APOE ϵ 4 and risk for Alzheimer's disease: Do regionally distributed white matter hyperintensities play a role?

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Abstract

Background: We previously demonstrated that parietal lobe white matter hyperintensities (WMH) increase the risk for Alzheimer's disease (AD). Here, we examined whether individuals with apolipoprotein E gene (*APOE* ϵ 4) have increased parietal WMH volume.

Methods: Participants were from the Washington Heights-Inwood Columbia Aging Project (WHICAP; $n = 694$, 47 with dementia) in northern Manhattan and the Etude Santé Psychologique Prévalence Risques et Traitement study (ESPRIT; $n = 539$, 8 with dementia) in Montpellier. The association between regional WMH and *APOE* ϵ 4 was examined separately in each group and then in a combined analysis.

Results: In WHICAP, ϵ 4 carriers had higher WMH volume particularly in parietal and occipital lobes. In ESPRIT, ϵ 4 carriers had elevated WMH particularly in parietal and temporal lobes. In the combined analysis, ϵ 4 carriers had higher WMH in parietal and occipital lobes. Increased WMH volume was associated with increased frequency of dementia irrespective of *APOE* ϵ 4 status; those with the ϵ 4 were more likely to have dementia if they also had increased parietal WMH.

Conclusions: *APOE* ϵ 4 is associated with increased parietal lobe WMH.

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Keywords:

APOE; Alzheimer's disease; White matter hyperintensities

1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative condition that likely has multiple pathogenic factors contributing to disease presentation and course. Several modifiable

risk factors have been identified, including hypertension, diabetes, heart disease, obesity, and stroke [1]. These risk factors tend to be vascular in nature, suggesting that vascular disease plays a primary role in disease pathogenesis, interacts with primary AD pathology, or is an alternative cause of dysfunction that is independent of primary AD pathology. The presence of the ϵ 4 allele of the polymorphic apolipoprotein E gene (*APOE* ϵ 4) is, by far, the strongest genetic risk factor for the AD [2]. There is at least a twofold risk for developing the

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disease among individuals with the *APOE* $\epsilon 4$ allele relative to those without the *APOE* $\epsilon 4$ allele [3,4]. The *APOE* $\epsilon 4$ allele is thought to confer risk for AD via increased the aggregation of A β protein and deposition of plaques [5–7], although more recent work emphasizes the role of *APOE* $\epsilon 4$ in decreasing clearance of toxic forms of A β [8]. Recent investigations, however, have shown that *APOE* $\epsilon 4$ affects glucose metabolism, a marker of neurodegeneration, in key AD-related brain regions independently of the effects of fibrillar forms of amyloid beta (A β) [9]. *APOE* $\epsilon 4$ is also directly associated with vascular markers, such as blood brain barrier breakdown [10], which may precede the neurodegenerative changes associated with AD and complicate vascular clearance of A β [11]. Findings thus suggest that *APOE* $\epsilon 4$ may link vascular risk factors in AD with a primary mechanistic pathway for AD pathogenesis. However, studies that have examined the association between *APOE* $\epsilon 4$ and radiologically-confirmed cerebrovascular disease have been mixed [12–18] and few have looked at its regional distribution.

The accumulation of small vessel cerebrovascular disease is best visualized *in vivo* as white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI). White matter hyperintensities are strong correlates of cognition among older adults, and, more recently, we showed that they potentially play an independent role in AD specifically. The severity of WMH is increased among individuals at greatest risk for future development of AD [19,20] and predicts the rate of cognitive decline among individuals with prevalent AD [21]. We demonstrated that increased WMH burden in parietal regions specifically predicts which cognitively normal older adults will develop AD in the future [22], suggesting that the regional distribution of WMH is important for disease risk [23]. Here, we sought to determine whether *APOE* $\epsilon 4$ is associated with the regional distribution of WMH among older adults. We carried out the study in two independent samples of older adults, the Washington Heights Inwood Columbia Aging Project (WHICAP) in New York and the Etude Santé Psychologique Prévalence Risques et Traitement (ESPRIT) in Montpellier France. These studies have similar evaluation protocols, including the acquisition of neuroimaging for quantitative analysis of brain morphology. Given our earlier findings [22], we hypothesized that *APOE* $\epsilon 4$ would be associated particularly with parietal lobe WMH and that the risk for dementia associated with parietal WMH is elevated in the presence of *APOE* $\epsilon 4$.

2. Methods

2.1. Subjects

2.1.1. WHICAP

WHICAP is a community-based study of cognitive aging and dementia in northern Manhattan, New York. Participants were initially recruited in two recruitment waves, beginning

in 1992 and in 1999 [24]. Longitudinal visits are spaced apart by 18–24 month intervals; at each visit, participants receive a full medical, neurological, and neuropsychological evaluation. Starting in 2004, active members of the sample ($n = 2776$) who did not meet criteria for dementia at their preceding visit were invited to participate in an MRI study [25] and 769 subjects underwent scanning [25]. Of these 769 individuals 52 met criteria for dementia (all but 1 with AD) at the visit closest to the MRI scan; thus, patients with dementia were prevalent cases with relatively recent onset. Compared with those who were eligible for MRI but refused participation ($n = 407$), those who received MRI scans were about 1 year younger (80 versus 81 years old), less likely to be women (67% versus 75%), and more likely to be African American (34% versus 23%) [25].

2.1.2. ESPRIT

ESPRIT is a longitudinal community-based study of aging and dementia that was carried out in Montpellier, France [26]. Between 1999 and 2001, 1863 individuals age 65 years or older were recruited and followed at 2-, 4-, and 7-year intervals with standardized interviews, neuropsychological testing, and neurological examination and 760 participants under the age of 80 years were randomly selected and invited to have an MRI scan of the brain at baseline.

2.2. MRI

2.2.1. WHICAP

MRI scan acquisition was performed on a 1.5 Tesla Philips Intera scanner. Images were acquired in the axial orientation and included T1-weighted (repetition time [TR] = 20 ms, echo time [TE] = 2.1 ms, field-of-view [FOV] = 240 cm, 256×160 matrix, and 1.3 mm slice thickness) and T2-weighted fluid-attenuated inversion recovery (FLAIR; TR = 11,000 ms, TE = 144.0 ms, inversion time [TI] = 2800 ms, FOV = 25 cm, number of excitations = 2, and 256×192 matrix with 3 mm slice contiguous thickness) sequences. Regional WMH volumes were derived following procedures developed in our laboratory [22,27]. Briefly, a Gaussian curve was fit to map the voxel intensity values and seeds labeled hyperintense regions that were more than three standard deviations of the image mean on the FLAIR images. Each seed was passed through an iterative seed growing algorithm, which labeled adjacent voxels that fell within 5% of the mean intensity of the seed, and continued iteratively, such that labeled voxels were added to the image and a new seed means were created. To derive WMH volumes in the frontal, temporal, parietal, and occipital lobes, a “lobar” atlas was spatially normalized to each subject’s labeled FLAIR image. Regional volumes were defined by the intersection of each atlas lobe with the labeled WMH voxels in that region; labeled voxel values were multiplied by voxel dimensions and summed to yield volumes in cm^3 (Fig. 1).

Fig. 1. Example of quantitated white matter hyperintensity (WMH) volume by cerebral lobe in a single subject.

2.2.2. ESPRIT

Magnetic resonance imaging was carried out on a 1.5 T Signa Advantage EchoSpeed scanner (GE Healthcare, Milwaukee, WI). T1-weighted volumetric scans were obtained in the axial orientation with a spoiled gradient echo sequence (TR = 97 ms, TE = 4 ms, 1 mm slice thickness). T2-weighted data were acquired axially with a two dimensional transversal fast multiple slice double echo sequence (TR = 4400 ms, TE1/TE2 = 16 ms/98 ms, slice thickness = 4 mm with 0.4 mm gap, 256×256 matrix size, and a 0.98×0.98 mm in-plane resolution). Regional WMH volume was determined with a semiautomatic method that has been described previously [27]. Briefly, supratentorial areas that appeared hyperintense on the T2-weighted sequence were defined with a manual threshold using MRIcro software [28]. In a second step, gross regions-of-interest were manually outlined to include hyperintense voxels in the parenchyma but to exclude areas that appear as hyperintense outside of the brain (e.g., dermal fat). The intersection between the first and second steps defined the WMH areas and volume was determined by multiplying labeled areas by the voxel dimensions. Regional WMH volumes were defined as above. Interrater and intrarater-intraclass correlation coefficients showed good to excellent agreement (0.79 and 0.95, respectively). It should be noted that we did not use the full-automated

approach to quantify WMH in the ESPRIT sample because the T2-weighted MRI scans did not have fluid attenuation. The intensity values of voxels falling in the cerebrospinal fluid in the lateral ventricles and sulci appear fall within the same intensity distribution as hyperintense voxels in the tissue and need to be distinguished via visual inspection. We previously demonstrated excellent agreement between values obtained via the automatic technique used in WHICAP versus the semi-automatic approach used in ESPRIT [29].

2.2.3. APOE genotyping

APOE genotype was established for WHICAP, and for ESPRIT as previously described [26,30]. For primary analyses, participants were classified by the presence (homozygous or heterozygous) or absence of the *APOE* $\epsilon 4$ and individuals without *APOE* $\epsilon 4$ served as the reference group. We re-ran all primary analyses limiting the reference group to only those who were homozygous for the $\epsilon 3$ allele. Similarly, we re-ran all primary analyses excluding individuals with $\epsilon 4/\epsilon 2$ alleles.

2.3. Covariates

The history of vascular disease, including diabetes, heart disease, hypertension, and clinical stroke, was

evaluated, as previously described [26,31]. Vascular disease was ascertained by self-report, which incorporated current or past diagnosis and/or treatment of hypertension, diabetes, heart disease, or clinical stroke. Affirmative responses to each were coded as “1” and otherwise coded as “0”. These dichotomous variables were summed to create a single “vascular summary score” for each subject. The diagnosis of dementia was made similarly in both samples and involved review of available neuropsychological, medical, and neurological history by a consensus panel [22,32].

This work was approved by local ethics committees and all participants gave informed consent.

2.4. Statistical analysis

Descriptive statistics were generated in the two samples and compared between *APOE* $\epsilon 4$ and non-*APOE* $\epsilon 4$ carriers with t-tests for continuous data and χ^2 tests for categorical variables. A general linear modeling (GLM) framework was used for hypothesis testing for both samples separately. *APOE* status (*APOE* $\epsilon 4$, non-*APOE* $\epsilon 4$ carrier) and sex were treated as between-subjects factors. White matter hyperintensity volume in each lobar region (frontal, temporal, parietal, and occipital) was treated as a four-level within-subjects factor. A main effect of *APOE* status would indicate an overall difference in WMH burden between *APOE* $\epsilon 4$ and non-*APOE* $\epsilon 4$ carriers. A main effect of sex would indicate overall differences in WMH burden between men and women. We were particularly interested in *APOE* status $\times$ lobar region and *APOE* status $\times$ sex $\times$ lobar region interactions, which would indicate that WMH volume varied differentially across region by *APOE* status and by *APOE* status and sex. Because the statistical assumption of sphericity was not met in the overall models (i.e., the variance in WMH volume differed across lobar regions), we relied on the results of multivariate-corrected models. The models were run with age at the time of scanning, vascular summary scores, and dementia status (0 = nondemented, 1 = demented) as covariates. In the case of significant interactions involving lobar regions, simple

effects were tested with separate analysis of variance for each lobe with the same covariates.

A combined analysis of patient data was conducted by pooling data from the two samples into one data set. Demographic and key variables of interest were compared between the two samples with t-tests and χ^2 analysis. The GLM was re-run with the same covariates as above and an additional covariate indicating sample (WHICAP versus ESPRIT). Follow-up univariate ANOVAs were run in the case of significant interactions involving *APOE* $\epsilon 4$, as above. We examined the relationship between the vascular risk summary score and regional WMH volumes with Spearman's rank correlation. We created four mutually exclusive groups that comprised non-*APOE* $\epsilon 4$ carriers with low regional WMH, *APOE* $\epsilon 4$ carriers with high regional WMH, non-*APOE* $\epsilon 4$ carriers with low regional WMH, and *APOE* $\epsilon 4$ carriers with high regional WMH. The low and high WMH distinction was defined as volumes lower than (or equal to) or higher than the median of the regional volume. We compared the proportion of individuals with dementia across these groups with χ^2 analysis.

3. Results

3.1. WHICAP sample

Six hundred ninety-four participants from the WHICAP study had complete *APOE* and WMH data. Among *APOE* $\epsilon 4$ carriers ($n = 182$), 14 (7.6%) were homozygous for $\epsilon 4/\epsilon 4$, 141 (77.4%) were heterozygous for $\epsilon 4/\epsilon 3$, and 27 (14.8%) were heterozygous for $\epsilon 4/\epsilon 2$. Among non- $\epsilon 4$ carriers ($n = 512$), 410 (80%) were homozygous for $\epsilon 3/\epsilon 3$, 4 (0.8%) were homozygous for $\epsilon 2/\epsilon 2$, and 98 (19%) were heterozygous for $\epsilon 2/\epsilon 3$. *APOE* $\epsilon 4$ and non- $\epsilon 4$ carriers did not differ in age, sex distribution, and frequency of hypertension, diabetes, heart disease, clinical stroke, total vascular risk scores, and proportion of individuals with dementia (Table 1). African American and Hispanic participants were more likely to be *APOE* $\epsilon 4$ carriers than Whites. Forty-seven of the 694 included in the analyses met criteria

Table 1
Descriptive statistics for WHICAP subjects included in the analyses

	$\epsilon 4 -$	$\epsilon 4 +$	Total sample	Statistic
N	512	182	694	N/A
Age, mean yrs (SD)	80.46 (5.77)	80.06 (5.30)	80.36 (5.65)	$t(692) = 0.820, P = .412$
Sex, N (%) women	344 (67%)	118 (65%)	462 (67%)	$\chi^2(1) = 0.334, P = .563$
Race/ethnicity, N (% within race/ethnicity)				$\chi^2(2) = 12.551, P = .002$
White or other	164 (82%)	36 (18%)	200	
Hispanic	187 (73.6%)	67 (26.4%)	254	
Black	161 (67%)	79 (33%)	240	
Hypertension, N (%)	343 (67%)	119 (65%)	462 (66.5%)	$\chi^2(1) = 0.156, P = .693$
Diabetes, N (%)	122 (24%)	32 (17.6%)	154 (22%)	$\chi^2(1) = 3.034, P = .082$
Heart disease, N (%)	115 (22.4%)	36 (20%)	151 (21.8%)	$\chi^2(1) = 0.567, P = .452$
Stroke, N (%)	58 (11%)	26 (14%)	84 (12%)	$\chi^2(1) = 1.104, P = .293$
Total Vascular risk, mean (SD)	1.24 (0.91)	1.17 (0.940)	1.22 (0.92)	$t(692) = 0.953, P = .341$
Dementia, N (%)	33 (6.4%)	14 (7.6%)	47 (6.8%)	$\chi^2(1) = 0.331, P = .565$

Abbreviations: WHICAP, Washington Heights Inwood Columbia Aging Project; SD, standard deviation; N/A, not available.

for dementia; all but one met criteria for AD (36 with probable AD, six with AD and stroke, four with AD with other concomitant disease, and one with vascular dementia).

APOE $\epsilon 4$ carriers had a higher WMH volume than noncarriers in posterior lobes (i.e., parietal and occipital) but similar distributions in anterior lobes (i.e., frontal and temporal; *APOE* status $\times$ lobe interaction, $F(3, 685) = 3.049$, $P = .028$; see Fig. 2); this effect remained when we limited the reference group to only homozygous $\epsilon 3$ carriers (*APOE* status $\times$ lobe interaction, $F(3, 583) = 5.12$, $P = .002$) or when we excluded individuals with $\epsilon 4/\epsilon 2$ (*APOE* status $\times$ lobe interaction, $F(3, 658) = 2.837$, $P = .013$). Simple effects analysis confirmed the trend for higher WMH volumes in parietal lobe ($P = .069$) and occipital lobes ($P = .036$) among *APOE* $\epsilon 4$ carriers, and similar frontal lobe ($P = .315$) and temporal ($P = .858$) lobe WMH volumes between the two groups. This pattern was slightly different in men and women (*APOE* status $\times$ lobe $\times$ sex interaction, $F(3, 687) = 2.625$, $P = .050$). The difference in occipital lobe WMH volume between *APOE* $\epsilon 4$ carriers and non-*APOE* $\epsilon 4$ carriers was greater in men than in women (lobe $\times$ sex interaction for occipital lobe, $P = .020$; all other lobes $P > .050$).

3.2. ESPRIT sample

Five hundred thirty-nine participants from ESPRIT had complete *APOE* and regional WMH data. Among *APOE* $\epsilon 4$ carriers ($n = 115$), 6 (5.2%) were homozygous for $\epsilon 4/\epsilon 4$, 99 (86%) were heterozygous for $\epsilon 4/\epsilon 3$, and 10 (8.7%) were het-

erozygous for $\epsilon 4/\epsilon 2$. Among non- $\epsilon 4$ carriers ($n = 424$), 360 (85%) were homozygous for $\epsilon 3/\epsilon 3$, 4 (1%) were homozygous for $\epsilon 2/\epsilon 2$, and 60 (14%) were heterozygous for $\epsilon 2/\epsilon 3$. *APOE* $\epsilon 4$ carriers were more likely to have a history of hypertension and a diagnosis of dementia; otherwise, no differences were observed regarding age; sex; frequencies of diabetes, heart disease, clinical stroke; and total vascular risk summary scores (Table 2). Eight participants included the analyses had dementia, all but one met criteria for AD (four with probable AD, two with possible AD, one with “mixed” dementia due to vascular disease and AD, and one with dementia of unknown etiology).

As in WHICAP, the regional distribution of WMH differed between the two *APOE* $\epsilon 4$ groups (*APOE* status $\times$ lobe interaction, $F(4, 486) = 3.729$, $P = .011$, see Fig. 3); this effect remained when the reference group was limited to those with $\epsilon 3$ allele homozygosity (*APOE* status $\times$ lobe interaction, $F(3, 425) = 3.93$, $P = .009$) and when individuals with $\epsilon 2/\epsilon 4$ were excluded (*APOE* status $\times$ lobe interaction, $F(3, 486) = 3.729$, $P = .01$). Simple effects analysis demonstrated higher WMH volume among *APOE* $\epsilon 4$ carriers in the parietal lobes ($P = .011$) and temporal lobes ($P = .028$), but similar WMH volumes in frontal ($P = .668$) and occipital lobes ($P = .195$). Unlike in the WHICAP sample, there was no interaction with sex.

3.3. Combined analysis

Individuals in the WHICAP sample were older ($t(1313) = 28.27$, $P < .001$); had a higher proportion of

Fig. 2. Plot displaying the significant apolipoprotein E gene (*APOE* $\epsilon 4$) status $\times$ lobe interaction in the Washington Heights-Inwood Columbia Aging Project (WHICAP) cohort. Values are adjusted mean white matter hyperintensity (WMH) volume and error bars are standard errors. Differences between carriers and noncarriers were significant for parietal lobe (at trend level) and occipital lobe but not frontal and temporal lobes.

Table 2
Descriptive statistics for ESPRIT subjects included in the analyses

	$\epsilon 4$ -	$\epsilon 4$ +	Total sample	Statistic
N	424	115	539	N/A
Age, mean yrs (SD)	71.37 (3.99)	71.67 (4.18)	71.43 (4.03)	$t(537) = 0.707, P = .480$
Sex, N (%) women	220 (52%)	63 (55%)	283 (52.5%)	$\chi^2(1) = 0.304, P = .581$
Hypertension, N (%)	130 (30.7%)	48 (42.5%)	178 (33%)	$\chi^2(1) = 5.55, P = .019$
Diabetes, N (%)	40 (9.4%)	7 (6%)	47 (8.7%)	$\chi^2(1) = 1.27, P = .259$
Heart disease, N (%)	23 (5.4%)	8 (7%)	31 (5.8%)	$\chi^2(1) = 0.392, P = .531$
Stroke, N (%)	12 (3%)	2 (1.7%)	14 (2.6%)	$\chi^2(1) = 0.438, P = .508$
Total Vascular risk, mean (SD)	0.49 (0.68)	0.58 (0.74)	0.50 (0.69)	$t(531) = 1.25, P = .211$
Dementia, N (%)	3 (0.8%)	5 (5%)	8 (1.6%)	$\chi^2(1) = 8.73, P = .011$

Abbreviations: ESPRIT, Etude Santé Psychologique Prévalence Risques et Traitement study; SD, standard deviation; N/A, not available.

women ($\chi^2(1) = 28.98, P < .001$), individuals with dementia ($\chi^2(1) = 18.21, P < .001$), individuals with the *APOE* $\epsilon 4$ allele ($\chi^2(1) = 4.06, P < .044$); had higher proportion of individuals with hypertension ($\chi^2(1) = 145.527, P < .001$), diabetes ($\chi^2(1) = 42.54, P < .001$), heart disease ($\chi^2(1) = 65.38, P < .001$), and stroke ($\chi^2(1) = 39.71, P < .001$); and higher overall vascular burden ($t(1305) = 15.662, P < .001$) compared with the ESPRIT sample. WHICAP participants also had higher WMH volume in all lobes ($t > 3.15, P < .001$).

In the combined analysis, *APOE* $\epsilon 4$ carriers had more severe overall WMH burden (main effect of *APOE* status, $F(1,1187) = 4.573, P = .033$), but this effect varied across regions (*APOE* status $\times$ lobe interaction, $F(1,1181) = 5.125, P = .024$) such that *APOE* $\epsilon 4$ carriers had more severe WMH distribution in posterior brain regions (Fig. 4). Differences between groups were significant

for parietal ($P = .003$) and occipital ($P = .013$) lobes but not for frontal ($P = .203$) or temporal ($P = .203$) lobes. The vascular risk summary score correlated significantly ($P < .001$) with WMH in all regions; the highest correlation coefficients emerged for frontal and parietal lobes ($\rho = 0.209$ and $\rho = 0.217$, respectively) versus temporal and occipital lobes ($\rho = 0.144$ and $\rho = 0.195$, respectively).

Figure 5 displays the proportion of individuals with dementia across parietal lobe WMH and *APOE* $\epsilon 4$ groups. The proportion of individuals with dementia increased across groups ($\chi^2(3) = 12.85, P = .005$, linear-by-linear association, $P < .001$); increased WMH volume was associated with an increased frequency of dementia irrespective of *APOE* $\epsilon 4$ status and those with the *APOE* $\epsilon 4$ allele had the greatest proportion of subjects with dementia if they also had increased parietal WMH.

Fig. 3. Plot displaying the significant apolipoprotein E gene (*APOE* $\epsilon 4$) status $\times$ lobe interaction in the Etude Santé Psychologique Prévalence Risques et Traitement study (ESPRIT) cohort. Values are adjusted mean white matter hyperintensity (WMH) volume and error bars are standard errors. Differences between carriers and noncarriers were significant for temporal and parietal lobes.

Fig. 4. Combined analysis showing regional differences in white matter hyperintensity (WMH) volume across $\epsilon 4$ groups in the two samples combined. Parietal and occipital lobe WMH volumes significantly differed between groups.

4. Discussion

We hypothesized that *APOE* $\epsilon 4$ would be associated with increased WMH in parietal regions and we confirmed this hypothesis across two independent large samples of older adults. We also showed that WMH in the parietal lobes was associated with a higher proportion of dementia and that *APOE* $\epsilon 4$ carriers were most likely to have dementia if they also had increased parietal lobe WMH. Our findings suggest that regionally distributed small vessel cerebrovascular disease is one potential mechanism through which *APOE* $\epsilon 4$ may confer risk for AD. Because of its association

with the primary genetic risk, the findings also raise the possibility of a mechanistic role of small vessel cerebrovascular disease in the pathogenesis of AD.

The *APOE* gene, of course, was initially investigated because of its role in lipoprotein metabolism [33], so it is not surprising that there is a link with cerebrovascular disease as well. Indeed, some reports [15,16,34], including a recent meta-analysis [18], have shown that *APOE* $\epsilon 4$ is associated with WMH or that *APOE* $\epsilon 4$ interacts with severity of WMH to predict dementia status [35]. However, several studies have also found no association between

Fig. 5. Proportion of individuals with dementia as a function of $\epsilon 4$ status and parietal lobe white matter hyperintensity (WMH) burden.

APOE $\epsilon 4$ and WMH [12–14,17]. There are two primary possibilities that may explain these inconsistent results. First, studies showing an association between *APOE* $\epsilon 4$ and WMH have been carried out generally in larger community-based samples than the smaller samples represented in the negative studies. Second, studies have not examined the lobar distribution of WMH. In the current study, in addition to a main effect of *APOE* $\epsilon 4$ in the combined analysis, which indicates that there was an overall increased burden of WMH irrespective of regional distribution, there was an interaction between *APOE* $\epsilon 4$ status and lobar distribution of WMH that showed increased severity among *APOE* $\epsilon 4$ carriers in some regions but not others. Although there were slight differences between the two samples in regional distribution as a function of *APOE* $\epsilon 4$ status (i.e., in WHICAP there were differences in occipital lobe and ESPRIT there were temporal lobe differences), the two converged in evidencing increased parietal lobe WMH among *APOE* $\epsilon 4$ carriers, which was most evident in the combined analysis. We are aware of only one study that has examined lobar distribution of WMH as a function of *APOE* status [36], which showed that $\epsilon 2$ carriers had elevated frontal lobe WMH volume relative to non- $\epsilon 2$ carriers and no differences between *APOE* $\epsilon 4$ carriers and non-carriers in a study of normal cognitive aging.

Apart from regional WMH severity, *APOE* $\epsilon 4$ was associated with dementia diagnosis in the ESPRIT study but not in WHICAP. We attribute the lack of observed association to a few nonmutually exclusive factors. First, while the *APOE* $\epsilon 4$ is consistently associated with risk of late onset AD among non-Hispanic whites, findings have been inconsistent among African Americans and Hispanics, with general agreement that the $\epsilon 4$ allele still confers risk in these populations but with relatively lower magnitude [37]. Given the high proportion of African Americans and Hispanics, comprising about 70% of the WHICAP sample, we can expect the association to be relatively weaker. Second, there was a small number of individuals with dementia in the sample and, despite the fact that there was a relatively higher proportion of *APOE* $\epsilon 4$ among those with dementia, there may not have been sufficient power for statistical significance. Third, the overall findings suggest that WMH burden may be an effect modifier for the relationship between *APOE* $\epsilon 4$ and dementia risk. As seen in Fig. 3, the difference in proportion of *APOE* $\epsilon 4$ carriers and noncarriers is greater among those with higher amounts of parietal lobe WMH than among those with lower amounts of parietal lobe WMH.

Furthermore, in WHICAP but not in ESPRIT, we found that the difference in occipital lobe WMH volume between *APOE* $\epsilon 4$ and non-*APOE* $\epsilon 4$ carriers was greater for men than women. Previous work, if at all, reported slightly an increased amount of WMH in anterior regions among women [38]. One notable difference between WHICAP and ESPRIT (and between WHICAP and other large samples reported in the extant literature) is the relatively older

age of the participants. One possibility is that more posterior distribution reflects more severe disease [39] and men tend to “age faster” than women [40], differences that may not manifest until later in life.

Why *APOE* $\epsilon 4$ is associated with parietal lobe WMH specifically is unclear, although the parietal lobes have been implicated in AD for quite some time. Neuroimaging studies that have utilized positron emission tomography consistently implicate parietal regions in early AD [41–43], particularly among *APOE* $\epsilon 4$ carriers [44], and the earliest deposition of amyloid plaque pathology occurs in posterior association areas [45,46]. The regional selectivity we observed suggests that the pathological features of WMH may vary across lobar regions in the context of AD and AD risk, reflecting ischemic disease with other pathological markers [23]. For example, amyloid angiopathy, which has a propensity for posterior brain regions in AD [47], is more severe among *APOE* $\epsilon 4$ carriers than among those without the *APOE* $\epsilon 4$ allele [48]. The parietal lobes and entorhinal cortex, where early dysfunction is apparent in AD [49], are strongly interconnected, so damage to parietal lobes may reflect Wallerian-type degeneration secondary to primary pathology in the entorhinal cortex or perhaps in other cortical regions; indeed, a recent report showed the “spread” of AD-related dysfunction from regions in the medial temporal lobe to the parietal lobes [50]. Shared vascularization between medial temporal and parietal regions may implicate a primary hemodynamic role in AD-associated regional dysfunction and damage. Recent pathological correlates studies [51] suggest that WMH accumulation is likely driven primarily by cerebrovascular disease but also might be secondary to neurodegenerative changes; thus WMH might increase risk for developing AD but might also reflect a neurodegenerative process already in place. Future research will need to disambiguate the nature of the relationships among these factors and determine how regional WMH may be implicated in risk for AD more mechanistically.

Current hypothetical models of AD pathogenesis emphasize the initiating role of A β in a sequence of pathological events that ultimately leads to the neuropsychological syndrome that defines the disease clinically [52,53]. Although acknowledging its potential additive role to disease presentation, these models do not consider cerebrovascular disease to be central to pathogenesis or mechanistically related to “primary” disease pathology. While more work is needed to establish the mechanistic link between small vessel cerebrovascular disease and AD, we and others have shown repeatedly that it is related to risk for AD, predicts the course of the disease, and discriminates between individuals with and without clinical AD [19,21–23,32]. Recently, we showed that WMH predict the risk for AD and is associated with markers of neurodegeneration as much as measures of fibrillar A β [54,55]. *APOE* $\epsilon 4$ is a risk factor for the development of AD and not a biological marker of AD, as many

individuals without *APOE* $\epsilon 4$ develop the disease and many individuals with *APOE* $\epsilon 4$ do not despite the increased risk. Our findings suggest that the risk associated with *APOE* $\epsilon 4$ may be partially dependent on the severity of WMH (Fig. 3).

Our study has a number of strengths. First, we tested our hypotheses across two large samples, with very similar methods. Second, we used quantitative methods to define precisely regionally distributed WMH burden. Third, the community-based nature of these samples increases confidence in the external validity of our findings. Fourth, while the methodology employed was very similar, the two samples included in this study were distinct in terms of ethnicity, vascular risk factors, and, likely, life-time environmental exposures, yet the findings across the two were remarkably consistent, and clear when data from the two samples were combined. Finally, the findings have clinically relevant implications. Several of the risk factors for WMH are known, so successful prevention and management of these conditions may have a direct impact on risk for AD and may mitigate the effect of *APOE* $\epsilon 4$ on disease risk.

In terms of weaknesses, the study employed a cross-sectional design, which limits the ability to draw definitive conclusions about causal relationships. Despite the large overall sample size, the number of *APOE* $\epsilon 4$ carriers and subjects with dementia was relatively low. In WHICAP, the direct relationship between *APOE* and dementia was weak, possibly because of diminished statistical power, the inclusion of prevalent dementia cases, and the varying risk associated with *APOE* $\epsilon 4$ across racial/ethnic groups [56]. Furthermore, subtle differences in scanning protocols and techniques to quantify WMH across the two samples may have been a source of some error, although we showed excellent reliability and previously showed excellent agreement between the analysis approaches [27].

In summary, by examining the association of *APOE* $\epsilon 4$ and regionally distributed WMH across two large, separate community-based samples, our findings implicate a potential role of parietal lobe WMH. Individuals with the $\epsilon 4$ allele are more likely to have dementia if they also have increased parietal WMH.

Acknowledgments

This work was supported in part by grants from National Institutes of Health (AG037212, AG007232, AG029949, and AG034189), regional government of Languedoc-Roussillon (<http://www.laregion.fr>), the Agence Nationale de la Recherche (ANR: <http://www.agence-nationale-recherche.fr>), and an unconditional grant from Novartis (<http://www.novartis.fr>). Additional support by France Alzheimer (<http://www.francealzheimer.org/>). TNA is supported by the Languedoc-Roussillon Region (Chercheur d'avenir Grant 2011).

The authors report no actual or potential conflicts of interest.

RESEARCH IN CONTEXT

1. Systematic review: Several lines of investigation suggest that there is a link of cerebrovascular disease with the clinical presentation, and possibly pathogenesis, of Alzheimer's disease (AD). Small vessel cerebrovascular disease is best visualized on magnetic resonance imaging (MRI) scans as white matter hyperintensities (WMH), areas of increased signal on T2-weighted scans. We previously showed that WMH, when distributed in parietal regions in particular, are associated with risk and diagnosis of AD. Here, we asked the question of whether apolipoprotein E gene (*APOE* $\epsilon 4$), the strongest known genetic risk factor for late onset AD, is associated with the regional distribution of WMH in two large, independent cohorts. We reviewed the extant literature (via bibliographic search in PubMed) and drew from our previous research on this topic to evaluate the accumulated knowledge related to this research.
2. Interpretation: Our findings suggest that *APOE* $\epsilon 4$, a strong genetic risk factor for AD, is associated with parietal lobe WMH, which in turn increases risk for AD.
3. Future directions: Future work should consider longitudinal associations among *APOE*, WMH, and AD.

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