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Research Article

Impact of age and apolipoprotein E ε4 status on regional white matter hyperintensity volume and cognition in healthy aging

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Abstract

Objective: White matter hyperintensity (WMH) volume is a neuroimaging marker of lesion load related to small vessel disease that has been associated with cognitive aging and Alzheimer's disease (AD) risk. **Method:** The present study sought to examine whether regional WMH volume mediates the relationship between APOE ε4 status, a strong genetic risk factor for AD, and cognition and if this association is moderated by age group differences within a sample of 187 healthy older adults (APOE ε4 status [carrier/non-carrier] = 56/131). **Results:** After we controlled for sex, education, and vascular risk factors, ANCOVA analyses revealed significant age group by APOE ε4 status interactions for right parietal and left temporal WMH volumes. Within the young-old group (50-69 years), ε4 carriers had greater right parietal and left temporal WMH volumes than non-carriers. However, in the old-old group (70-89 years), right parietal and left temporal WMH volumes were comparable across APOE ε4 groups. Further, within ε4 non-carriers, old-old adults had greater right parietal and left temporal WMH volumes than young-old adults, but there were no significant differences across age groups in ε4 carriers. Follow-up moderated mediation analyses revealed that, in the young-old, but not the old-old group, there were significant indirect effects of ε4 status on memory and executive functions through left temporal WMH volume. **Conclusions:** These findings suggest that, among healthy young-old adults, increased left temporal WMH volume, in the context of the ε4 allele, may represent an early marker of cognitive aging with the potential to lead to greater risk for AD.

Keywords: APOE ε4 status; regional white matter hyperintensities; cognitive aging; preclinical Alzheimer's disease risk; memory; executive functions

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Introduction

White matter hyperintensity (WMH) volume is a neuroimaging marker of white matter lesion load that is thought to reflect chronic ischemia related to cerebral small vessel disease (Biesbroek et al., 2017; Prins & Scheltens, 2015). Over the past several years, research has highlighted the important role of WMH volume in Alzheimer's disease (AD), with previous studies observing WMH's may influence both the development and progression of AD (Birdsill et al., 2014; Brickman, 2013; Brickman et al., 2014, 2015). Even within healthy older adults, elevated total WMH volume has been related to poorer cognition, particularly in age-sensitive functions, including memory, executive functions, and processing speed (Alexander et al., 2012b; Glisky, 2007, Park & Reuter-Lorenz, 2009; Salthouse, 1992). Fewer studies, however, have considered how the regional distribution of WMH volume may differentially affect these cognitive functions. Additionally, the extant findings with regional WMH volumes are mixed, and separate studies have observed significant associations between different cognitive functions and WMH volume within various cerebral lobes (frontal, parietal, temporal, and/or occipital; Brugulat-Serrat et al., 2020; Garnier-Crussard et al., 2020; Gunning-Dixon & Raz, 2003; Lampe et al., 2019; Smith et al., 2011). More research is needed to further elucidate how regional WMH volumes impact cognition in healthy older adults, which may contribute to greater cognitive aging and AD risk.

Although WMH volume is often related to increased vascular risk factors, WMH's are also commonly observed in older adults

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without significant vascular conditions (Wardlaw et al., 2014) suggesting other factors may contribute to their aggregation in aging. APOE ε4 carrier status is a strong genetic risk factor for late-onset AD (Bertram et al., 2010; Corder et al., 1993) that is also associated with vascular disease mechanisms (Liu et al., 2013; Raichlen & Alexander, 2014), including greater total (Godin et al., 2009; Rojas et al., 2018; Schilling et al., 2013) and regional WMH volumes, particularly in parietal, temporal, and occipital lobes (Brickman et al., 2014). Additionally, previous studies have suggested the influence of regional WMH volume on aging and AD risk may, in part, depend on APOE ε4 status. Brickman et al. (2014) observed that ε4 carriers with increased parietal WMH volume were at greater risk of AD than ε4 carriers with low levels of WMH volume in parietal regions and ε4 non-carriers with high or low parietal WMH volumes. Moreover, a previous study from our lab (Van Etten et al., 2021) found that hippocampal volume, a neuroimaging marker associated with preclinical AD, may be vulnerable to the impact of elevated temporal WMH volumes in ε4 carriers, but not non-carriers, in middle-aged to older adults. Thus, the accumulation of regional WMH volume may have greater detrimental effects on brain aging and the risk for AD in APOE ε4 carriers than non-carriers.

Although the APOE ε4 genotype is associated with subsequent development of dementia, its association with cognition before the onset of cognitive impairment and/or AD has been variable (Small et al., 2004; Wisdom et al., 2011). Some studies have not observed a significant relationship between ε4 status and cognition (Driscoll et al., 2005; O'Donoghue et al., 2018), whereas others have found that, compared to non-carriers, ε4 carriers demonstrate poorer performance across multiple cognitive domains in healthy older adults (Luck et al., 2015; O'Hara et al., 2008; Wetter et al., 2005). Notably, memory decline, a hallmark feature of AD, may be especially affected by APOE genotype (Bondi et al., 1995; Caselli et al., 2004; Caselli et al., 2009; Jacobson et al., 2005). These cognitive differences may reflect the accumulation of brain alterations that occur in ε4 carriers prior to the onset of overt clinical symptoms, including the aggregation of WMH volume (Tondelli et al., 2012).

Age differences may be an important factor to consider in relation to the influence of APOE ε4 status on dementia risk. Previous findings have indicated that the ε4 allele has the greatest observable impact on risk of AD in middle-aged to young-older adults, with diminishing effects in later age groups (Bonham et al., 2016; Farrer et al., 1997; Valerio et al., 2014), and a meta-analysis suggested that this may occur at an age of 70 years (Farrer et al., 1997). However, fewer studies have investigated if this pattern is observed when examining brain and cognitive differences associated with the APOE ε4 allele. In individuals with AD and MCI, previous findings indicate that, in young-old (YO) adults (55–75; 60–75 years), ε4 carriers had reductions in hippocampal volume, greater memory decline, and poorer executive functions and processing speed compared to non-carriers (Chang et al., 2014; Tang et al., 2015). In contrast, there were no significant gray matter or cognitive differences between ε4 groups in the old-old (OO) adults (80–92 years; Chang et al., 2014; Tang et al., 2015). Whether and how age and APOE ε4 status interact to affect cognitive and brain aging, including regional WMH volumes in cognitively healthy adults, remains unclear.

The present study investigated the interactive effects of age group and APOE ε4 status on the regional lobar distribution of WMH volumes in a cohort of healthy adults. Further, we examined whether differences in regional WMH volume mediate the relationship between ε4 status and cognition. Similar to findings examining the effects of the ε4 allele on regional WMH volumes (Brickman et al., 2014), we hypothesized that, compared to YO ε4 non-carriers, YO ε4 carriers would have significantly greater regional WMH volumes, particularly within parietal, temporal, and occipital lobes, and this difference between APOE ε4 carriers and non-carriers would be diminished within the OO group. As previous studies examining associations between regional WMH volumes and cognitive functions are mixed, we sought to test the general hypothesis that these age group by APOE ε4 carrier differences in regional WMH volumes would be associated with cognition. In this case, we hypothesized that within the YO group, ε4 carriers would display poorer cognitive performance than non-carriers, and this difference between APOE ε4 status would be attenuated within the OO group.

Method

Participants

Participants included 187 individuals aged 50–89 years that were drawn from a cohort of 210 community-dwelling healthy adults, as part of a study on cognitive aging. The sample was largely white non-Hispanic (89.8%), with an average education of 15.98 years (SD = 2.56). Seven participants were excluded due to missing data. Outliers who were ±3.5 or more SD's away from the mean in one or more lobes of WMH volumes ($n = 16$; Van Etten et al., 2021) were removed from the analyses to enhance normality, as their values remained skewed after a log transformation and adjustment for total intracranial volume (TIV). Participants were split into groups by median age of our original cohort (Franchetti et al., 2020) into YO (ages = 50–69 years; $n = 90$) and OO (ages = 70–89 years; $n = 97$) groups.

The data for the current study was drawn from a larger cohort of the Brain Aging and Memory Study at the University of Arizona, and participants were recruited from the Tucson-metro area community through local newspaper advertisements. The larger study was aimed at investigating how vascular health, aerobic fitness, and APOE genotype influence regional brain structural changes, and participants were asked to complete a blood draw, brain MRI scans, an aerobic fitness test, health status questionnaires, and a neuropsychological test battery. Participants were screened for exclusion if they were not able to take part in these aspects of the study (more details of the larger study are provided in Supplemental materials and are also described in Nguyen et al., 2016; Franchetti et al., 2020; and Van Etten et al., 2021). To exclude individuals with significant neurological, medical, or psychiatric disorders before enrollment in the study, participants underwent a comprehensive medical screen, which included a physical and neurological examination performed by a neurologist specialized in aging. Participants completed the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and the Mini Mental Status Exam (MMSE; Folstein et al., 1975) and were excluded from the study if they had a HAM-D score greater than 9 or MMSE score less than 26. The research was completed in accordance with the Helsinki Declaration, all participants provided written consent, and procedures were approved by the Institutional Review Board at the University of Arizona.

APOE genotyping

As described previously (Van Etten et al., 2021), APOE genotype was determined with extracted DNA assayed via restriction

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fragment length polymorphism according to published methods (Addya et al., 1997). There were 56 APOE ε4 carriers (homozygous: $n = 7$, heterozygous: $n = 49$) and 131 APOE ε4 non-carriers in our sample.

Cognitive measures

Measures of processing speed, executive functions, and memory known to be sensitive to aging (Alexander et al., 2012b; Glisky, 2007, Park & Reuter-Lorenz, 2009; Salthouse, 1992) were selected from a larger battery of neuropsychological tests. Processing speed was measured with the coding subtest from the WAIS-IV (Wechsler, 2008) and the Trail Making Test part A (TMT A; Reitan, 1956). Aspects of executive functions were evaluated with the Trail Making Test part B (TMT B; Reitan, 1956) and Stroop Color-Word Interference (Golden & Freshwater, 1978). Finally, the 12-item, 12-trial Buschke Selective Reminding Test (BSRT) total sum recall and consistent long-term retrieval (CLTR; Buschke, 1973) were used to measure memory.

We additionally included measures of language naming and fluency, as aspects of language abilities tend to decline early in the AD process and have been associated with temporal lobe atrophy (Monsch et al., 1992). These measures included the total score from the Boston Naming Test (BNT; Kaplan et al., 1983) and category fluency (animals; Rosen, 1980).

Health measures

Participant height and weight were measured and utilized to calculate body mass index (BMI). Cholesterol, hypertension, and statin medication status and number of years smoking were recorded from participants self-reported history.

Magnetic resonance imaging

The MRI scans were acquired on a 3T GE Signa scanner (HD Signa Excite, General Electric, Milwaukee, WI), including volumetric T1-weighted Spoiled Gradient Echo (SPGR; slice thickness = 1.0 mm, TR = 5.3 ms, TE = 2.0 ms, TI = 500 ms) and T2 Fluid-Attenuation Inversion Recovery (FLAIR) scans (slice thickness = 2.6 mm, TR = 11000 ms, TE = 120 ms, TI = 2250 ms).

Image processing

T1 and T2 FLAIR scans were used to compute total WMH volume with the lesion segmentation toolbox (LST; Schmidt et al., 2012) for SPM12. As described in our prior work (Franchetti et al., 2020; Van Etten et al., 2021), in a subset of 35 participants, the LST's lesion growth algorithm (LGA) accuracy was assessed across an array of kappa thresholds (0.05–1.00) using manually segmented reference WMH maps produced with ITK-SNAP (www.itksnap.org; Yushkevich et al., 2006). Global WMH maps generated at the 0.35 kappa threshold produced the highest spatial and volumetric correspondence with the reference WMH maps. Then, LGA lesion probability maps were generated for all participants at this optimal kappa threshold (0.35) and were visually inspected for accuracy before computing total WMH volumes.

Our approach for processing regional WMH volumes has been detailed previously (Franchetti et al., 2020; Van Etten et al., 2021). Briefly, the MNI152 template was initially processed using FreeSurfer v5.3. Cortical labels for the four major brain lobes for each cerebral hemisphere were generated by combining the regional labels from the Desikan-Killiany atlas (Desikan et al., 2006) per FreeSurfer's standard lobar schema (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation) and propagated into the white matter to generate the lobar template. The Advanced Normalization Tools' Greedy SyN algorithm (ANTs; Avants et al., 2011) was used to non-linearly register the lobar template to each participant's T1 scan to generate T1 native space lobar ROIs. These ROIs were used with the LST-generated lesion probability maps to extract the regional WMH volumes for each participant. The eight hemispheric lobar WMH volumes were then log-transformed and residualized using linear regressions to adjust for differences in TIV, which was computed in native brain space (Alexander et al., 2012a).

Statistical analyses

Demographic characteristic differences between APOE ε4 carriers and non-carriers were evaluated using independent sample t-tests or chi-square tests, where appropriate. Separate two-way analysis of covariance's (ANCOVA's) were used to test the effects of age group (YO vs OO), APOE ε4 status (carriers vs non-carriers), and their interaction on regional WMH volumes. Covariates included sex, education, BMI, years smoking, and hypertension, cholesterol, and statin medication status. False discovery rate (FDR) corrections (Benjamini & Hochberg, 1995), which have been recommended for use in health studies (Glickman et al., 2014), were used to adjust for multiple comparisons. All ANCOVA models with significant two-way interactions after FDR corrections were followed by FDR-corrected simple effect analyses.

Moderated mediation analyses were performed using the PROCESS macro for SPSS (v3.5; Hayes, 2017) to examine whether observed significant differences in regional WMH volumes (related to APOE ε4 status and age group interactive effects) were, in turn, associated with cognitive performance differences. Since moderated mediation models in PROCESS do not allow for corrections of multiple comparisons, we initially performed linear regressions to identify candidates for the full moderated mediation analyses. Each regression model included age group, APOE ε4 status, and their interaction entered first, followed by those regional WMH volumes that had significant interactive effects from the ANCOVA analyses, and the dependent variables were cognitive measures, which were adjusted for multiple comparisons using FDR corrections.

Cognitive measures that were significantly associated with regional WMH volumes in our linear regression analyses were then followed by the full moderated mediation analyses to examine whether differences in regional WMH volumes mediated the relationship between APOE ε4 status and cognition that was moderated by age group. All moderated mediation analyses were performed using the PROCESS macro for SPSS (v3.5; Hayes, 2017), using non-parametric percentile bootstrap resampling with 10,000 iterations to produce 95% percentile confidence intervals, which indicate significance when they do not include zero. Separate moderated mediation models were performed to test the mediation of the relation between APOE ε4 status (independent variable [x]) and cognition (dependent variable [y]) by regional WMH volume (mediator [m]) with age group (YO = 50–69 years, OO = 70–89 years) as the moderator (w). Sex, education, BMI, years smoking, and hypertension, cholesterol, and statin medication status were included as covariates. Given the primary motivation of the present study was to understand whether and how the interactive effects of APOE ε4 status and age group relate to regional WMH volumes and associated differences in cognition, the models tested the moderation of age group on the relation

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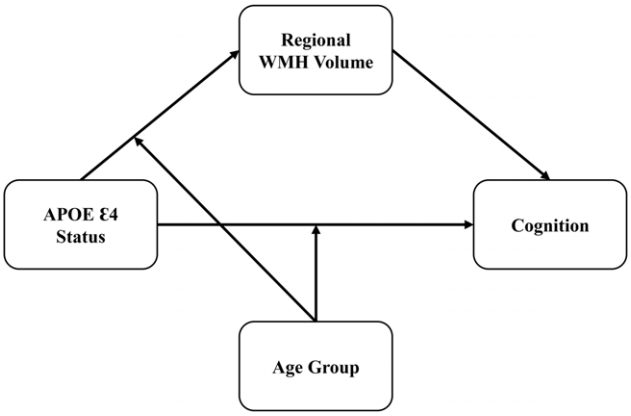

Figure 1. Illustration of the hypothesized moderated mediation model of the relationship between APOE ε4 status and cognition mediated by regional white matter hyperintensity volume and moderated by age group (young-old and old-old).

between ε4 status and regional WMH volume, as well as between ε4 status and cognitive performance (see Figure 1). Each analysis tested the direct and indirect effects of the relations between APOE ε4 status, regional WMH volume, and cognition and how these associations differ between YO and OO adults within one model (Hayes, 2017).

Results

Demographics

As shown in Table 1, the APOE ε4 carrier and non-carrier groups significantly differed in the distribution of cholesterol status and statin medication use but did not differ in any other demographic or clinical characteristic. Although there were no significant differences in the distribution of ε4 status between age groups, the OO group had a numerically higher percentage of ε4 carriers (31.96%) than the YO group (27.78%).

ANCOVA analyses

After we controlled for all covariates, significant main effects of age group were observed for left ($F(1,185) = 24.14$, $FDRp =$ 8.0E-6, $\eta_p^2 = .121$) and right ($F(1,185) = 24.82$, $FDRp = 8.0E\text{-}6$, $\eta_p^2 = .124$) frontal, left ($F(1,185) = 22.06$, $FDRp = 8.0E\text{-}6$, $\eta_p^2 = .111$) and right ($F(1,185) = 20.62$, $FDRp = 1.3E\text{-}5$, $\eta_p^2 = .105$) parietal, and left ($F(1,185) = 23.23$, $FDRp = 8.0E\text{-}6$, $\eta_p^2 = .117$) and right ($F(1,185) = 17.53$, $FDRp = 8.0E\text{-}6$, $\eta_p^2 = .091$) temporal WMH volumes, with the OO group having greater WMH volumes than the YO group across all regions. There were no significant main effects of age group for left ($F(1,185) = 2.55$, $FDRp = .128$, $\eta_p^2 = .014$) or right ($F(1,185) = 1.69$, $FDRp = .195$, $\eta_p^2 = .010$) occipital WMH volumes. There were no significant main effects of APOE ε4 status observed in left ($F(1,185) = .113$, $FDRp = .998$, $\eta_p^2 = .001$) or right ($F(1,185) = 2.40$, $FDRp = .984$, $\eta_p^2 = .013$) frontal, left ($F(1,185) = .000$, $FDRp = .998$, $\eta_p^2 = 2.2E\text{-}8$), or right ($F(1,185) = .382$, $FDRp = .998$, $\eta_p^2 = .002$) parietal, left ($F(1,185) = 1.08$, $FDRp = .998$, $\eta_p^2 = .006$) or right ($F(1,185) = .259$, $FDRp = .998$, $\eta_p^2 = .001$) temporal, or left ($F(1,185) = .040$, $FDRp = .998$, $\eta_p^2 = 2.3E\text{-}4$) or right ($F(1,185) = .004$, $FDRp = .998$, $\eta_p^2 = 2.2E\text{-}5$) occipital WMH volumes with all covariates included (see Table 2).

With all covariates included, significant interactive effects for age group and APOE ε4 status were observed for left temporal ($F(1,185) = 9.25$, $FDRp = .022$, $\eta_p^2 = .050$) and right parietal ($F(1,185) = 7.61$, $FDRp = .026$, $\eta_p^2 = .041$) WMH volumes (see Figures 2 and 3). There were no significant interactive effects of age group and ε4 status for left ($F(1,185) = 3.64$, $FDRp = .116$, $\eta_p^2 =$ .020) or right ($F(1,185) = 5.36$, $FDRp = .058$, $\eta_p^2 = .030$) frontal, left ($F(1,185) = 1.19$, $FDRp = .278$, $\eta_p^2 = .007$) or right ($F(1,185) = 3.27$, $FDRp = .116$, $\eta_p^2 = .018$) occipital, left parietal ($F(1,185) = 2.58$, $FDRp = .147$, $\eta_p^2 = .014$), or right temporal ($F(1,185) = 1.59$, $FDRp = .240$, $\eta_p^2 = .009$) WMH volumes. Follow-up simple effect analyses of the significant interactions revealed that, within the YO group, ε4 carriers had greater right parietal (FDR$p = .046$) and left temporal (FDR$p = .012$) WMH volumes than non-carriers. However, in the OO group, right parietal (FDR$p = .165$) and left temporal (FDR$p = .203$) WMH volumes were comparable across ε4 status. Within ε4 non-carriers, OO adults had greater right parietal (FDR$p = 8.20E\text{-}8$) and left temporal (FDR$p = 4.64E\text{-}11$) WMH volumes than YO adults, but there were no significant differences across age groups in ε4 carriers for right parietal (FDR$p = .235$) or left temporal (FDR$p = .233$).

Table 1. Table of demographic characteristics

Variable	APOE ε4 non-carrier	APOE ε4 carrier	*p*
Age Group (YO/OO)	65/66	25/31	.632
Sex, F/M	62/69	30/26	.523
Education (years; M SD)	15.91 (2.56)	16.14 (2.56)	.567
Body Mass Index (M SD)	25.55 (3.75)	25.32 (3.90)	.706
Years Smoking (M SD)	7.91 (13.27)	10.16 (16.24)	.323
Hypertension Status (y/n)	43/88	20/36	.737
Cholesterol Status (y/n)	52/79	33/23	.017
Statin Medication Status (y/n)	43/88	29/27	.021

Note: M (SD) = Mean (standard deviation, YO/OO = young-old/old-old, F/M = female/male, y/n = yes/no.

Linear regression analyses

After we controlled for age group, APOE ε4 status, and their interactive effects, linear regressions revealed significant relationships between left temporal WMH volume and TMT A ($\beta = 2.19$, $FDRp = .036$, R^2 change = .023), TMT B ($\beta = 7.92$, $FDRp = .016$, R^2 change = .038), Stroop Color-Word Interference ($\beta = -2.29$, $FDRp = .010$, R^2 change = .045), BSRT sum recall ($\beta = -3.90$, $FDRp = .026$, R^2 change = .027), and BSRT CLTR ($\beta = -7.01$, $FDRp = .026$, R^2 change = 0.026), but not the WAIS-IV coding subtest ($\beta = -1.32$, $FDRp = .232$, R^2 change = .006). There were no significant relationships between right parietal WMH volume and any cognitive measure before or after an FDR correction (p's > .05).

Linear regressions with language measures revealed no significant relationships between left temporal WMH volume and Boston Naming Test ($\beta = -.202$, FDR$p = .487$, R^2 change = .002) or category fluency ($\beta = -.778$, FDR$p = .337$, R^2 change = .015). There were no significant relationships between right parietal WMH volume and Boston Naming Test ($\beta = -.323$, $FDRp = .337$, R^2 change = .007) or category fluency ($\beta = -.504$, $FDRp = .337$, R^2 change = .007).

Moderated mediation models

Given we only included cognitive measures that were significantly related to regional WMH volumes in the regression analyses, we limited our moderated mediation models to those showing significant associations with regional WMH volumes, which included TMT A, TMT B, Stroop Color-Word Interference, BSRT

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Table 2. Effects of APOE ε4 status, age group, and their interaction on regional white matter hyperintensity volumes

	Young-old		Old-old		*p*-values		
Variable	APOE ε4 non-carrier	APOE ε4 carrier	APOE ε4 non-carrier	APOE ε4 carrier	APOE	Age	APOExAge
Left Frontal WMH	−.435 (.872)	.474 (.692)	−.112 (.784)	.367 (.941)	.737	**2.0E-6****	.058
Right Frontal WMH	−.505 (.921)	.469 (.694)	−.000 (.678)	.442 (.703)	.123	**1.0E-6****	.022
Left Parietal WMH	−.404 (.956)	.466 (.773)	−.164 (.734)	.316 (.876)	.998	**5.0E-6****	.110
Right Parietal WMH	−.486 (.954)	.510 (.711)	−.016 (.581)	.304 (.873)	.537	**1.0E-5****	**.006***
Left Occipital WMH	−.194 (.930)	.242 (.971)	−.047 (.752)	.093 (1.06)	.842	.112	.278
Right Occipital WMH	−.246 (.933)	.259 (.866)	.054 (.808)	.066 (1.32)	.951	.195	.072
Left Temporal WMH	−.642 (.970)	.517 (.713)	−.063 (.984)	.362 (.860)	.300	**3.0E-6****	**.003***
Right Temporal WMH	−.475 (1.01)	.376 (.799)	−.180 (.860)	.393 (1.06)	.611	**4.5E-5****	.210

Note: Means and standard deviation for each group are presented. White matter hyperintensity volumes are log-transformed and corrected for total intracranial volume. $^{**}p < .001$, $^{*}p < .01$. Significant effects are bolded after FDR correction. Abbreviations: WMH = white matter hyperintensity; FDR = false discovery rate.

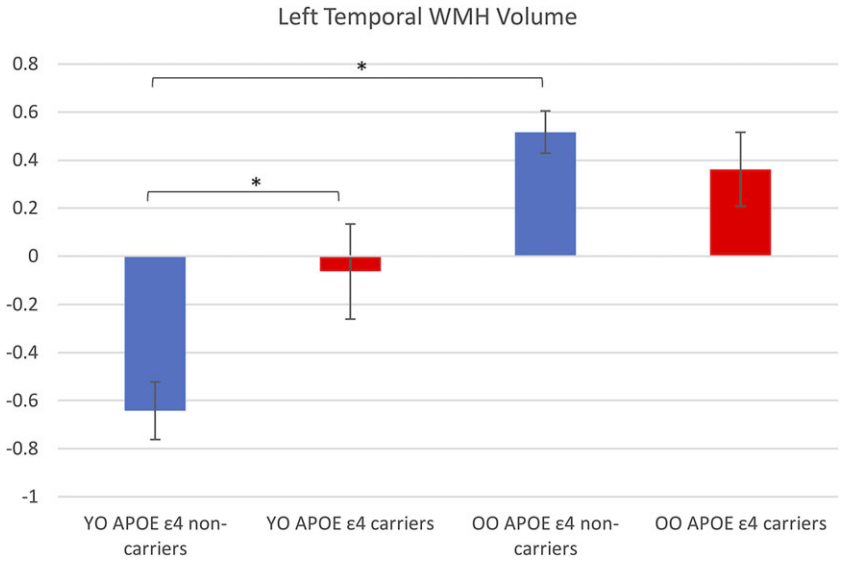

Figure 2. The mean and standard error of left temporal WMH volume for age group and APOE ε4 status. Analysis of covariance (ANCOVA) showed that, after controlling for sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status, there was a significant main effect for age group (FDRp = 8.0E-6); there was no main effect for APOE ε4 status (FDRp = .998); and there was a significant age group by APOE ε4 status interaction (FDRp = .022). *Simple effects analyses revealed young-old APOE ε4 carriers had significantly greater left temporal (FDR*p* = .012) WMH volumes than young-old APOE ε4 non-carriers; old-old APOE ε4 non-carriers had significantly greater left temporal (FDR*p* = 4.64E-11) WMH volumes young-old APOE ε4 non-carriers; there were no significant differences across age groups within ε4 carriers; there were no significant differences across ε4 groups within the old-old. Blue bars represent APOE ε4 non-carriers and red bars represent APOE ε4 carriers. *Note.* WMH = white matter hyperintensity; YO = young-old; OO = old-old; APOE = apolipoprotein E.

sum recall, and BSRT CLTR. Moderated mediation models, after controlling for all covariates, revealed that the mediation of the relationship between APOE ε4 status and TMT B (−6.82(SE = 3.57), 95%CI, [−14.88, −1.14]; see Figure 4A), Stroop Color-Word Interference (1.97(SE = .967), 95%CI, [.444, 4.12]; see Figure 4B), BSRT sum recall (3.19(SE = 1.75), 95%CI, [.418, 7.11]; see Figure 4C), and BSRT CLTR (6.01(SE = 3.32), 95% CI, [.796, 13.71]; see Figure 4D) by left temporal WMH volume were each moderated by age group. YO adults showed significant indirect effects of ε4 status on TMT B (4.60(SE = 2.67), 95%CI, [.545, 10.81]), Stroop Color-Word Interference (−1.33(SE = .707), 95%CI, [−2.96, −.229]), BSRT sum recall (−2.15(SE = 1.24), 95% CI, [−4.98, −.216]), and BSRT CLTR (−4.05(SE = 2.36), 95%CI, [−9.56, −.387]) through left temporal WMH volumes. However, in the OO group, left temporal WMH volume did not significantly mediate the relation between APOE ε4 status and TMT B (−2.22(SE = 1.75), 95%CI, [−6.07, .751]), Stroop Color-Word Interference (.643(SE = .501), 95%CI, [−.212, 1.77]), BSRT sum recall (1.04(SE = .899), 95%CI, [−.325, 3.14]), and BSRT CLTR(1.96 (SE = 1.71), 95%CI, [−.634, 6.05]). There was no significant moderated mediation between ε4 status and TMT A by left temporal WMH volumes moderated by age group with all covariates (−1.69(SE = 1.17), 95%CI [−4.31, .233]).

Examination of the individual associations of the significant moderated mediation models showed there were no significant direct relations between APOE ε4 status and cognition for TMT B (−.375(SE = 8.03), 95%CI, [−16.22, 15.47], $p = .963$), Stroop Color-Word Interference (.751(SE = 2.06), 95%CI, [−3.32, 4.82, $p = .716$]), BSRT sum recall (.374(SE = 4.33), 95%CI, [−8.18, 8.93], $p = .931$), and BSRT CLTR (7.38(SE = 8.07), 95%CI, [−8.54, 23.30], $p = .362$). Further, these direct relations were not significantly moderated by age group for TMT B (−7.43(SE = 10.93), 95%CI, [−14.13, 29.00], $p = .497$), Stroop Color-Word Interference (−2.35(SE = 2.81), 95% CI, [−7.89, 3.20], $p = .405$), BSRT sum recall (−2.08(SE = 5.90), 95% CI, [−13.72, 9.56], $p = .723$), and BSRT CLTR (−9.85(SE = 10.98), 95%CI, [−31.51, 11.82], $p = .371$). For indirect associations, each model showed a significant overall positive relation between ε4 status and left temporal WMH volume (.571(SE = .205), 95%CI,

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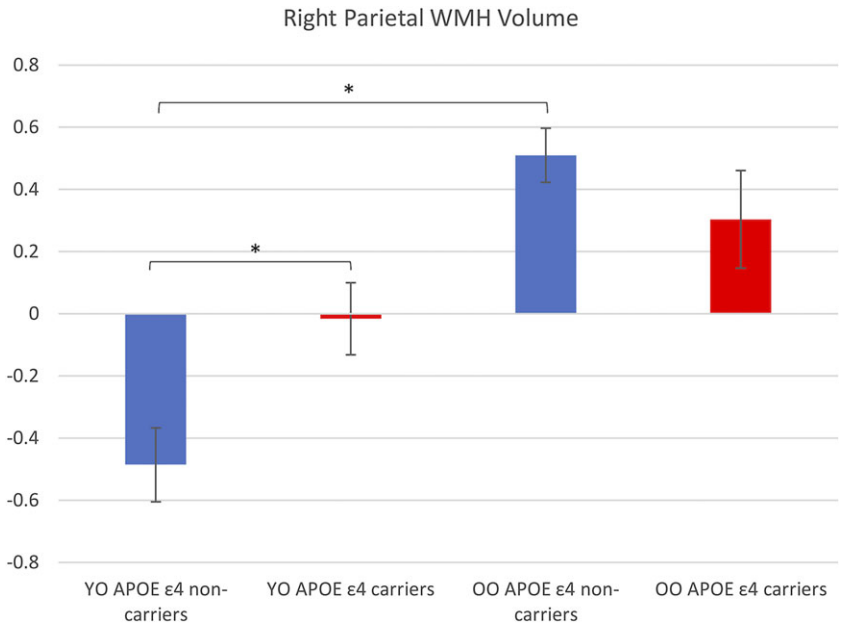

Figure 3. The mean and standard error of right parietal WMH volume for age group and APOE ε4 status. Analysis of covariance (ANCOVA) showed that, after controlling for sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status, there was a significant main effect for age group (FDRp = 1.3E-5); there was no main effect for APOE ε4 status (FDRp = .998); and there was a significant age group by APOE ε4 status interaction (FDRp = .026). *Simple effects analyses revealed young-old APOE ε4 carriers had significantly greater right parietal WMH volumes (FDRp = .046) than young-old APOE ε4 non-carriers; old-old APOE ε4 non-carriers had significantly greater right parietal WMH volumes (FDRp = 8.20E-8) young-old APOE ε4 non-carriers; there were no significant differences across age groups within ε4 carriers; there were no significant differences across ε4 groups within the old-old. Blue bars represent APOE ε4 non-carriers and red bars represent APOE ε4 carriers. *Note.* WMH = white matter hyperintensity; YO = young-old; OO = old-old; APOE = apolipoprotein E.

[.166, .976], p = .006]), and this association was moderated by age group (−.846(SE = .278), 95%CI, [−1.40, −.297], p = .003). In the YO group, APOE ε4 status was significantly positively related to left temporal WMH volume (.571(SE = .205), 95%CI, [.166, .976], p = .006), but in the OO group, ε4 status was not significantly related to left temporal WMH volume (−.276(SE = .192), 95%CI, [−.654, .103], p = .152). There were significant overall relations between left temporal WMH volume and TMT B (8.06(SE = 2.89), 95%CI, [2.37, 13.75], p = .006), Stroop Color-Word Interference (−2.33 (SE = .741), 95%CI, [−3.79, −.867], p = .002), BSRT sum recall (−3.76(SE = 1.56), 95%CI, [−6.84, −.690], p = .017), and BSRT CLTR (−7.10(SE = 2.90), 95%CI, [−12.82, −1.38], p = .015), indicating higher left temporal volume was associated with poorer cognitive functions.

Discussion

In a cohort of cognitively healthy adults, we found that in YO (50–69 years) but not OO (70–89 years) groups, ε4 carriers had greater WMH volumes in the left temporal and right parietal lobes than ε4 non-carriers. Additionally, OO adults had greater right parietal and left temporal WMH volumes than YO adults within ε4 non-carriers, yet there were no significant differences across age groups in ε4 carriers. This indicates that the regional distribution of WMH volumes may differ by APOE ε4 status and age group among healthy adults. Using moderated mediation models, we observed that differences in left temporal WMH volumes were, in turn, related to poorer memory and executive function performance within YO ε4 carriers. In contrast, right parietal WMH volume did not significantly predict differences in cognition. Notably, our healthy adult sample had low vascular risk, and all analyses included covariates to adjust for vascular health conditions, indicating these effects may be separable from the influence of vascular risk on brain structure and cognition in older adults. Our findings suggest that, among healthy YO ε4 carriers, increased left temporal WMH volume may represent an early marker of cognitive aging, and could be a harbinger of increased risk for AD.

One previous study observed that ε4 carriers showed greater WMH volume accumulation in parietal, temporal, occipital lobes than ε4 non-carriers (Brickman et al., 2014). Our study found no significant main effects of APOE ε4 status on regional WMH volumes, but significant ε4 status and age group interactions only within the right parietal and left temporal lobes. Although not statistically significant after FDR correction, it is notable that a trend for an ε4 status and age group interaction was observed within right frontal WMH volume that followed the same pattern as the left temporal and right parietal WMH volumes. Thus, this interaction could emerge for right frontal WMH volume in a larger sample of healthy adults that had more power to detect smaller effects. Given the ε4 allele has been associated with multiple vascular mechanisms, including increased cerebrovascular disease and breakdown of the blood brain barrier (Liu et al., 2013; Montagne et al., 2020; Raichlen & Alexander, 2014), our findings suggest that left temporal and right parietal WMH volumes may be especially vulnerable to ε4-related vascular mechanisms in YO adults, which appears to be lessened in OO ages. Previous studies in individuals with MCI and/or AD have observed significantly reduced hippocampal volume and morphology, poorer cognition, and increased parietal and temporal

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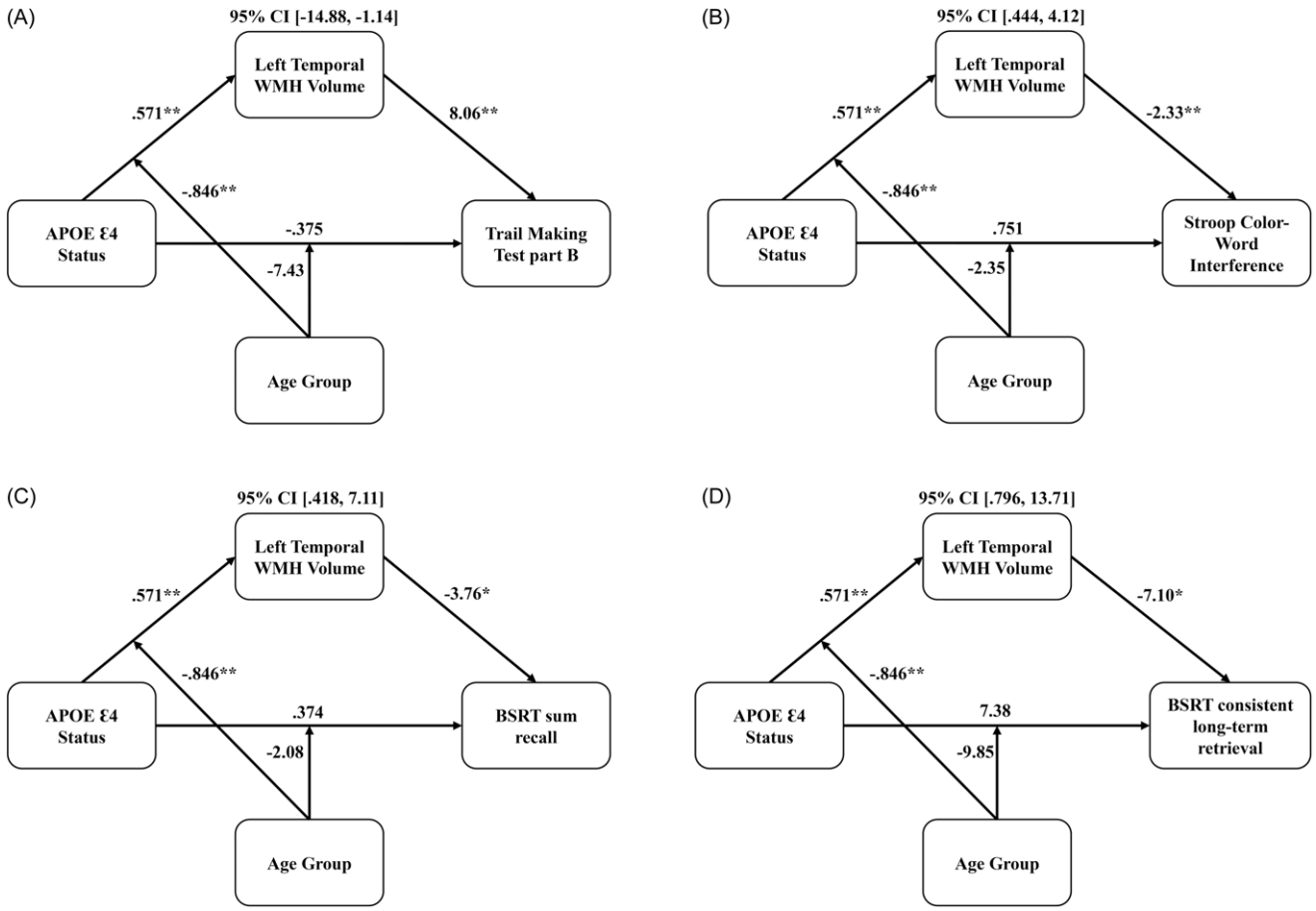

Figure 4. A. The relationship between APOE ε4 status and Trail Making Test part B mediated by left temporal WMH volume and moderated by age group. Coefficients of the moderated mediation model with sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status included as covariates. Percentile bootstrap resampling was performed with 10,000 iterations to produce 95% confidence intervals (CI). Regression coefficients significant; *$p < .05$, **$p < .01$; WMH, white matter hyperintensity. **B.** The relationship between APOE ε4 status and Stroop Color-Word Interference mediated by left temporal WMH volume and moderated by age group. Coefficients of the moderated mediation model with sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status included as covariates. Percentile bootstrap resampling was performed with 10,000 iterations to produce 95% confidence intervals (CI). Regression coefficients significant; *$p < .05$, **$p < .01$; WMH, white matter hyperintensity. **C.** The relationship between APOE ε4 status and Buschke Selective Reminding Test sum recall mediated by left temporal WMH volume and moderated by age group. Coefficients of the moderated mediation model with sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status included as covariates. Percentile bootstrap resampling was performed with 10,000 iterations to produce 95% confidence intervals (CI). Regression coefficients significant; *$p < .05$, **$p < .01$; WMH, white matter hyperintensity; BSRT, Buschke Selective Reminding Test. **D.** The relationship between APOE ε4 status and Buschke Selective Reminding Test consistent long-term retrieval mediated by left temporal WMH volume and moderated by age group. Coefficients of the moderated mediation model with sex, education, BMI, years smoking, hypertension, cholesterol, and statin medication status included as covariates. Percentile bootstrap resampling was performed with 10,000 iterations to produce 95% confidence intervals (CI). regression coefficients significant; *$p < .05$, **$p < .01$; WMH, white matter hyperintensity; BSRT, Buschke Selective Reminding Test.

cortical thinning in YO ε4 carriers, compared to YO ε4 non-carriers, and no significant differences in gray matter or cognitive functions between ε4 status in OO groups (Chang et al., 2014; Tang et al., 2015). Furthermore, the APOE ε4 genotype has been associated with greater AD-related pathology, including increased amyloid and tau deposition (Therriault et al., 2020; Zerbinatti et al., 2004), and it has been suggested that temporal and parietal lobes may be preferentially vulnerable to amyloid or tau accumulation in the earliest stages of AD (Berron et al., 2021; Insel et al., 2020; Ossenkoppele et al., 2012). Thus, the results of the present study, along with previous findings, suggest that the ε4 allele may affect multiple pathologies within the temporal and parietal lobes early in the AD course, which is observable in cognitively healthy YO adults.

Our findings may indicate that the impact of age on regional WMH volume may differ between APOE ε4 groups. It is important to note, however, as a study of healthy aging, the participants in our cohort underwent an extensive screening and were only eligible if they were determined to be neurologically and cognitively healthy. It is possible that older ε4 carriers in the community may have been less likely than non-carriers to meet our study's inclusion criteria because of detectable cognitive difficulties in OO ages. However, both groups were acquired from the community in an identical manner, and there were no significant differences in the distribution of APOE ε4 status between the YO and OO groups. In fact, the OO group had a slightly numerically higher percentage of ε4 carriers (31.96%) than the YO group (27.78%), suggesting at least some of the OO

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ε4 carriers were not implicitly systematically excluded by our inclusion criteria for healthy aging. Our findings could indicate ε4 carriers that are neurologically healthy at older ages may rely on other health, lifestyle, or genetic factors to compensate for higher burden of regional WMH volumes. Given the current study is cross-sectional, research with longitudinal data is needed to examine how APOE ε4 status and age may interact to influence changes in regional WMH volume over time.

Previous findings with regional WMH volumes in relation to cognition are mixed, with separate studies observing significant associations between different cognitive functions and WMH volume within various cerebral lobes (Brugulat-Serrat et al., 2020; Garnier-Crussard et al., 2020; Gunning-Dixon & Raz, 2003; Lampe et al., 2019; Smith et al., 2011). However, we found only left temporal WMH volumes was associated with performance on memory and executive function measures. While the mechanisms of how WMH volume contribute to cognitive decline is not fully understood, one potential explanation is that WMH volume accumulation may influence disconnection among networks in aging that leads to poorer cognition (Reijmer et al., 2015). Another possibility is that WMH volume may impact cognitive functions by promoting ischemic-related axonal loss and subsequent cortical atrophy through Wallerian degeneration (Schmidt et al., 2011) or tau hyperphosphorylation (Zlokovic, 2011). Although the present study did not examine potential mechanisms, it is possible that left temporal WMH volumes are positioned in a region that could preferentially disrupt frontal-temporal connections or impact reductions in proximal neuroanatomical structures, such as the hippocampus, that in turn, influence poorer memory and executive function abilities. Additionally, WMH volumes may reflect a biomarker of cognitive dysfunction through its potential association with other causal vascular mechanisms.

Within healthy aging, APOE ε4 differences in cognition have been variable, with some studies observing no significant associations between ε4 status and cognition (Driscoll et al., 2005; O'Donoghue et al., 2018), and other studies finding ε4 carriers demonstrating poorer cognitive performance (Luck et al., 2015; O'Hara et al., 2008; Wetter et al., 2005), particularly on memory measures (Bondi et al., 1995; Caselli et al., 2004; Caselli et al., 2009; Jacobson et al., 2005) relative to ε4 non-carriers. We did not find significant ε4 group differences or ε4 status and age group interactions directly related to cognitive performance but observed that ε4 status impacted memory and executive functions only through the mediational role of left temporal WMH volume. These findings suggest elevated left temporal WMH volume may influence memory and executive function, but not processing speed or language abilities, in YO ε4 carriers. Further, this demonstrates the benefit of moderated mediation models, which may help in detecting the earliest effects of the ε4 allele on brain and cognitive aging.

This study has several limitations. First, our sample largely consists of white individuals with a generally higher level of education and health status. This lack of diversity in our sample limits the generalizability of our findings and could, in part, reflect the methods used to include the healthy cognitively unimpaired individuals with low levels of vascular health factors in our sample. Recent findings have suggested that cognitive screening measures may not accurately reflect cognitive status of those belonging to some racial and ethnic groups (Carson et al., 2018). This may be due to bias in neuropsychological tests and multiple sociocultural factors that contribute to racial health disparities (Zahodne et al., 2021). Additionally, the APOE ε4 allele has been found to be a strong genetic AD risk factor within non-Hispanic white adults but may be less related to AD risk in other racial and ethnic groups (Raichlen & Alexander, 2014). More research is needed to investigate whether and how ε4 status, and APOE variants (Deters et al., 2021), may influence brain and cognitive aging in diverse samples. Finally, the present study uses cross-sectional data. Our study presented important differences in regional WMH volumes and cognition within healthy older adults, but additional longitudinal research would be important to examine if APOE ε4 status leads to greater regional WMH volume accumulation and cognitive decline over time, and if these effects differ by age.

Conclusions

Within cognitively healthy older adults with lower vascular risk, YO carriers of the ε4 allele had elevated left temporal and right parietal WMH volumes, compared to YO ε4 non-carriers. This suggests these regions are sensitive to ε4-related vascular disease mechanisms and highlights the impact the ε4 allele has on brain aging in early old age. Moreover, increases in left temporal WMH volumes were related to poorer memory and executive functions in only the YO ε4 carriers. The results of the present study suggest that elevated left temporal WMH volume, within ε4 carriers in younger older adults, may be indicative of accelerated cognitive aging and may potentially lead to greater risk for AD. Evaluation of intervention therapies that lessen the accumulation of WMH's may be particularly beneficial in ε4 carriers in YO age ranges to help reduce AD risk.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617724000122.

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Competing interests. The authors have no actual or potential conflicts of interest.

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