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Authors

Membreno, Rachel

Thomas, Kelsey R

Calcetas, Amanda T

et al.

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Regional White Matter Hyperintensities Relate to Specific Cognitive Abilities in Older Adults Without Dementia

Rachel Membreno, Kelsey R. Thomas, PhD,†‡ Amanda T. Calcetas, BS,‡ Lauren Edwards, MS,§ Maria Bordyug, BS,‡ Maya Showell, MS,† Morgan Stanfill, BS,† Einat K. Brenner, PhD,‡ Kayla S. Walker,* Lindsay J. Rotblatt, PhD,‖‡ Adam M. Brickman, PhD,¶#** Emily C. Edmonds, PhD,††‡‡ and Katherine J. Bangen, PhD,†‡ for the Alzheimer's Disease Neuroimaging Initiative*

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From the *Department of Psychology, San Diego State University; †Research Service, VA San Diego Healthcare System; ‖Psychology Service, VA San Diego Healthcare System; ‡Department of Psychiatry, University of California San Diego; §San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA; ¶Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University; #Gertrude H. Sergievsky Center, Columbia University; **Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY; ††Banner Alzheimer's Institute; and ‡‡Department of Psychology, University of Arizona, Tucson, AZ.

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Reprints: Katherine J. Bangen, PhD, 3350 La Jolla Village Drive (151B), San Diego, CA 92161 (e-mail: kbangen@health.ucsd.edu).

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Introduction: White matter hyperintensities (WMHs) are magnetic resonance imaging markers of small vessel cerebrovascular disease that are associated with cognitive decline and clinical Alzheimer disease. Previous studies have often focused on global or total WMH; less is known about associations of regional WMHs and cognitive abilities among older adults without dementia.

Methods: A total of 610 older adults with normal cognition (n = 302) or mild cognitive impairment (n = 308) from the Alzheimer's Disease Neuroimaging Initiative underwent neuropsychological testing and magnetic resonance imaging. Linear regression models examined associations between regional WMH volumes and cognition, adjusting for age, sex, education, apolipoprotein E ε4 allele frequency, and pulse pressure.

Results: Among all participants, greater regional WMH volume in all lobes was associated with poorer performance on memory and speed/executive functioning. Among participants with normal cognition, greater temporal and occipital WMH volumes were associated with poorer memory, whereas no regional WMH volumes were associated with speed/executive function.

Discussion: Results show that greater regional WMH volume relates to poorer cognitive functioning—even among those with normal cognition. Together with results from previous studies, our findings raise the possibility that WMH may be a useful therapeutic target and/or important effect modifier in treatment or prevention dementia trials.

Key Words: white matter hyperintensities, Alzheimer disease cognition, neuropsychology, magnetic resonance imaging, cerebrovascular disease

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White matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI) are common in older adults.[1,2] Although pathologically heterogenous, WMH are thought to reflect small vessel cerebrovascular disease[3] and have been associated with cognitive decline and increased risk of mild cognitive impairment (MCI) and dementia including Alzheimer disease (AD).[4–8]

Many previous studies examining associations of WMH and cognitive functioning have focused on global or total WMH volume,[9–11] although some studies have suggested differential relationships of regional WMH with specific cognitive abilities. Recent work by Moura et al[12] found that larger anterior WMH volume in particular was associated with poorer executive function although other studies have found that WMH impair executive function

regardless of location.[13] A recent study by Kamal et al[14] found that greater WMH volumes in frontal, temporal, parietal, and occipital lobes were associated with poorer episodic memory and executive function among individuals with normal cognition and MCI. Studies examining cognition categorically by comparing cognitive groups have demonstrated that WMH in parietal, temporal, and/or occipital regions in particular are most closely associated with subtle cognitive decline, MCI, and AD.[5,7,8,15]

Given the relatively limited number of studies that have focused on the effect of regional WMH volumes on cognitive function, as well as inconsistent findings across studies, we sought to clarify the associations of lobar WMH volumes with episodic memory and executive function in a well-characterized sample of older adults who underwent neuropsychological assessment. We hypothesized that (1) greater frontal WMH volume would be associated with poorer executive functioning, and (2) greater parietal, temporal, and occipital WMH volumes would be associated with lower episodic memory performance.

METHODS

The ADNI Data Set

In preparation for this study, data were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI began in 2003 as public-private partnership led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to examine whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Data Availability

ADNI data were obtained from adni.loni.usc.edu and are accessible to scientific investigators who have been approved by the ADNI Data Sharing and Publication Committee and who agree to the terms of the ADNI Data Use Agreement for the purpose of the replication of procedures and results.

Participants

Enrollment criteria for ADNI 1 have been previously described in detail.[16] Briefly, participants from ADNI ranged from 55 to 90 years old, had $\geq$ 6 years of education, were English or Spanish speakers, were free of any significant systemic illness or neurological disease, had a score of <6 on the Geriatric Depression Scale, had a score <5 on the modified Hachinski Ischemic Scale, adequate vision and hearing for neuropsychological assessment, and had a reliable study partner. The current study included 608 older adults free of dementia who had available neuropsychological and lobar WMH volume at baseline. ADNI was approved by the institutional review boards at all the participating institutions. Written informed consent was obtained from all participants at each participating study site.

Cognitive Groups

Participants were classified as having either normal cognition (CN) or MCI utilizing an actuarial neuropsychological diagnostic method.[17,18] Six neuropsychological measures were used in this diagnostic classification and selected given their routine use in determining early cognitive changes in AD, they assessed multiple cognitive domains, and they have been used by numerous previous studies applying these criteria to classify MCI within ADNI.[17,19,20] These 6 measures included 2 measures of episodic memory: Rey Auditory Verbal Learning Test 30-minute delayed free recall (number of words recalled) and Rey Auditory Verbal Learning Test recognition (number of words correctly recognized minus false-positive errors); 2 measures of language Animal Fluency total score and 30-item Boston Naming Test total score; and 2 measures of speed/executive function: Trail Making Test, Parts A and B (times to completion). Raw neuropsychological scores for each measure were converted to an age-, education-, and sex-adjusted z-score based on a sample of individuals who remained classified as cognitively normal throughout their participation in the ADNI study.[21,22] Participants were classified as MCI if they had an impaired score (defined as > 1 SD below the demographically adjusted normative mean) on both measures within at least 1 cognitive domain (ie, memory, language, or speed/executive function) or had an impaired score (defined as > 1 SD below the demographically adjusted normative mean) on 1 measure in each of the 3 cognitive domains sampled. Participants who did not meet the actuarial neuropsychological MCI criteria were classified as cognitively normal.

Neuropsychological Composites Scores

Domain composite scores for episodic memory and speed/executive functioning were calculated as the mean of the 2 demographically adjusted z-scores within each domain. As described above, the 2 measures of episodic memory were Rey Auditory Verbal Learning Test 30-minute delayed free recall and Rey Auditory Verbal Learning Test recognition. The 2 measures of speed/executive functioning were Trail Making Test, Parts A and B times to completion.

MRI Acquisition

MRI data were collected as part of ADNI 1, the first phase of the ADNI project study. An in-depth description of ADNI MRI data acquisition is located online (https://www.loni.usc.edu). A standardized protocol was applied and verified across ADNI sites and platforms.[23] All imaging was performed on 1.5 T systems. A three-dimensional T1-weighted magnetization prepared rapid gradient echo sequence was acquired in the sagittal orientation. For WMH quantification, an additional proton density/T2-weighted fast spin each sequence was obtained in the axial orientation. All imaging sites were required to pass phantom-based monitoring and scanner validation tests.[23]

MR Image Processing

MR imaging data used in this study were previously processed and downloaded from https://www.loni.usc.edu. Briefly, T1-weighted structural scans were motion-corrected and segmented and parcellated using an analysis based on FreeSurfer to obtain measures of total intracranial volume.[24] WMH were detected using an automated method using coregistered T1-weighted, T2-weighted, and PD-weighted images.[25,26] The T1-weighted image was skull-stripped and nonlinearly aligned to a minimum deformation template.[27,28] Nonbrain tissues were removed from T2-weighted and PD-weighted images, which were warped to the space of the minimum deformation format scan based on the T1 alignment and warping parameter. WMH were detected in minimum deformation template space based on image intensities of the PD, T1, and T2 images combined

with a spatial prior (ie, the prior probability of WMH occurring at a given voxel) and a contextual prior (ie, the conditional probability of WMH occurring at a given voxel based on the presence of WMH at neighboring voxels). WMH volumes quantified with this method have been shown to agree strongly with WMH volumes estimated on fluid-attenuated inversion recovery MRI).[26] Regional WMH volumes of the frontal, temporal, parietal and occipital lobes were obtained using an a priori lobar atlas.[29] To obtain volumes, voxels labeled as WMHs were summed and multiplied by voxel dimensions.

Statistical Analyses

Analysis of variance or χ^2 tests examined differences in demographic and clinical characteristics by cognitive group (CN, MCI). Hierarchical linear regression models were used to examine the relationship between regional WMH and cognition. Eight separate regression models were run. Each of the 4 regional WMH volumes was examined in 2 separate models: 1 model with the episodic memory composite score serving as the dependent variable and a second model with the speed/executive function composite score serving as the dependent variable. For all models, we adjusted for demographic data (ie, age, sex, and education), apolipoprotein E (APOE) ε4 allele frequency (0, 1, and 2), and pulse pressure (calculated as systolic blood pressure minus diastolic blood pressure). Pulse pressure was included as a covariate, given the potential importance of arterial stiffness and blood pressure in WMH development.[30] For all models, covariates were entered in step 1 and regional WMH was entered as the independent variable of interest in step 2. The distributions of WMH volumes were highly positively skewed for all regions, so a log-transformation was applied, and transformed WMH volumes were used in all analyses.

Sensitivity analyses were performed, examining whether the main results remained the same in the subgroup of CN participants (ie, excluding participants with MCI). To address potential inflation of type I error resulting from multiple comparisons, we applied the Benjamini-Hochberg procedure[31] to control the false discovery rate (FDR). For all analyses, we set alpha at 0.05 to test for statistical significance. Analyses were conducted using Statistical Package for Social Science (SPSS) version 28 (SPSS IBM, New York, NY).

RESULTS

Participants Characteristics

Demographic and clinical characteristics of the total sample and by cognitive status (CN vs. MCI) are presented in Table 1. The mean age of the sample was 75.3 years, and 40.1% of the sample were women. The sample was highly educated, with a mean education of 15.8 years. The MCI group was slightly younger, more likely to be APOE ε4 carriers, and, as expected, performed more poorly on episodic memory and speed/executive function measures relative to the CN group. There were no differences between the cognitive groups in terms of education, sex, race, ethnicity, or vascular risk burden (ie, pulse pressure or Hachinski risk score).

Associations of Regional WMH Volume and Cognitive Performance Across the Entire Sample

Adjusting for age, sex, education, APOE ε4 frequency, and pulse pressure, greater regional WMH volume in all 4 lobes was associated with worse episodic memory and worse speed/executive function performance across all participants. See Table 2 and Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A456 for associations with episodic memory and Table 3 and Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/WAD/A456 for associations with speed/executive functioning.

Associations of Regional WMH Volume and Cognitive Performance Among Participants With Normal Cognition

When models were rerun in the subsample restricted to CN participants, adjusting for the covariates above, greater temporal and occipital WMH volume were associated with poorer episodic memory performance. Regional WMH volume was not associated with speed/executive function performance. See Table 4 and Supplemental Figure 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A456 for associations with episodic memory and Table 5 and Supplemental Figure 4, Supplemental Digital Content 1, http://links.lww.com/WAD/A456 for associations with speed/executive functioning.

FDR

The statistical significance of all reported findings was retained under a 0.05 FDR.

DISCUSSION

In a large, well-characterized sample of older adults free of dementia, we found that higher regional WMH volumes were associated with poorer functioning in cognitive abilities. Specifically, across the entire sample, we found higher WMH volume in all 4 lobes was associated with poorer episodic memory and speed/executive function. When the sample was restricted to CN participants only, findings were attenuated, and only those associations between temporal and occipital WMH volumes and episodic memory remained significant. The pattern of findings suggests that WMH may affect multiple cognitive functions regardless of location, although only occipital and temporal WMH were associated with cognition when including individuals with normal cognition only.

We hypothesized that frontal WMH volume would relate to speed/executive functioning, whereas parietal, temporal, and occipital WMH volumes would be associated with episodic memory performance. Inconsistent with these regionally specific hypotheses, our findings across the entire sample showed that WMH related to speed/executive function and episodic memory regardless of location. Notably, our finding for speed/executive function is consistent with previous research suggesting that WMH may impair this domain regardless of location.[13] Findings from previous studies relating regional WMH to episodic memory have been mixed, although frontal, parietal, temporal, and occipital WMH volume have all been associated with this deficit in this cognitive domain.[5,7,8,13,15] Notably, most of these previous studies have focused on group comparisons of mean WMH volume among individuals with and without memory impairment or elevated risk for developing AD. In contrast, we examined neuropsychological performance as a continuous variable. We found that WMH may impair episodic memory and speed/executive function regardless of location, which is consistent with evidence that WMH may disrupt

TABLE 1. Participant Characteristics for the Entire Sample and by Cognitive Status

Variable	Total sample (n = 610)	CN (n = 302)	MCI (n = 308)	F or χ^2	*P*
Demographics and clinical variables					
Age, years, mean (SD)	75.30 (6.63)	75.93 (6.15)	74.69 (7.02)	5.34	0.021
Education, years, mean (SD)	15.83 (2.93)	16.00 (2.84)	15.67 (3.00)	1.95	0.163
Women/men, n (%)	245/365 (40.2/59.8)	126/176 (41.7/58.3)	119/189 (38.6/61.3)	—	0.437
Pulse pressure, mm Hg, mean (SD)	60.14 (15.62)	59.33 (14.70)	60.93 (16.46)	1.59	0.208
Hachinski risk score, mean (SD)	0.60 (0.70)	0.58 (.66)	0.62 (0.74)	0.36	0.548
Race, n (%)	—	—	—	2.490	0.477
American Indian or Alaskan Native	1 (0.2)	0	1 (0.3)	—	—
Asian	12 (2.0)	5 (1.7)	12 (3.9)	—	—
Black or African American	30 (4.9)	12 (4.0)	18 (5.8)	—	—
White	567 (93.0)	285 (94.4)	282 (91.6)	—	—
Ethnicity, n (%)	—	—	—	3.17	0.156
Hispanic or Latino	13 (2.1)	3 (1.0)	10 (3.2)	—	—
Not Hispanic or Latino	593 (97.2)	297 (98.3)	296 (96.1)	—	—
Unknown	4 (0.7)	2 (0.7)	2 (0.6)	—	—
APOE ε4, n (%)	—	—	—	41.54	< 0.001
0 alleles	343 (56.2)	208 (68.9)	135 (43.8)	—	—
1 allele	215 (35.2)	81 (26.8)	134 (43.5)	—	—
2 alleles	52 (8.5)	13 (4.3)	39 (12.7)	—	—
Cognitive functioning*, mean (SD)					
Episodic memory	−0.88 (1.24)	−0.03 (0.79)	−1.71 (1.01)	—	< 0.001
Speed/executive function	−0.66 (1.55)	0.03 (0.73)	−1.34 (1.83)	—	< 0.001

APOE indicates apolipoprotein E; CN, cognitively normal; MCI, mild cognitive impairment; mm Hg, millimeters of mercury.
*Cognitive composite z-scores were computed as the average of demographically adjusted z-scores of measures within that cognitive domain.

networks and have both local and remote effects, thereby affecting multiple cognitive domains.[1,32]

When we restricted the analysis to the subsample of participants with normal cognition, it was revealed that temporal and occipital WMH in particular related to cognition, which is consistent with findings from previously published reports examining regional WMH-cognition associations across different groups.[8] For instance, we previously showed that within the ADNI cohort, individuals classified with objectively defined subtle cognitive decline show elevated temporal and occipital WMH volume relative to cognitively unimpaired adults.[5] In addition, we previously showed that temporal and occipital WMH in particular predict a decline in everyday functioning among older adults without clinical dementia. Others showed increased WMH volume particularly in posterior regions (and most prominently in occipital and parietal regions) among individuals with autosomal dominant genetic mutation for AD.[15] These results demonstrated that WMHs were present several years before the predicted onset of symptoms of dementia among individuals with autosomal dominant genetic mutations for AD, suggesting WMHs—particularly in posterior regions—reflect pathologic changes that contribute to onset and progression of clinical symptoms. Taken together, this growing body of research examining regional WMH in aging and dementia risk suggest that WMH in temporal, parietal, and/or occipital regions may play a particularly important role in cognitive decline and AD risk.

There may be multiple pathways by which WMH affect cognition. WMH are pathologically heterogeneous and may reflect processes related to demyelination, axonal loss due to ischemia or neuronal death, microglia and endothelial activation, or cerebral amyloid angiopathy.[3,15,33] Growing evidence highlights the heterogeneity of WMH pathophysiology and suggests that nonvascular mechanisms (eg, neurodegeneration and neuroinflammation) could play a role in AD-related WMH.[34] Overall, a better understanding of WMH heterogeneity may be important for precision medicine and predicting individual cognitive trajectories.

The present study is not without limitations, including the relatively homogeneous sample given participants were generally highly educated, White, and had relatively low vascular risk burden (ie, potential participants were excluded for Hachinski Ischemic Scale scores > 4), which may result in our findings being less generalizable to other populations. However, although our sample is relatively healthy in terms of vascular risk, our results demonstrating WMH volume-cognition associations suggest that even relatively subtle cerebrovascular changes may affect cognition function. Another important limitation is the cross-sectional design, which limits our ability to make causal inferences or examine cognitive trajectories. Strengths of the present study include a well-characterized and large sample of older adults enrolled in a national study on aging and AD, examination of multiple cognition domains, and quantification of regional WMH volumes.

In conclusion, we showed that greater WMH volume relates to poorer cognition in specific abilities among older adults without dementia. Among all participants, greater regional WMH volume in all lobes was associated with poorer performance on episodic memory and speed/executive functioning measures. Among participants with normal cognition only, greater temporal and occipital WMH volumes were associated with poorer episodic memory performance, whereas regional WMH volumes were not associated with speed/executive function. Given this sample has a relatively low vascular risk burden based on study inclusion criteria, results suggest that even relatively mild cerebrovascular changes may affect cognitive abilities. Future longitudinal studies should examine whether reducing modifiable vascular risk factors improves or slows the decline in cognitive

TABLE 2. Effects of Hierarchical Linear Regression Models Examining Associations of Regional WMH Volume and Episodic Memory Across the Entire Sample (n = 610)

	Frontal					Temporal					Parietal					Occipital				
	B	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**
Block 1																				
Age	0.028	0.007	0.149	**< 0.001**	0.144	0.028	0.007	0.149	**< 0.001**	0.144	0.028	0.007	0.149	**< 0.001**	0.144	0.028	0.007	3.724	**< 0.001**	0.144
Educ	−0.010	0.017	−0.023	0.566	−0.022	−0.010	0.017	−0.023	0.566	−0.022	−0.010	0.017	−0.023	0.566	−0.022	−0.010	0.017	−0.575	0.566	−0.022
Sex	0.022	0.099	0.009	0.828	0.008	0.022	0.099	0.009	0.828	0.008	0.022	0.099	0.009	0.828	0.008	0.022	0.099	0.217	0.828	0.008
APOE ε4 sum	−0.465	0.075	−0.244	**< 0.001**	−0.240	−0.465	0.075	−0.244	**< 0.001**	−0.240	−0.465	0.075	−0.244	**< 0.001**	−0.240	−0.465	0.075	−6.201	**< 0.001**	−0.240
PP	−0.002	0.003	−0.029	0.465	−0.028	−0.002	0.003	−0.029	0.465	−0.028	−0.002	0.003	−0.029	0.465	−0.028	−0.002	0.003	−0.731	0.465	−0.028
Block 2																				
Age	0.031	0.008	0.166	**< 0.001**	0.157	0.035	0.008	0.185	**< 0.001**	0.174	0.031	0.008	0.168	**< 0.001**	0.158	0.032	0.008	4.225	**< 0.001**	0.163
Educ	−0.010	0.017	−0.023	0.561	−0.023	−0.011	0.016	−0.025	0.520	−0.025	−0.011	0.017	−0.027	0.494	−0.026	−0.010	0.017	−0.592	0.554	−0.023
Sex	0.017	0.099	0.007	0.860	0.007	−0.003	0.099	−0.001	0.975	−0.001	0.025	0.099	0.010	0.802	0.010	0.002	0.099	0.021	0.983	0.001
APOE ε4 sum	−0.466	0.075	−0.244	**< 0.001**	−0.241	−0.453	0.074	−0.238	**< 0.001**	−0.234	−0.465	0.075	−0.244	**< 0.001**	−0.240	−0.464	0.075	−6.222	**< 0.001**	−0.240
PP	−0.002	0.003	−0.024	0.534	−0.024	−0.001	0.003	−0.017	0.655	−0.017	−0.002	0.003	−0.024	0.544	−0.023	−0.002	0.003	−0.545	0.586	−0.021
WMH volume	−0.062	0.030	−0.083	**0.038**	−0.080	−0.081	0.022	−0.149	**< 0.001**	−0.143	−0.048	0.024	−0.080	**0.047**	−0.077	−0.064	0.025	−2.569	**0.010**	−0.099

Bold *P*-values are significant $P < 0.05$. Block 1 included all covariates and Block 2 added regional WMH volume as the primary independent variable to the model. Regional WMH volumes were examined in separate models. APOE indicates apolipoprotein E; Educ, education; sr, semipartial correlation coefficient; WMH, white matter hyperintensities.

TABLE 3. Effects of Hierarchical Linear Regression Models Examining Associations of Regional WMH Volume and Speed/Executive Functioning Across the Entire Sample (n = 610)

	Frontal					Temporal					Parietal					Occipital				
	B	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**	**B**	**SE**	**β**	***P***	**sr**
Block 1																				
Age	0.036	0.010	0.155	**< 0.001**	0.150	0.036	0.010	0.155	**< 0.001**	0.150	0.036	0.010	0.155	**< 0.001**	0.150	0.036	0.010	0.155	**< 0.001**	0.150
Educ	0.057	0.021	0.107	**0.008**	0.105	0.057	0.021	0.107	**0.008**	0.105	0.057	0.021	0.107	**0.008**	0.105	0.057	0.021	0.107	**0.008**	0.105
Sex	0.222	0.128	0.070	0.084	0.069	0.222	0.128	0.070	0.084	0.069	0.222	0.128	0.070	0.084	0.069	0.222	0.128	0.070	0.084	0.069
APOE ε4 sum	−0.143	0.097	−0.060	0.138	−0.059	−0.143	0.097	−0.060	0.138	−0.059	−0.143	0.097	−0.060	0.138	−0.059	−0.143	0.097	−0.060	0.138	−0.059
PP	−0.004	0.004	−0.039	0.337	−0.038	−0.004	0.004	−0.039	0.337	−0.038	−0.004	0.004	−0.039	0.337	−0.038	−0.004	0.004	−0.039	0.337	−0.038
Block 2																				
Age	0.040	0.010	0.171	**< 0.001**	0.163	0.045	0.010	0.191	**< 0.001**	0.179	0.042	0.010	0.180	**< 0.001**	0.170	0.046	0.010	0.198	**< 0.001**	0.187
Educ	0.056	0.021	0.107	**0.008**	0.105	0.055	0.021	0.104	**0.009**	0.103	0.054	0.021	0.101	**0.012**	0.099	0.056	0.021	0.106	**0.008**	0.104
Sex	0.217	0.128	0.068	0.091	0.067	0.191	0.127	0.060	0.134	0.059	0.227	0.128	0.072	0.075	0.071	0.177	0.126	0.056	0.162	0.055
APOE ε4 sum	−0.145	0.096	−0.061	0.133	−0.060	−0.129	0.096	−0.054	0.179	−0.053	−0.144	0.096	−0.060	0.136	−0.059	−0.142	0.095	−0.059	0.136	−0.059
PP	−0.003	0.004	−0.035	0.392	−0.034	−0.003	0.004	−0.028	0.493	−0.027	−0.003	0.004	−0.032	0.424	−0.032	−0.003	0.004	−0.025	0.525	−0.025
WMH volume	−0.077	0.038	−0.082	**0.045**	−0.080	−0.101	0.028	−0.149	**< 0.001**	−0.143	−0.082	0.031	−0.108	**0.009**	−0.104	−0.148	0.032	−0.189	**< 0.001**	−0.182

Bold *P*-values are significant $P < 0.05$. Block 1 included all covariates and Block 2 added regional WMH volume as the primary independent variable to the model. Regional WMH volumes were examined in separate models. APOE indicates apolipoprotein E; Educ, education; sr, semipartial correlation coefficient; WMH, white matter hyperintensities.

TABLE 4. Effects of Hierarchical Linear Regression Models Examining Associations of Regional WMH Volume and Episodic Memory Among the Subsample of Cognitively Normal Participants (n = 302)

	Frontal					Temporal					Parietal					Occipital				
	B	SE	β	*P*	sr	B	SE	β	*P*	sr	B	SE	β	*P*	sr	B	SE	β	*P*	sr
Block 1																				
Age	0.010	0.007	0.078	0.182	0.076	0.010	0.007	0.078	0.182	0.076	0.010	0.007	0.078	0.182	0.076	0.010	0.007	0.078	0.182	0.076
Educ	0.029	0.016	0.106	0.072	0.102	0.029	0.016	0.106	0.072	0.102	0.029	0.016	0.106	0.072	0.102	0.029	0.016	0.106	0.072	0.102
Sex	0.304	0.094	0.191	**0.001**	0.185	0.304	0.094	0.191	**0.001**	0.185	0.304	0.094	0.191	**0.001**	0.185	0.304	0.094	0.191	**0.001**	0.185
APOE ε4 sum	−0.025	0.081	−0.018	0.753	−0.018	−0.025	0.081	−0.018	0.753	−0.018	−0.025	0.081	−0.018	0.753	−0.018	−0.025	0.081	−0.018	0.753	−0.018
PP	0.001	0.003	0.011	0.844	0.011	0.001	0.003	0.011	0.844	0.011	0.001	0.003	0.011	0.844	0.011	0.001	0.003	0.011	0.844	0.011
Block 2																				
Age	0.012	0.007	0.093	0.114	0.090	0.015	0.008	0.120	0.044	0.113	0.012	0.008	0.097	0.106	0.092	0.014	0.008	0.107	0.071	0.102
Educ	0.029	0.016	0.107	0.070	0.103	0.029	0.016	0.105	0.071	0.102	0.028	0.016	0.102	0.083	0.098	0.030	0.016	0.107	0.067	0.104
Sex	0.301	0.093	0.189	**0.001**	0.183	0.297	0.093	0.187	**0.001**	0.180	0.310	0.094	0.195	**0.001**	0.188	0.295	0.093	0.186	**0.002**	0.179
APOE ε4 sum	−0.015	0.081	−0.011	0.855	−0.010	0.002	0.080	0.002	0.977	0.002	−0.011	0.081	−0.008	0.897	−0.007	−0.021	0.080	−0.015	0.789	−0.015
PP	0.001	0.003	0.012	0.829	0.012	0.001	0.003	0.015	0.796	0.015	0.001	0.003	0.014	0.808	0.014	0.001	0.003	0.016	0.779	0.016
WMH volume	−0.047	0.028	−0.094	0.102	−0.093	−0.057	0.020	−0.168	**0.004**	−0.161	−0.031	0.023	−0.080	0.176	−0.077	−0.052	0.023	−0.131	**0.025**	−0.127

Bold *P*-values are significant $P < 0.05$. Block 1 included all covariates and block 2 added regional WMH volume as the primary independent variable to the model. Regional WMH volumes were examined in separate models. APOE indicates apolipoprotein E; Educ, education; sr, semipartial correlation coefficient; WMH, white matter hyperintensities.

TABLE 5. Effects of Hierarchical Linear Regression Models Examining Associations of Regional WMH Volume and Speed/Executive Function Among the Subsample of Cognitively Normal Participants (n = 302)

	Frontal					Temporal					Parietal					Occipital				
	B	SE	β	*P*	sr	B	SE	β	*P*	sr	B	SE	β	*P*	sr	B	SE	β	*P*	sr
Block 1																				
Age	0.019	0.007	0.159	**0.007**	0.156	0.019	0.007	0.159	**0.007**	0.156	0.019	0.007	0.159	**0.007**	0.156	0.019	0.007	0.159	**0.007**	0.156
Educ	−0.010	0.015	−0.039	0.506	−0.038	−0.010	0.015	−0.039	0.506	−0.038	−0.010	0.015	−0.039	0.506	−0.038	−0.010	0.015	−0.039	0.506	−0.038
Sex	0.068	0.088	0.046	0.441	0.044	0.068	0.088	0.046	0.441	0.044	0.068	0.088	0.046	0.441	0.044	0.068	0.088	0.046	0.441	0.044
APOE ε4 sum	−0.061	0.075	−0.047	0.417	−0.046	−0.061	0.075	−0.047	0.417	−0.046	−0.061	0.075	−0.047	0.417	−0.046	−0.061	0.075	−0.047	0.417	−0.046
PP	0.000	0.003	0.007	0.908	0.007	0.000	0.003	0.007	0.908	0.007	0.000	0.003	0.007	0.908	0.007	0.000	0.003	0.007	0.908	0.007
Block 2																				
Age	0.018	0.007	0.152	**0.011**	0.147	0.020	0.007	0.171	**0.005**	0.162	0.018	0.007	0.155	**0.011**	0.147	0.020	0.007	0.171	**0.005**	0.163
Educ	−0.010	0.015	−0.040	0.504	−0.038	−0.010	0.015	−0.040	0.504	−0.038	−0.010	0.015	−0.038	0.518	−0.037	−0.010	0.015	−0.039	0.511	−0.038
Sex	0.069	0.088	0.047	0.432	0.045	0.066	0.088	0.044	0.454	0.043	0.066	0.088	0.045	0.450	0.043	0.064	0.088	0.043	0.465	0.042
APOE ε4 sum	−0.066	0.076	−0.051	0.386	−0.050	−0.054	0.076	−0.042	0.475	−0.041	−0.065	0.076	−0.050	0.397	−0.048	−0.060	0.076	−0.046	0.428	−0.045
PP	0.000	0.003	0.006	0.914	0.006	0.000	0.003	0.008	0.896	0.007	0.000	0.003	0.006	0.917	0.006	0.000	0.003	0.009	0.884	0.008
WMH volume	0.019	0.027	0.042	0.466	0.042	−0.014	0.019	−0.045	0.449	−0.043	0.007	0.022	0.019	0.747	0.018	−0.018	0.022	−0.050	0.395	−0.049

Bold *P*-values are significant $P < 0.05$. Block 1 included all covariates and block 2 added regional WMH volume as the primary independent variable to the model. Regional WMH volumes were examined in separate models. APOE indicates apolipoprotein E; Educ, education; sr, semipartial correlation coefficient; WMH, white matter hyperintensities.

functioning and whether this relationship is mediated by WMH.

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