Received: 9 October 2022 | Accepted: 28 November 2022

DOI: 10.1111/ene.15656

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Effect of *APOE* ε4 genotype on amyloid-β, glucose metabolism, and gray matter volume in cognitively normal individuals and amnestic mild cognitive impairment

Weihua Li[1,2] | Runtian Li[3] | Shaozhen Yan[1,2] | Zhilian Zhao[1,2] | Yi Shan[1,2] | Zhigang Qi[1,2] | Jie Lu[1,2] | for the Alzheimer's Disease Neuroimaging Initiative

[1]Department of Radiology and Nuclear Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China

[2]Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics, Beijing, China

[3]Limpid Medical Imaging, Beijing, China

Correspondence
Jie Lu, Department of Radiology and Nuclear Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China.
Email: imaginglu@hotmail.com

Funding information
Beijing Brain Initiative from Beijing Municipal Science & Technology Commission (Z201100005520018)

Abstract

Background and purpose: The presence of apolipoprotein E ε4 (*APOE* ε4) is associated with an increased risk of developing Alzheimer disease (AD). The aim of this study was to assess the effects of *APOE* ε4 on amyloid-β (Aβ) pathology, glucose metabolism, and gray matter (GM) volume and their longitudinal changes in healthy control (HC) and amnestic mild cognitive impairment (aMCI).

Methods: We included 50 HCs and 109 aMCI patients from the Alzheimer's Disease Neuroimaging Initiative phase 2/GO based on availability of baseline T1-weighted magnetic resonance imaging, ^{18}F-florbetapir positron emission tomography (PET), and ^{18}F-fluorodeoxyglucose (FDG) PET. Of these, 35 HCs and 67 aMCI patients who underwent 24-month scans were included for follow-up study.

Results: Voxelwise analysis revealed that *APOE* ε4 carriers exhibited greater baseline Aβ deposition than *APOE* ε4 noncarriers in both diagnostic groups. However, there was no significant difference between *APOE* ε4 noncarriers and *APOE* ε4 carriers in terms of ^{18}F-FDG PET standardized uptake value ratio and GM volume. Region of interest-based analysis showed statistically significant greater Aβ deposition in *APOE* ε4 carriers than *APOE* ε4 noncarriers only in aMCI patients. Furthermore, *APOE* ε4 carriers generally exhibited a greater magnitude and spatial extent of longitudinal changes in Aβ deposition than *APOE* ε4 noncarriers in both diagnostic groups.

Conclusions: Our findings suggest a differential effect of *APOE* ε4 on Aβ pathology, glucose metabolism, and GM volume. Studying *APOE* ε4-related brain changes with neuroimaging biomarkers in preclinical AD offers an opportunity to further our understanding of the pathophysiology of AD at an early stage.

KEYWORDS
amyloid-β, apolipoprotein E ε4, glucose metabolism, mild cognitive impairment, positron emission tomography

INTRODUCTION

The apolipoprotein E (*APOE*) gene is the most significant genetic modulator of late onset Alzheimer disease (AD) [1], with three major allelic variants, $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$ [2].The $\varepsilon 4$ allele of the *APOE* gene raises the risk of AD while decreasing the age of onset [3]. *APOE* isoforms regulate amyloid-β (Aβ) clearance variably, with *APOE* $\varepsilon 4$ being less effective than *APOE* $\varepsilon 2$ or *APOE* $\varepsilon 3$ [4]. Previous studies have demonstrated that *APOE* $\varepsilon 4$ carriers have increased Aβ deposition [5, 6], a greater percentage of individuals who tested positive for Aβ [7, 8], and earlier and speedier Aβ accumulation [9]. The results of studies investigating the effect of *APOE* $\varepsilon 4$ on glucose metabolism were inconsistent, demonstrating lower glucose metabolism [3], no genotype effect [10], and higher glucose metabolism in *APOE* $\varepsilon 4$ carriers compared to *APOE* $\varepsilon 4$ noncarriers [11]. Numerous studies have used T1-weighted magnetic resonance imaging (MRI) to investigate the effect of *APOE* $\varepsilon 4$ on brain structure, but the results are contradictory [12]. Several studies found reduced hippocampal volume in *APOE* $\varepsilon 4$ carriers compared with noncarriers in elderly individuals [13, 14]. Nonetheless, there have also been some studies reporting no significant differences in hippocampal volume between *APOE* $\varepsilon 4$ carriers and noncarriers [15, 16].

Only a few studies have evaluated the effect of *APOE* $\varepsilon 4$ on various neuroimaging modalities. Gonneaud et al. [6] assessed the effect of *APOE* $\varepsilon 4$ on brain volume, glucose metabolism, and Aβ deposition in cognitively normal individuals. They found no significant effect of *APOE* $\varepsilon 4$ on brain volume and glucose metabolism, but Aβ deposition was significantly higher in *APOE* $\varepsilon 4$ carriers than in noncarriers. Baek et al. [17] assessed the effects of *APOE* $\varepsilon 4$ on Aβ and tau deposition and their longitudinal changes in the AD spectrum. They found increased baseline Aβ and tau deposition in *APOE* $\varepsilon 4$ carriers compared with noncarriers, and the tau accumulation rate was higher in *APOE* $\varepsilon 4$ carriers. In patients with mild cognitive impairment (MCI), the presence of *APOE* $\varepsilon 4$ allele increases the risk of conversion to AD [5]. However, the effect of the *APOE* $\varepsilon 4$ on brain Aβ pathology, glucose metabolism, and brain volume in patients with amnestic MCI (aMCI) is not fully understood. Studies assessing the effect of *APOE* $\varepsilon 4$ on several neuroimaging biomarkers and their longitudinal changes in patients with aMCI are rare.

In this study, we sought to characterize the effect of *APOE* $\varepsilon 4$ on Aβ pathology as measured by ^{18}F-florbetapir (AV45) positron emission tomography (PET), glucose metabolism as measured by ^{18}F-fluorodeoxyglucose (FDG) PET, and gray matter (GM) volume as measured by T1-weighted MRI and their longitudinal changes in healthy controls (HCs) and patients with aMCI.

MATERIALS AND METHODS

Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). The ADNI study was approved by the institutional review boards of all participating institutions. Informed written consent was obtained from all participants at each site.

In this study, we selected ADNI-GO/2 participants meeting the diagnostic criteria for aMCI who had Mini-Mental State Examination (MMSE) scores between 24 and 30, a Clinical Dementia Rating (CDR) score of 0.5, a memory complaint, objective memory loss measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II, and absence of loss in other cognitive domains [18]. At baseline, 50 HCs and 109 aMCI patients were selected on the basis of the availability of T1-weighted MRI, ^{18}F-AV45 PET, ^{18}F-FDG PET, *APOE* genotyping, cerebrospinal fluid (CSF), and neuropsychological assessments. Of these, 35 HCs and 67 aMCI patients who underwent 24-month scans were included for follow-up study. A complete list of ADNI inclusion and exclusion criteria is available at https://adni.loni.usc.edu/methods/documents/.

Neuropsychological assessment

Neuropsychological tests were performed by certified raters using standardized ADNI protocols. Participants underwent a comprehensive battery of neuropsychological tests; we evaluated performance on the MMSE, Rey Auditory Verbal Learning Test (RAVLT; immediate), and Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) consisting of 11 (ADAS-Cog11) and 13 (ADAS-Cog13) items in this study. The neuropsychological test data for study participants were obtained from the ADNI files "MMSE.csv," "CDR.csv," and "ADNIMERGE.csv," respectively.

APOE genotyping

Peripheral blood was collected from study participants to be used for *APOE* $\varepsilon 4$ genotyping. *APOE* $\varepsilon 4$ carriers were defined as individuals with one or two copies of allele $\varepsilon 4$ (either $\varepsilon 4/\varepsilon 4$, $\varepsilon 4/\varepsilon 3$, or $\varepsilon 4/\varepsilon 2$), and noncarriers were defined as individuals with no allele $\varepsilon 4$. *APOE* $\varepsilon 4$ genotyping methods are described at https://adni.loni.usc.edu in detail.

CSF measurements

The ADNI procedures for lumbar puncture can be found at https://adni.loni.usc.edu. CSF concentrations of $A\beta_{1-42}$, phosphorylated tau (p-tau), and total tau were measured using Elecsys immunoassays on a Cobas e 601 analyzer (software version 05.02) as described previously [19, 20]. All participants who were included in this study had their CFS data obtained from the ADNI site.

MRI and PET acquisition and processing

Preprocessed ^{18}F-AV45 PET, ^{18}F-FDG PET, and corresponding raw T1-weighted MRI images in the DICOM (Digital Imaging and

Communication in Medicine) format were downloaded from the ADNI database (https://adni.loni.usc.edu). All structural MRI images obtained in this study were acquired using 3.0-T scanners. PET images were acquired following the intravenous injection of 370 MBq (10 mCi) of ^{18}F-AV45 (50–70 min postinjection) and 185 MBq (5 mCi) of ^{18}F-FDG (30–60 min postinjection). ^{18}F-AV45 and ^{18}F-FDG PET were acquired within 1 week of each other, and the corresponding MRI images were acquired close to the time of the ^{18}F-AV45 PET scan. The preprocessed PET images were averaged, spatially aligned, reoriented, and then interpolated into a standard image and voxel size (image volume 160×160×96, 1.5×1.5×1.5 mm in x, y, z) and smoothed to a common resolution of 8-mm full width at half maximum (FWHM). Detailed methods for PET data acquisition and preprocessing are available at https://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/.

Structural MRI and PET data were analysed using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/) and in-house software implemented in MATLAB 2019b (MathWorks). In brief, structural MRI images were brain-extracted, segmented into GM, white matter, and CSF, normalized to the standard Montreal Neurological Institute (MNI) space, and then smoothed with an 8-mm FWHM Gaussian filter. PET images were partial volume corrected (PVC) [21]. The PVC PET pictures were coregistered with the corresponding structural MRI, and then the transformation parameters established by MRI spatial normalization were applied to the spatial normalization of the T1-coregistered PET images to the standard MNI space. Standardized uptake value ratio (SUVR) images were created by normalizing the uptake to the cerebellar GM mean value.

Four regions of interest (ROIs), including middle temporal gyrus, posterior cingulate cortex, inferior parietal lobule, and prefrontal cortex, were created based on the Automatic Anatomical Labeling atlas [22] in the MNI space. These four regions were selected as a priori ROIs due to their importance in cognitive function and vulnerability to AD.

Voxelwise analysis

The voxelwise analysis was performed to assess differences in baseline ^{18}F-AV45 PET SUVR,^{18}F-FDG PET SUVR, and GM volume between HC and aMCI using two-sample *t*-tests in SPM12 with age, gender, years of education, and *APOE* ε4 status as covariates. The voxelwise analysis was also performed to assess the effects of *APOE* ε4 on Aβ pathology, glucose metabolism, and GM volume. We implemented two-sample *t*-tests with age, gender, and years of education as covariates, comparing ^{18}F-AV45 PET SUVR,^{18}F-FDG PET SUVR, and GM volume separately for *APOE* ε4 noncarriers and *APOE* ε4 carriers in HC and aMCI. All SPM statistical maps were thresholded at voxel level at $p < 0.001$ uncorrected and cluster level false discovery rate (FDR) corrected at $p_{FDR} < 0.05$, voxel size $k > 100$.

Longitudinally, difference ^{18}F-AV45 PET SUVR and ^{18}F-FDG PET SUVR images were created by voxel-based subtraction (Δ: follow-up − baseline) using the SPM12 "ImCalc" function. Mean difference ^{18}F-AV45 PET SUVR and ^{18}F-FDG PET SUVR images were averaged over all *APOE* ε4 noncarriers and *APOE* ε4 carriers in each diagnostic group.

Statistical analysis

SPSS Statistics for Macintosh version 26 (IBM) was used for the statistical analysis of demographic, clinical, and ROI-based data. Continuous and categorical variables were compared between the *APOE* ε4 noncarriers and *APOE* ε4 carriers using independent-samples *t*-test and chi-squared test, respectively. ROI-based longitudinal changes in ^{18}F-AV45 PET SUVR, ^{18}F-FDG PET SUVR, and GM volume were compared between *APOE* ε4 noncarriers and *APOE* ε4 carriers by using a linear mixed-effects model with baseline age, gender, and years of education as fixed factors. Pearson correlations were run to assess the relationship between neuroimaging measures and clinical measures in aMCI *APOE* ε4 noncarriers and aMCI *APOE* ε4 carriers. We considered results statistically significant at $p < 0.05$.

RESULTS

Participant characteristics

Demographics and clinical characteristics of the study participants at baseline are summarized in Table 1. There were no significant differences between *APOE* ε4 noncarriers and *APOE* ε4 carriers in age, gender, years of education, and any neuropsychological assessments at baseline. CSF level of $A\beta_{1-42}$, p-tau, and total tau were significantly affected by *APOE* ε4 status.

APOE ε4 noncarriers showed higher levels of $A\beta_{1-42}$ than *APOE* ε4 carriers, but levels of p-tau and total tau were lower in *APOE* ε4 carriers.

Effects of *APOE* ε4 on ^{18}F-AV45 PET SUVR, ^{18}F-FDG PET SUVR, and GM volume at baseline

Voxelwise analysis of ^{18}F-AV45 PET SUVR revealed that *APOE* ε4 carriers exhibited greater baseline Aβ deposition than *APOE* ε4 noncarriers in both diagnostic groups. In HCs, *APOE* ε4 carriers showed greater Aβ deposition in the right posterior cingulate cortex, left fusiform gyrus, and bilateral supramarginal gyrus than *APOE* ε4 noncarriers. In aMCI patients, *APOE* ε4 carriers show greater Aβ deposition in the left anterior cingulate cortex, left dorsolateral prefrontal cortex, right anterior prefrontal cortex, right middle temporal gyrus, and bilateral insula than *APOE* ε4 noncarriers (Figure 1a, Table 2). In terms of ^{18}F-FDG PET SUVR and GM volume, voxelwise analysis revealed that there was no significant difference between *APOE* ε4 noncarriers and *APOE* ε4 carriers in both diagnostic groups.

For the ROI-based analysis, aMCI *APOE* ε4 carriers showed significantly higher ^{18}F-AV45 PET SUVR than aMCI *APOE* ε4

noncarriers. In HCs, *APOE* ε4 carriers showed higher ^{18}F-AV45 PET SUVR than *APOE* ε4 noncarriers, but this was not statistically significant (Figure 1b). In both diagnostic groups, there were no statistically significant differences in regional ^{18}F-FDG PET SUVR and GM volume between *APOE* ε4 noncarriers and *APOE* ε4 carriers. However, the overall ^{18}F-FDG PET SUVR and GM volume of four ROIs were slightly higher in *APOE* ε4 carriers than in *APOE* ε4 noncarriers (Figure 1c).

Effects of *APOE* ε4 on longitudinal changes in ^{18}F-AV45 PET SUVR, ^{18}F-FDG PET SUVR, and GM volume

Mean difference PET SUVR images visually illustrating the effects of *APOE* ε4 on longitudinal changes in Aβ deposition and glucose metabolism in each diagnostic group are shown in Figure 2a,b. In both diagnostic groups, *APOE* ε4 carriers generally exhibited greater magnitude and spatial extent of longitudinal changes in Aβ deposition than *APOE* ε4 noncarriers. Longitudinal regional changes (Δ: follow-up − baseline) in ^{18}F-AV45 PET SUVR, ^{18}F-FDG PET SUVR, and GM volume are demonstrated in Figure 2c. *APOE* ε4 carriers showed significantly greater longitudinal increase in Aβ deposition compared with *APOE* ε4 noncarriers in the middle temporal gyrus in both diagnostic groups ($p < 0.05$), and in the inferior parietal lobule in aMCI ($p < 0.05$). For both HC and aMCI, *APOE* ε4 carriers also showed greater longitudinal increased in Aβ deposition than *APOE* ε4 noncarriers in the posterior cingulate cortex and prefrontal cortex, but this was not statistically significant. aMCI *APOE* ε4 carriers showed a greater longitudinal decline in glucose metabolism than aMCI *APOE* ε4 noncarriers, with statistical significance only in the inferior parietal lobule ($p < 0.05$). HC *APOE* ε4 carriers demonstrated a higher longitudinal decline in glucose metabolism than HC *APOE* ε4 noncarriers in the posterior cingulate cortex and prefrontal cortex, but a lesser decline in the middle temporal gyrus and inferior parietal lobule. *APOE* ε4 carriers had either higher or lesser longitudinal reductions in GM volume than *APOE* ε4 noncarriers in both diagnostic groups.

Effect of *APOE* ε4 on relationship between neuroimaging measures and cognitive performance in aMCI at baseline

In aMCI *APOE* ε4 noncarriers, ^{18}F-AV45 PET SUVR and GM volume in four ROIs were significantly correlated with the RAVLT-immediate, ADAS-Cog11, and ADAS-Cog13 (Figure 3a). Only ^{18}F-AV45 PET

TABLE 1 Demographic and clinical characteristics of the study participants at baseline

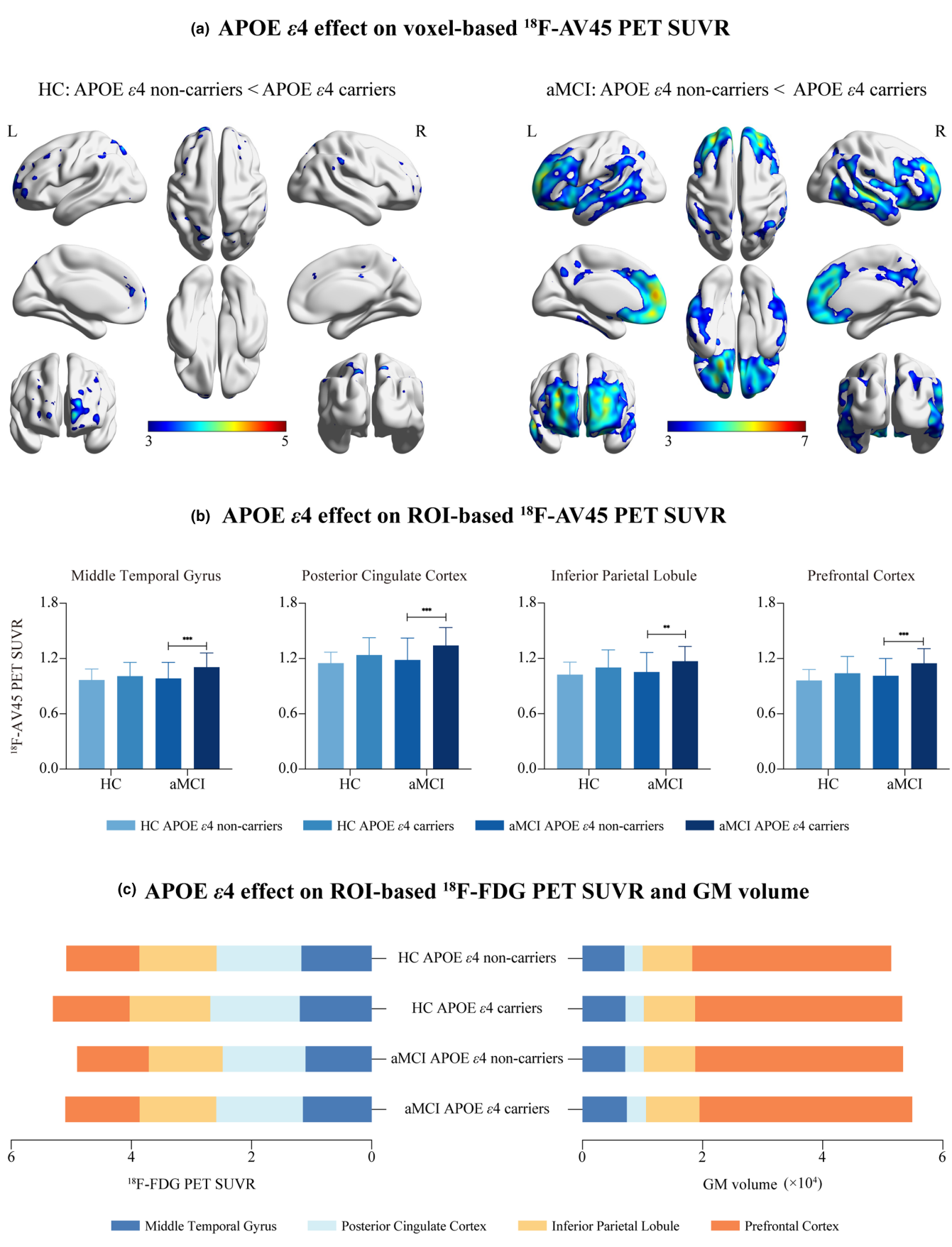
	HC, $n = 50$			aMCI, $n = 109$		
Characteristic	***APOE* ε4 noncarriers, $n = 33$**	***APOE* ε4 carriers, $n = 17$**	***p***	***APOE* ε4 noncarriers, $n = 50$**	***APOE* ε4 carriers, $n = 27$**	***p***
Age, years	72.90 ± 5.88	72.91 ± 6.38	0.999	70.47 ± 6.77	68.55 ± 7.15	0.159
Gender, M/F	17/16	9/8	0.924	40/26	19/24	0.093
Education, years	17.15 ± 2.24	17.47 ± 2.24	0.635	16.33 ± 2.65	15.93 ± 2.57	0.434
MMSE	29.27 ± 1.07	28.88 ± 1.45	0.285	28.50 ± 1.46	28.16 ± 1.65	0.265
RAVLT-immediate	47.42 ± 10.57	44.94 ± 11.75	0.452	39.77 ± 12.10	37.91 ± 10.54	0.410
ADAS-Cog11	5.24 ± 2.50	5.94 ± 3.27	0.404	7.86 ± 4.32	8.67 ± 3.65	0.320
ADAS-Cog13	8.03 ± 3.75	9.12 ± 4.91	0.387	12.35 ± 5.94	14.14 ± 6.45	0.142
CSF $A\beta_{1-42}$, pg/ml	1622.50 ± 585.10	1134.61 ± 774.59	0.023*	1461.38 ± 697.72	893.20 ± 458.23	<0.001*
CSF p-tau, pg/ml	18.67 ± 5.14	24.34 ± 9.34	0.012*	21.18 ± 12.42	30.47 ± 17.70	0.002*
CSF total tau, pg/ml	208.57 ± 61.11	262.35 ± 94.69	0.026*	232.20 ± 114.86	314.43 ± 159.73	0.003*

Note: Data are presented as mean ± SD.

Abbreviations: ADAS-Cog11, Alzheimer's Disease Assessment Scale Cognitive subscale consisting of 11 items; ADAS-Cog13, Alzheimer's Disease Assessment Scale Cognitive subscale consisting of 13 items; aMCI, amnestic mild cognitive impairment; CSF, cerebrospinal fluid; F, female; HC, healthy control; M, male; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test.

*$p < 0.05$.

FIGURE 1 Comparison of baseline ^{18}F-florbetapir (AV45) positron emission tomography (PET) standardized uptake value ratio (SUVR), ^{18}F-FDG PET SUVR, and gray matter (GM) volume between groups. (a) Voxelwise comparison of baseline ^{18}F-AV45 PET SUVR between *APOE* ε4 noncarriers and *APOE* ε4 carriers in healthy control (HC) and amnestic mild cognitive impairment (aMCI). The Statistical Parametric Mapping statistical maps were thresholded at the voxel level at $p < 0.001$ uncorrected and cluster-level false discovery rate (FDR) corrected at $p_{FDR} < 0.05$, voxel size $k > 100$. The colour bar represents the *T* value. (b) Region of interest (ROI)-based comparisons of baseline ^{18}F-AV45 PET SUVR between *APOE* ε4 noncarriers and *APOE* ε4 carriers in each diagnostic group. Data are presented as mean and SD; *p*-values for the comparison between *APOE* ε4 noncarriers and *APOE* ε4 carriers are shown: **$p < 0.01$, ***$p < 0.005$. (c) ROI-based comparisons of baseline ^{18}F-FDG PET SUVR and GM volume between *APOE* ε4 noncarriers and *APOE* ε4 carriers in each diagnostic group. No statistically significant result was found



SUVR was significantly correlated with cognitive functions in aMCI *APOE* ε4 carriers (Figure 3b). In both aMCI *APOE* ε4 noncarriers and aMCI *APOE* ε4 carriers, ^{18}F-FDG PET SUVR was not correlated with any measure of cognition.

DISCUSSION

In this study, we assessed the effects of *APOE* ε4 genotype on Aβ pathology, glucose metabolism, and GM volume and their longitudinal changes in HC and aMCI. We found that *APOE* ε4 carriers had greater baseline Aβ deposition than *APOE* ε4 noncarriers in both diagnostic groups, whereas there were no significant effects of *APOE* ε4 on baseline glucose metabolism and GM volume in either HCs or aMCI patients. Longitudinally, we found a faster rate of Aβ accumulation in *APOE* ε4 carriers compared with *APOE* ε4 noncarriers in both diagnostic groups. aMCI *APOE* ε4 carriers showed a greater longitudinal decline in glucose metabolism compared to aMCI *APOE* ε4 noncarriers. Regarding the effect of *APOE* ε4 on longitudinal GM volume changes, the results are contradictory. Our findings imply that *APOE* ε4 has a differential effect on Aβ pathology, glucose metabolism, and GM volume in HC and aMCI.

The vast majority of previous studies that assessed the effect of *APOE* ε4 on Aβ pathology in cognitively normal individuals found that *APOE* ε4 carriers have greater Aβ deposition than noncarriers [6, 23, 24]. Fleisher et al. [9] examined ^{18}F-AV45 PET imaging in 61 older HCs, 53 MCI patients, and 45 AD patients, and found that *APOE* ε4 carriers in each of the diagnostic group had higher ^{18}F-AV45 PET SUVRs, patterns of ^{18}F-AV45 PET elevations indicative of AD, and a greater proportion fulfilling ^{18}F-AV45 PET-positive criteria compared with *APOE* ε4 noncarriers. The effect of *APOE* ε4 on Aβ pathology was shown to be region-specific, although the primary effect regions varied across studies. Drzezga et al. [25] used ^{11}C-Pittsburgh compound B (PIB) PET to assess Aβ deposition in AD patients, and they found that *APOE* ε4 carriers had significantly stronger and more extended ^{11}C-PIB uptake in bilateral temporoparietal and frontal cortex than *APOE* ε4 noncarriers. Scheinin et al. [26] used ^{11}C-PIB PET to assess the effect of *APOE* ε4 on Aβ deposition in

TABLE 2 Clusters showing significant differences in ^{18}F-AV45 SUVR between *APOE* ε4 noncarriers and *APOE* ε4 carriers in HC and aMCI patients at baseline

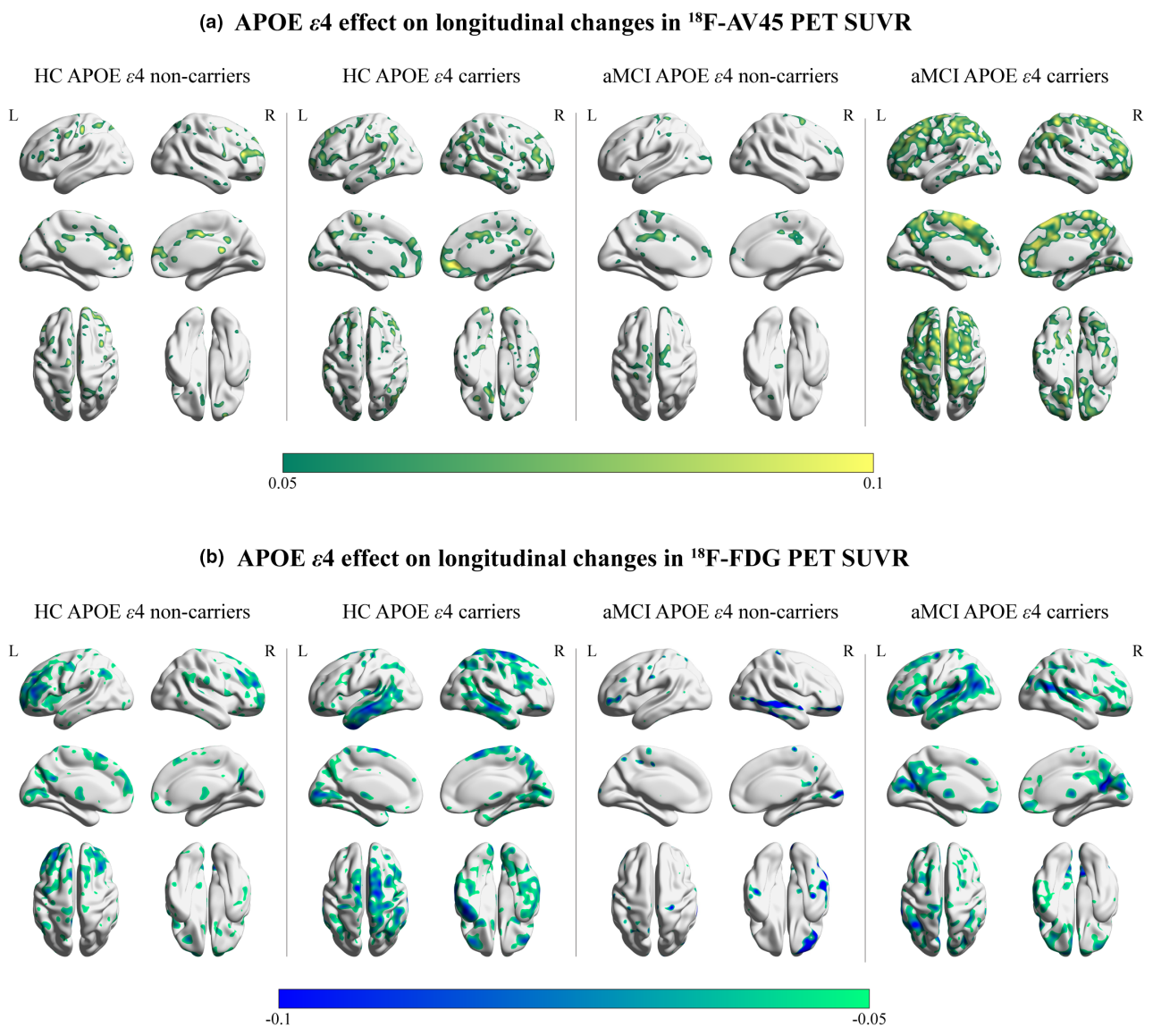
Comparison	Cluster level		Peak *T*	MNI coordinates			Brain region	Brodmann area
	p	*k*		x	y	z		
HC *APOE* ε4 noncarriers vs. HC *APOE* ε4 carriers								
	<0.0001	19,179	4.74	0	−26	34	Right posterior cingulate cortex	23
	0.042	1565	4.05	−56	−62	−18	Left fusiform gyrus	37
	0.018	2356	3.94	64	−21	12	Right supramarginal gyrus	40
	0.005	3231	3.91	−40	−50	51	Left supramarginal gyrus	40
aMCI *APOE* ε4 noncarriers vs. aMCI *APOE* ε4 carriers								
	<0.0001	7131	6.76	−2	44	8	Left anterior cingulate cortex	32
	0.001	756	5.92	28	44	27	Left dorsolateral prefrontal cortex	9
	0.021	300	5.62	24	62	0	Right anterior prefrontal cortex	10
	0.001	649	5.60	56	−18	−12	Right middle temporal gyrus	21
	0.022	316	5.58	−6	50	3	Left insula	13
	0.021	318	5.57	30	52	18	Right insula	13

Note: Threshold of $p < 0.001$ uncorrected at voxel level and $p < 0.05$ corrected for false discovery rate at cluster level, voxel size $k > 100$.

Coordinates of peak voxels (x, y, z) are given in MNI space.

Abbreviations: aMCI, amnestic mild cognitive impairment; AV45, florbetapir; HC, healthy control; MNI, Montreal Neurological Institute; SUVR, standardized uptake value ratio.

FIGURE 2 Effects of *APOE* ε4 on longitudinal changes in ^{18}F-florbetapir (AV45) positron emission tomography (PET) standardized uptake value ratio (SUVR), ^{18}F-fluorodeoxyglucose (FDG) PET SUVR, and gray matter (GM) volume. (a) Mean difference ^{18}F-AV45 PET SUVR images, visually illustrating the effects of *APOE* ε4 on longitudinal increases in Aβ deposition in healthy control (HC) and amnestic mild cognitive impairment (aMCI). (b) Mean difference ^{18}F-FDG PET SUVR images, visually illustrating the effects of *APOE* ε4 on longitudinal decline in glucose metabolism in HC and aMCI. (c) Region of interest (ROI)-based comparison of longitudinal changes in ^{18}F-AV45 PET SUVR, ^{18}F-FDG PET SUVR, and GM volume between *APOE* ε4 noncarriers and carriers in HC and aMCI. $^{*}p < 0.05$



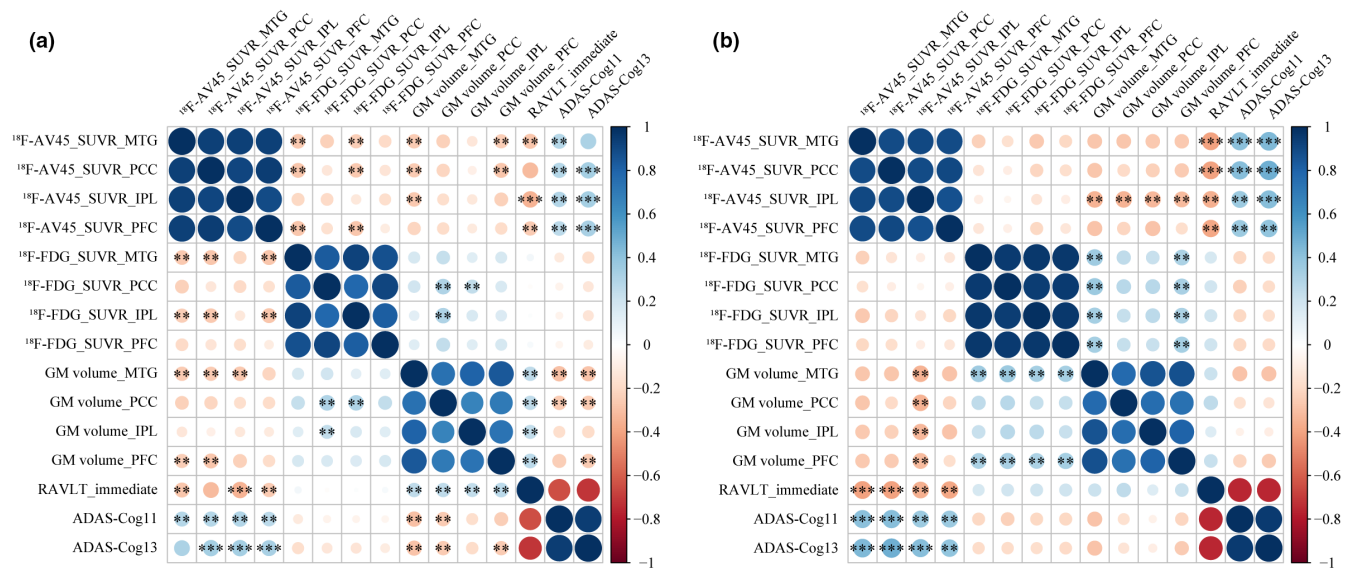


FIGURE 3 Heatmap illustrating the correlations between regional ^{18}F-florbetapir (AV45) positron emission tomography (PET) standardized uptake value ratio (SUVR), ^{18}F-fluorodeoxyglucose (FDG) PET SUVR, gray matter (GM) volume, and neuropsychological measures of *APOE* ε4 noncarriers (a) and *APOE* ε4 carriers (b) in amnestic mild cognitive impairment. Pearson correlation coefficient was used for the analysis. Blue indicates a positive association, and red indicates a negative association. $^{**}p < 0.01$, $^{***}p < 0.005$. ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; IPL, inferior parietal lobule; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PFC, prefrontal cortex; RAVLT, Rey Auditory Verbal Learning Test

cognitively normal individuals and reported that *APOE* ε4 appears to have a substantial effect on ^{11}C-PIB uptake, primarily in the frontal cortex. In this study, we found that *APOE* ε4 appears to have a significant effect on ^{18}F-AV45 uptake predominantly in the posterior cingulate cortex, parietal, and occipital regions of HC subjects, but predominantly in the anterior cingulate cortex, insula, frontal, and temporal regions of aMCI patients. Our findings suggest that the effect of *APOE* ε4 on Aβ pathology is stage- and region-specific.

Most of the study assessing the effect of *APOE* ε4 on Aβ pathology has been cross-sectional, with a limited number of studies assessing the longitudinal changes. Using ^{11}C-PIB PET imaging in cognitively normal middle-aged and elderly people, Mishra et al. [1] shown that *APOE* ε4 carriers had a greater longitudinal accumulation of Aβ pathology in the cortex than noncarriers. A longitudinal ^{11}C-PIB PET study showed that the presence of *APOE* ε4 is associated with a higher prevalence of Aβ-negative to Aβ-positive conversion, but *APOE* ε4 is not associated with rate of Aβ deposition after adjusting for age [27]. Our findings are in line with previous studies, suggesting that *APOE* ε4 carriers had greater longitudinal accumulation of Aβ pathology than *APOE* ε4 noncarriers. Furthermore, we found that the effect of *APOE* ε4 on longitudinal changes in Aβ deposition was significant in the middle temporal gyrus and inferior parietal lobule, but mild in the posterior cingulate cortex and prefrontal cortex. It is important to note that we included age, gender, and years of education as covariates in our analysis to exclude confounding factors; thus, it is unlikely that our findings reflect variations in these factors.

^{18}F-FDG PET studies assessing the effect of *APOE* ε4 on glucose metabolism are fewer in number than Aβ-PET studies, and the findings have been inconsistent. Previous studies have reported lower glucose metabolism in the *APOE* ε4 carriers compared with noncarriers [28], but higher glucose metabolism [10], and no effect has also been reported [11]. In this study, we found that *APOE* ε4 had no significant effect on baseline glucose metabolism in both diagnostic groups. It is in line with previous studies suggesting that the deleterious effect of *APOE* ε4 on glucose metabolism is more likely in larger samples [6], in *APOE* ε4 homozygotes [29], or those with a family history of AD [30]. Consistent with previous study [31], we found that *APOE* ε4 carriers had greater longitudinal decreases in glucose metabolism than *APOE* ε4 noncarriers in aMCI patients. However, the effect of *APOE* ε4 on longitudinal changes in glucose metabolism was only significant in the inferior parietal lobule. Taken together, our findings further support the idea that the effects of *APOE* ε4 on AD pathology are stage- and region-specific.

Imaging studies assessing the effect of *APOE* ε4 on brain structure are the most numerous and inconsistent [12]. *APOE* ε4 carriers have been shown to have significantly less GM volume than *APOE* ε4 noncarriers in both young and old adults, and this is most seen in regions that are sensitive to AD such as the hippocampus or other medial temporal structures [32, 33]. Our results agree with previous studies [34, 35] suggesting that *APOE* ε4 had no significant effect on baseline GM volume. Previous studies reported that *APOE* ε4 carriers undergo a faster rate of GM atrophy than *APOE* ε4 noncarriers [36, 37], but there have been observations to the contrary [38, 39]. In this study, *APOE* ε4 carriers showed either greater or lesser longitudinal changes in GM volume compared to *APOE* ε4 noncarriers, leaving the effect of *APOE* ε4 on longitudinal changes in GM volume unclear. Furthermore, we found correlations between GM volume and cognitive measures exclusively in *APOE* ε4 noncarriers, suggesting that *APOE* ε4 may modify the relationship between GM volume and concomitant cognitive performances [12].

Previous multimodal studies have demonstrated a graded effect of *APOE* ε4 on Aβ pathology, glucose metabolism, and GM atrophy. Chen

et al. [30] reported that the effect of *APOE* ε4 on glucose metabolism is stronger than that on GM volume. Our results showed that the effects of *APOE* ε4 on glucose metabolism and GM atrophy appear to be subtler than those on Aβ pathology. The strong effect of *APOE* ε4 on Aβ deposition is consistent with previous studies. It has been demonstrated that *APOE* ε4 has both Aβ-dependent and Aβ-independent effects on glucose metabolism and GM atrophy. Lowe et al. [40] found *APOE* ε4 carriers demonstrate decreased glucose metabolism was strongly associated with Aβ deposition. In contrast, the current study did not assess whether the *APOE* ε4 effects on glucose metabolism and GM density were associated with Aβ deposition. Knopman et al. [41] reported lower glucose metabolism in *APOE* ε4 carriers compared with noncarriers, and there was no interaction between Aβ deposition and *APOE* ε4 genotype with respect to glucose metabolism in Aβ-positive cognitively normal individuals older than 70 years. Similarly, Jagust et al. [42] reported significant effects of *APOE* ε4 on both Aβ deposition and glucose metabolism in cognitively normal elderly individuals, but showed that the lower glucose metabolism was independent of the presence of Aβ deposition. Furthermore, the presence of *APOE* ε4-related hypometabolism and GM atrophy in children [43], and young individuals [44], when Aβ deposition is considered absent, further argues for Aβ-independent effects of *APOE* ε4 on brain glucose metabolism and GM changes.

There are some limitations of our study. Due to the small sample size and limited number of *APOE* ε4 homozygotes, *APOE* ε4 homozygotes and heterozygotes have been pooled together in this study, which precluded us from investigating *APOE* ε4 allele dosage effects on Aβ deposition, glucose metabolism, and GM changes. A lack of sex-stratified analysis is also a limitation to our study. Recent studies have suggested that *APOE* ε4 carriers exhibit a greater risk of Aβ pathology, glucose hypometabolism, and GM atrophy in women compared with men. Future studies analysing sex-stratified associations between the *APOE* ε4 allele and multimodal neuroimaging biomarkers will be necessary. Lastly, a longer follow-up interval may provide additional evidence on the *APOE* ε4 effects on Aβ deposition, glucose metabolism, and GM volume.

In summary, our multimodal study provides a comprehensive view of the differential effect of *APOE* ε4 on three different neuroimaging biomarkers. The present study provides evidence that *APOE* ε4 has a significant effect on Aβ pathology, as well as more modest effects on glucose metabolism and GM volume. Using neuroimaging biomarkers to examine *APOE* ε4-related brain alterations in aMCI would provide an excellent chance to further our knowledge of the pathogenesis of AD at an early stage.

ACKNOWLEDGMENTS

We would like to extend our gratitude to all those who participated in this research and their families, because without them, none of this would be possible.

FUNDING INFORMATION

Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; National Institutes of Health [NIH] grant U19 AG024904). ADNI is made possible with funding from the NIH and private sector support raised by the Foundation for the NIH from the following organizations: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Araclon Biotech, BioClinica, Biogen, Bristol-Myers Squibb, CereSpir, Cogstate, Eisai, Elan Pharmaceuticals, Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche and its affiliated company Genentech, Fujirebio, GE Healthcare, IXICO, Janssen Alzheimer Immunotherapy Research & Development, Johnson & Johnson Pharmaceutical Research & Development, Lumosity, Lundbeck, Merck & Co., Meso Scale Diagnostics, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer, Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory of Neuro Imaging at the University of Southern California. This research was also supported by NIH grants P30 AG010129 and K01 AG030514, and the Beijing Brain Initiative of the Beijing Municipal Science & Technology Commission (Z201100005520018).

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

All the data for this study came from the ADNI database, which can be found at https://adni.loni.usc.edu.

ORCID

Weihua Li https://orcid.org/0000-0001-9530-4119

REFERENCES

1. Mishra S, Blazey TM, Holtzman DM, et al. Longitudinal brain imaging in preclinical Alzheimer disease: impact of APOE ε4 genotype. *Brain*. 2018;141(6):1828-1839.
2. Yamazaki Y, Painter MM, Bu G, Kanekiyo T. Apolipoprotein E as a therapeutic target in Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs*. 2016;30(9):773-789.
3. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat Rev Neurol*. 2019;15(9):501-518.
4. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. *Sci Transl Med*. 2011;3(89):89ra57.
5. Blautzik J, Kotz S, Brendel M, et al. Relationship between body mass index, ApoE4 status, and PET-based amyloid and neurodegeneration markers in amyloid-positive subjects with Normal cognition or mild cognitive impairment. *J Alzheimers Dis*. 2018;65(3):781-791.
6. Gonneaud J, Arenaza-Urquijo EM, Fouquet M, et al. Relative effect of APOE ε4 on neuroimaging biomarker changes across the lifespan. *Neurology*. 2016;87(16):1696-1703.
7. Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology*. 2014;82(20):1760-1767.

8. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-1938.
9. Fleisher AS, Chen K, Liu X, et al. Apolipoprotein E ε4 and age effects on florbetapir positron emission tomography in healthy aging and Alzheimer disease. *Neurobiol Aging*. 2013;34(1):1-12.
10. Yi D, Lee DY, Sohn BK, et al. Beta-amyloid associated differential effects of APOE ε4 on brain metabolism in cognitively Normal elderly. *Am J Geriatr Psychiatry*. 2014;22(10):961-970.
11. Samuraki M, Matsunari I, Chen W-P, et al. Glucose metabolism and gray-matter concentration in apolipoprotein E ε4 positive normal subjects. *Neurobiol Aging*. 2012;33(10):2321-2323.
12. Fouquet M, Besson FL, Gonneaud J, La Joie R, Chételat G. Imaging brain effects of APOE4 in cognitively normal individuals across the lifespan. *Neuropsychol Rev*. 2014;24(3):290-299.
13. Lind J, Larsson A, Persson J, et al. Reduced hippocampal volume in non-demented carriers of the apolipoprotein E epsilon4: relation to chronological age and recognition memory. *Neurosci Lett*. 2006;396(1):23-27.
14. Tohgi H, Takahashi S, Kato E, et al. Reduced size of right hippocampus in 39- to 80-year-old normal subjects carrying the apolipoprotein E epsilon4 allele. *Neurosci Lett*. 1997;236(1):21-24.
15. Jack CR Jr, Petersen RC, Xu YC, et al. Hippocampal atrophy and apolipoprotein E genotype are independently associated with Alzheimer's disease. *Ann Neurol*. 1998;43(3):303-310.
16. Hostage CA, Roy Choudhury K, Doraiswamy PM, Petrella JR. Dissecting the gene dose-effects of the APOE ε4 and ε2 alleles on hippocampal volumes in aging and Alzheimer's disease. *PLoS ONE*. 2013;8(2):e54483.
17. Baek MS, Cho H, Lee HS, Lee JH, Ryu YH, Lyoo CH. Effect of APOE ε4 genotype on amyloid-β and tau accumulation in Alzheimer's disease. *Alzheimers Res Ther*. 2020;12(1):140.
18. Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis*. 2014;42(1):275-289.
19. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-526.
20. Meyer PF, Pichet Binette A, Gonneaud J, Breitner JCS, Villeneuve S. Characterization of Alzheimer disease biomarker discrepancies using cerebrospinal fluid phosphorylated tau and AV1451 positron emission tomography. *JAMA Neurol*. 2020;77(4):508-516.
21. Mullergartner HW, Links JM, Prince JL, et al. Measurement of radiotracer concentration in brain gray-matter using positron emission tomography - Mri-based correction for partial volume effects. *J Cerebr Blood F Met*. 1992;12(4):571-583.
22. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273-289.
23. Kantarci K, Lowe V, Przybelski SA, et al. APOE modifies the association between Aβ load and cognition in cognitively normal older adults. *Neurology*. 2012;78(4):232-240.
24. Mathis CA, Kuller LH, Klunk WE, et al. In vivo assessment of amyloid-β deposition in nondemented very elderly subjects. *Ann Neurol*. 2013;73(6):751-761.
25. Drzezga A, Grimmer T, Henriksen G, et al. Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. *Neurology*. 2009;72(17):1487-1494.
26. Scheinin NM, Wikman K, Jula A, et al. Cortical ^{11}C-PIB uptake is associated with age, APOE genotype, and gender in "healthy aging". *J Alzheimers Dis*. 2014;41(1):193-202.
27. Vlassenko AG, Mintun MA, Xiong C, et al. Amyloid-beta plaque growth in cognitively normal adults: longitudinal [11C]Pittsburgh compound B data. *Ann Neurol*. 2011;70(5):857-861.
28. Small GW, Mazziotta JC, Collins MT, et al. Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *Jama*. 1995;273(12):942-947.
29. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996;334(12):752-758.
30. Chen K, Ayutyanont N, Langbaum JB, et al. Correlations between FDG PET glucose uptake-MRI gray matter volume scores and apolipoprotein E ε4 gene dose in cognitively normal adults: a cross-validation study using voxel-based multi-modal partial least squares. *Neuroimage*. 2012;60(4):2316-2322.
31. Paranjpe MD, Chen X, Liu M, et al. The effect of ApoE ε4 on longitudinal brain region-specific glucose metabolism in patients with mild cognitive impairment: a FDG-PET study. *NeuroImage Clin*. 2019;22:101795.
32. Honea RA, Vidoni E, Harsha A, Burns JM. Impact of APOE on the healthy aging brain: a voxel-based MRI and DTI study. *J Alzheimers Dis*. 2009;18(3):553-564.
33. O'Dwyer L, Lamberton F, Matura S, et al. Reduced hippocampal volume in healthy young ApoE4 carriers: an MRI study. *PLoS ONE*. 2012;7(11):e48895.
34. Bunce D, Anstey KJ, Cherbuin N, Gautam P, Sachdev P, Easteal S. APOE genotype and entorhinal cortex volume in non-demented community-dwelling adults in midlife and early old age. *J Alzheimers Dis*. 2012;30(4):935-942.
35. Dennis NA, Browndyke JN, Stokes J, et al. Temporal lobe functional activity and connectivity in young adult APOE varepsilon4 carriers. *Alzheimers Dement*. 2010;6(4):303-311.
36. Chen K, Reiman EM, Alexander GE, et al. Correlations between apolipoprotein E epsilon4 gene dose and whole brain atrophy rates. *Am J Psychiatry*. 2007;164(6):916-921.
37. Chiang GC, Insel PS, Tosun D, et al. Impact of apolipoprotein E4-cerebrospinal fluid β-amyloid interaction on hippocampal volume loss over 1 year in mild cognitive impairment. *Alzheimers Dement*. 2011;7(5):514-520.
38. Taylor JL, Scanlon BK, Farrell M, et al. APOE-epsilon4 and aging of medial temporal lobe gray matter in healthy adults older than 50 years. *Neurobiol Aging*. 2014;35(11):2479-2485.
39. Schuff N, Woerner N, Boreta L, et al. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*. 2009;132(Pt 4):1067-1077.
40. Lowe VJ, Weigand SD, Senjem ML, et al. Association of hypometabolism and amyloid levels in aging, normal subjects. *Neurology*. 2014;82(22):1959-1967.
41. Knopman DS, Jack CR Jr, Wiste HJ, et al. 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons. *Neurobiol Aging*. 2014;35(9):2096-2106.
42. Jagust WJ, Landau SM. Apolipoprotein E, not fibrillar β-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci*. 2012;32(50):18227-18233.
43. Shaw P, Lerch JP, Pruessner JC, et al. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. *Lancet Neurol*. 2007;6(6):494-500.
44. Reiman EM, Chen K, Alexander GE, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci USA*. 2004;101(1):284-289.

How to cite this article: Li W, Li R, Yan S, et al. Effect of *APOE ε*4 genotype on amyloid-β, glucose metabolism, and gray matter volume in cognitively normal individuals and amnestic mild cognitive impairment. *Eur J Neurol*. 2023;30:587-596. doi:10.1111/ene.15656