p-tau217 level (pg/mL)	0.42 ± 0.28
Plasma p-tau217 CV (%)	7.55 ± 5.08
Total WMH volume (cm ³)	7.05 ± 9.43

Table 1. Mean ± SD or frequency (%) of demographic and clinical variables.
APOE, apolipoprotein E; CV, coefficient of variation

A p-tau217-related rWMHV network pattern was characterized by greater WMH volume in bilateral temporal and left parietal regions with relative reductions in bilateral frontal, cerebellar, and brainstem areas.

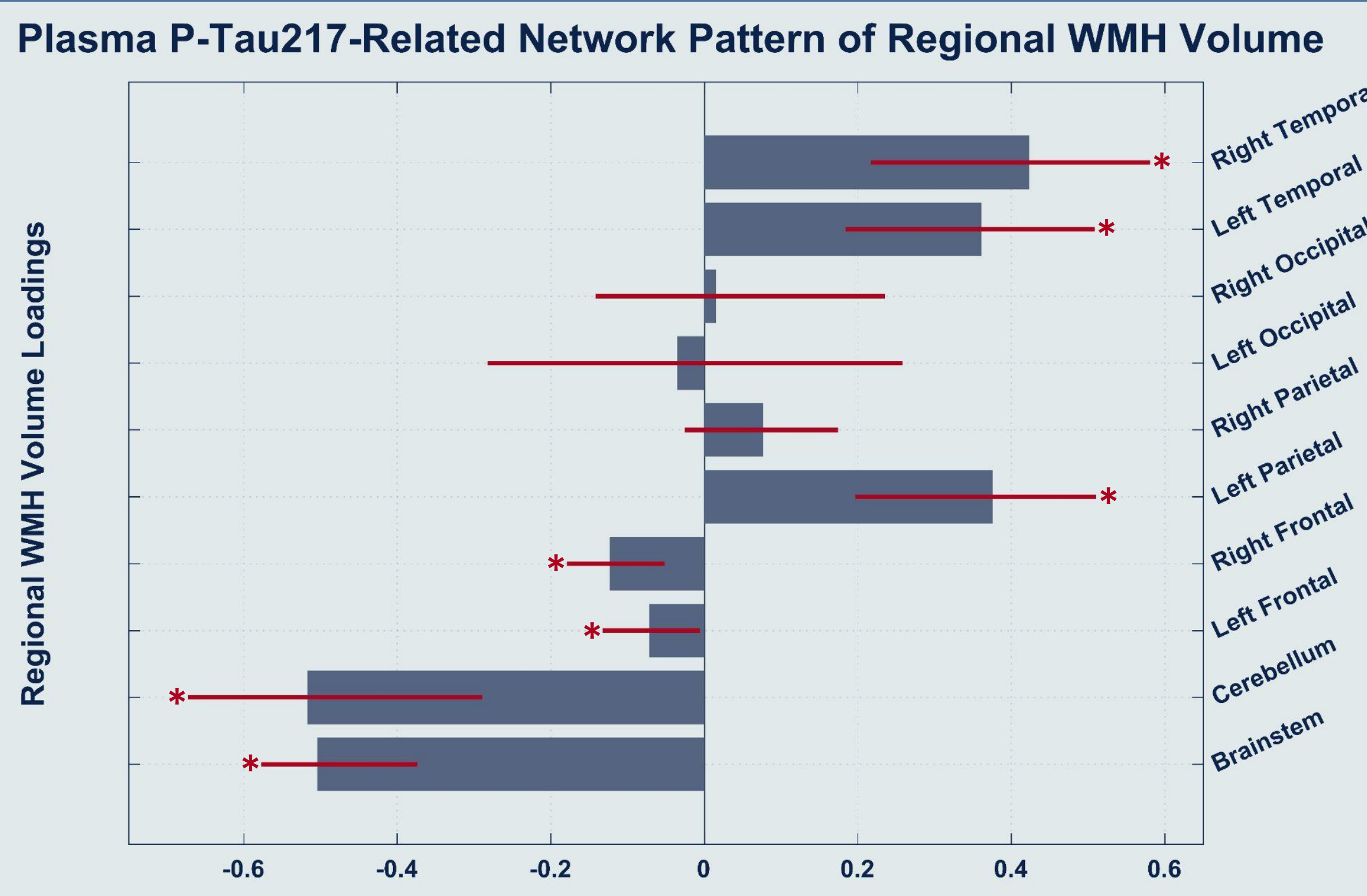


Figure 2. Plasma p-tau217-related loadings for the SSM network pattern of regional WMH lobar volume. The blue bars indicate point estimates for the loadings, the red lines indicate the 95% confidence intervals, and asterisks reflect significant lobes contributing to the covariance pattern.

Results

Greater pattern expression associated with increased plasma p-tau217 concentrations ($R^2 = 0.073$, $p = 7.234E-04$). Among demographic and clinical variables, only older age predicted greater pattern expression.

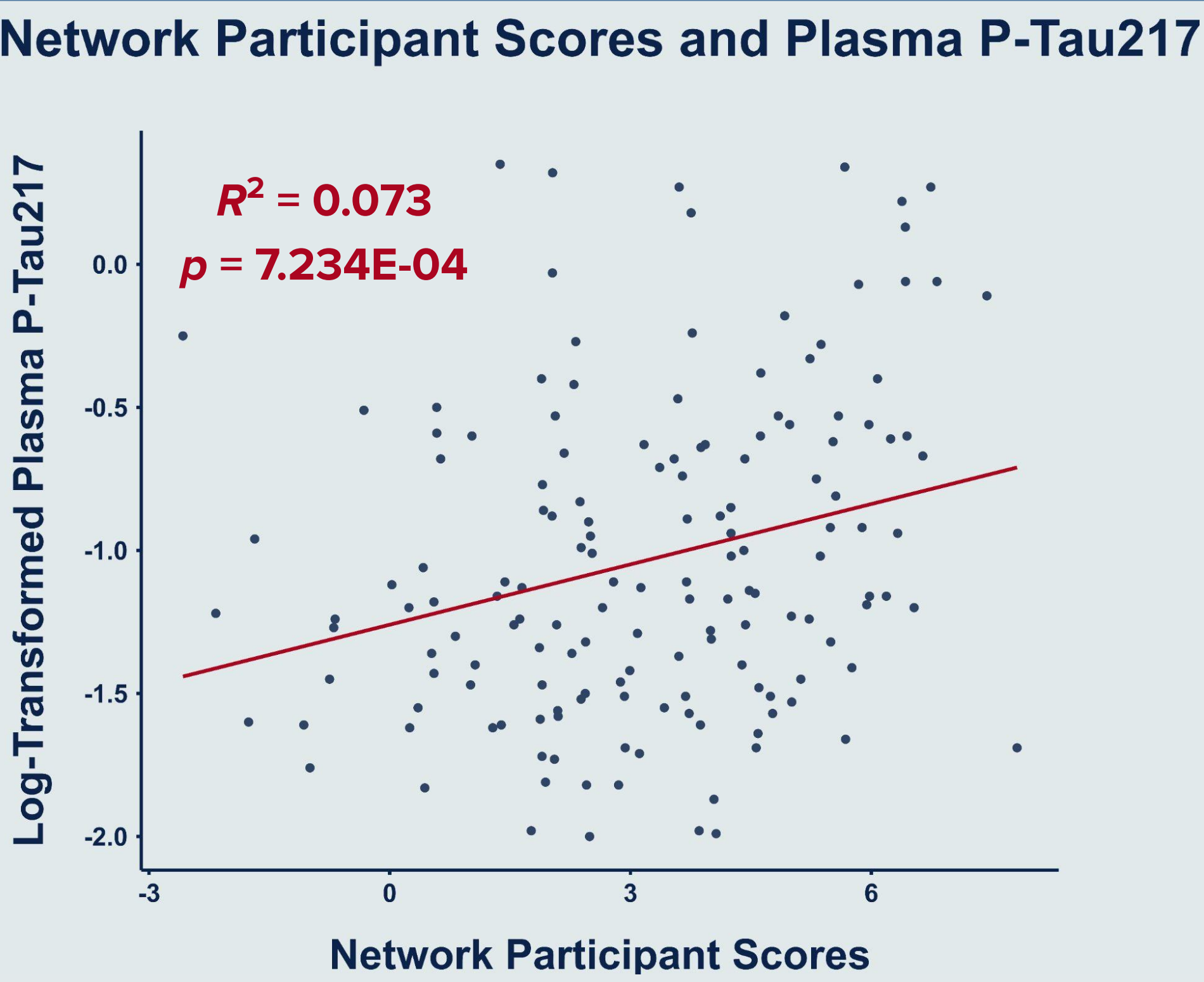


Figure 3. Scatterplot showing the relationship between p-tau217-related rWMHV network participant scores and log-transformed plasma p-tau217 levels.

After controlling for demographic and clinical covariates and FDR p-value correction, greater pattern expression was associated with worse Logical Memory retention.

Cognitive Measures		β [95% CI]	FDR-p
Memory	RAVLT Learning Trials A1-A5 Total Correct	-0.069 [-0.995, 0.371]	.368
	RAVLT Percent Forgetting (Trial A5 - Long Delay) / Trial A5	0.114 [-0.528, 2.835]	.265
	LM Percent Retention LM-II Total / LM-I Total	-0.245 [-2.385, -0.443]	.015
Executive Function	Stroop Color-Word Total Correct Items on Subtest	-0.097 [-0.964, 0.249]	.369
	NIH Examiner 2-Back Total Correct Items	-0.127 [-3.066, 0.438]	.369
	NIH Examiner Set-Shifting Total Correct Shift Items	0.065 [-0.006, 0.013]	.448
Processing Speed	Stroop Word Reading Total Correct Items on Subtest	0.060 [-0.567, 1.193]	.483
	CalCAP Reaction Time Simple Trial Mean Reaction Time	-0.086 [-14.302, 5.045]	.483
	NIH Examiner CPT Reaction Time Target Median Reaction Time	-0.081 [-0.007, 0.003]	.483

Figure 4. Regression analyses between p-tau217-related rWMHV pattern and cognition.
CalCAP, California Continuous Assessment Package; CPT, Cognitive Performance Test; LM, Logical Memory I and II subtests from Wechsler Memory Scale III; RAVLT, Rey Auditory Verbal Learning Test

Methods

Participants: 154 older adults with subjective cognitive complaints and a family history of dementia were included, screened to exclude cognitive impairment and major medical and psychiatric conditions, including kidney disease.

MRI Acquisition and Analysis: T1-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) brain scans were acquired on 3T Siemens Skyra (UA) and Prisma (UF) MRI scanners. Total intracranial volume (TIV) was derived using SPM12, and total and rWMHV was quantified from T1 and FLAIR scans using the Lesion Segmentation Toolbox with SPM12 and FreeSurfer (Figure 1).⁹

Plasma Acquisition and Analysis: Blood samples were drawn following standard procedures. Plasma p-tau217 levels were measured and replicated using the Quanterix Simoa platform. Mean concentration of the two assays was analyzed, and those with a coefficient of variation $\geq 20\%$ were excluded.

Cognition: Neurocognitive measures were selected a priori to reflect domains typically affected in healthy aging, including memory, executive function, and processing speed.

Statistical Analysis: Multivariate network covariance analysis was conducted, using the Scaled Subprofile Model (SSM)¹⁰⁻¹¹ with 10,000 bootstrap iterations, to identify a p-tau217-related rWMHV network pattern. Multiple regression examined associations of imaging (TIV, site), demographic (age, sex, race/ethnicity, education), and clinical (apolipoprotein E [APOE] ε4 carrier status, hypertension) covariates with SSM pattern scores. Linear regression tested associations between these pattern scores and cognitive performance with adjustment for the above covariates and false discovery rate (FDR) correction ($p < .05$) within cognitive domains.

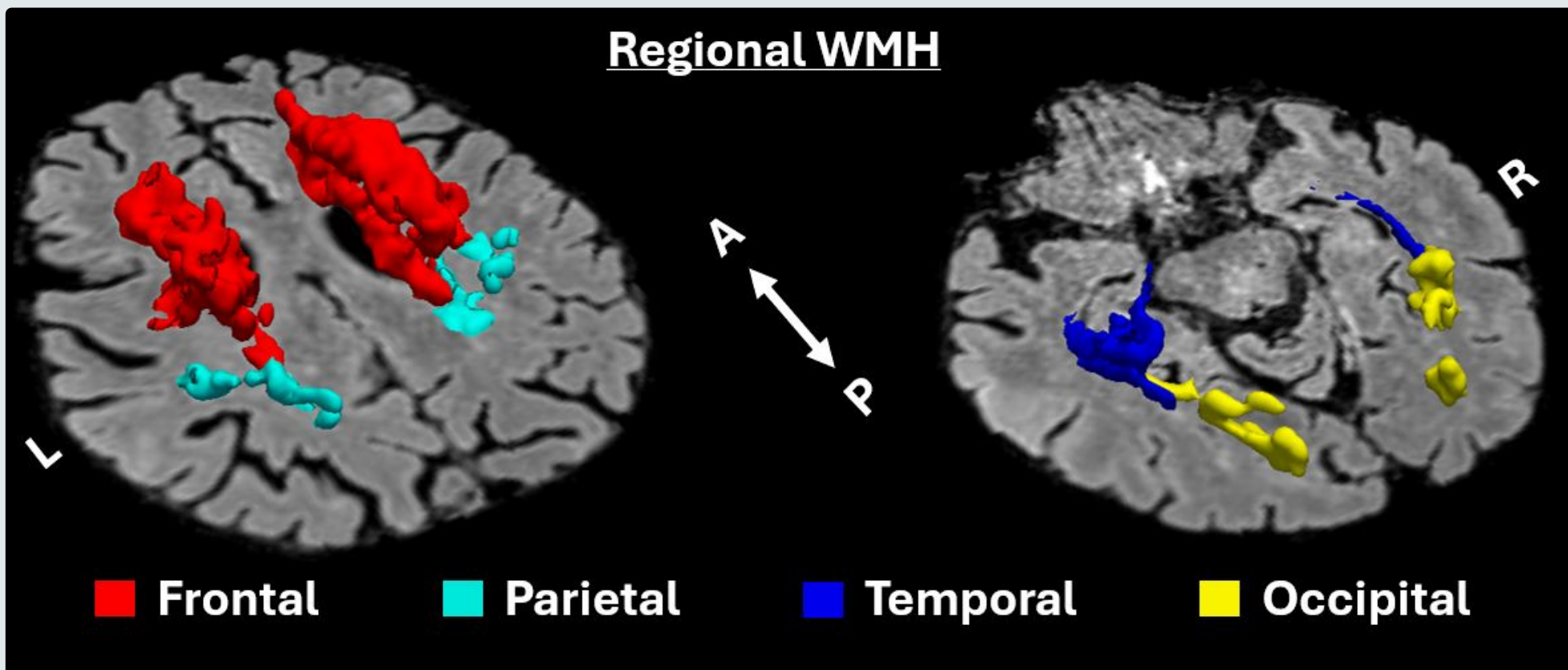


Figure 1. An illustration of regional white matter hyperintensity lobar volume segmentation

Conclusions

In healthy older adults with elevated AD dementia risk, plasma p-tau217 was related to a rWMHV network pattern, preferentially involving temporoparietal brain regions, whose expression was associated with older age and distinctly predicted worse memory retention.

Overall, these findings further support a link between early AD pathology and vascular brain health in the context of cognitive aging and dementia risk.

References

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