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Topographical APOE ε4 Genotype Influence on Cerebral Metabolism in the Continuum of Alzheimer's Disease: Amyloid Burden Adjusted Analysis

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Abstract.
Background: APOE ε4 contributes to Alzheimer's disease (AD) pathogenesis by amyloid-beta (Aβ)-dependent and Aβ-independent processes.
Objective: We investigated the APOE ε4 influence on regional cerebral glucose metabolism (rCMglc) in the continuum of AD after Aβ adjustment.
Methods: We included 318 cognitively normal (CN) elderly, 498 mild cognitive impairment (MCI), and 178 AD from the Alzheimer's Disease Neuroimaging Initiative database. They had [^{18}F] florbetapir positron emission tomography (PET) and [^{18}F] fluorodeoxyglucose (FDG)-PET conducted within 3 months of a clinical and cognitive assessment visit and APOE genotype. At first, the rCMglc differences between APOE ε4 carriers (ε4+) and non-carriers (ε4–) were estimated on a voxel-based analysis using a 'two-sample *t*-test' design. In the second analysis, Aβ was added as covariate.
Results: In CN, ε4+ showed reduced rCMglc compared to ε4– in the bilateral frontal, temporal, and the left parietal regions. In MCI, ε4+ showed reduced rCMglc compared to ε4– in the bilateral posterior parietal, temporal, and left frontal regions. In AD, ε4+ showed reduced rCMglc in the left hippocampus, right insular, and right temporal gyrus. However, after Aβ adjustment, the significant differences in the temporal regions were absent in CN and MCI, and none of the areas detected as significant in the first analysis were statistically significant in AD.

[1]Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). Therefore, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Conclusions: Our study demonstrated that Aβ-independent APOE ε4 influence on rCMglc is limited to the parietal and frontal, but not temporal lobes. These results suggest that APOE ε4 may predispose for regional vulnerability according to Aβ-independent and Aβ-dependent processes.

Keywords: Aβ burden, APOE, cerebral glucose metabolism, mild cognitive impairment

INTRODUCTION

The apolipoprotein E (APOE) ε4 allele is a major genetic risk factor for the development of late-onset Alzheimer's disease (AD) dementia [1, 2]. Mountains of evidence suggest that APOE ε4 contributes to AD pathogenesis by amyloid-beta (Aβ)-dependent and Aβ-independent processes [3–5]. It has also been shown that APOE ε4 has a detrimental effect on synaptic plasticity, dendritic spine integrity, and that it may also promote neurotoxicity [6].

Regional cerebral glucose metabolism (rCMglc), measured by [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET), displays a typical pattern of hypometabolism in the temporo-parietal cortex in AD [7–10]. Many studies have confirmed that FDG-PET imaging is highly sensitive in detecting early AD pathology as well as performing an AD prognosis [10–14].

A relationship between APOE ε4 and rCMglc has been described mainly in cognitively normal (CN) elderly population. For example, previous studies suggest that APOE ε4 carriers in CN elderly [15–17], CN with memory complaints, and CN with a family history of AD [18, 19] show a decrease of rCMglc in the regions typically affected by AD. APOE ε4 influence on rCMglc in AD is far less clear. Some studies reported more pronounced hypometabolism in APOE ε4 carriers [20–22], whereas others reported no APOE ε4 effects in AD [23, 24]. Few studies focused on individuals with mild cognitive impairment (MCI). These studies reported APOE ε4 -related hypometabolism in the temporo-parietal and frontal regions in MCI [25, 26], which is similar to patterns in the alterations observed in CN.

The important role that APOE ε4 plays in Aβ binding and clearance during AD pathogenesis has been well-characterized [4, 27]. In line with these roles, the effect of APOE ε4 on rCMglc is more robust in MCI with high Aβ burden than in MCI with low Aβ burden [25]. On the other hand, there seems to be Aβ-independent APOE ε4 effect on brain function via other neuropathological changes including tau, neuroinflammation, and neuronal plasticity [3, 5]. However, surprisingly few studies have investigated the influence of APOE ε4 on rCMglc after adjusting for the effect of Aβ burden level. Only two studies [15, 17] considered the Aβ burden influence when investigating the effects of APOE ε4 on rCMglc. Although both these studies found an Aβ burden-independent effect of APOE ε4 on rCMglc, the result pattern was different between the studies: Jagust et al. [15] detected an hypometabolism, while a significant hypermetabolism emerged in Yi et al. [17]. These two studies included only CN elderly. However, the distribution of APOE ε4 and Aβ burden levels are different in the AD continuum. Recent comprehensive meta-analysis revealed that small numbers of CN are Aβ-positive (24.4%) [28], whereas most AD dementia participants are Aβ-positive (88%) [29]. Similarly, prevalence of APOE ε4 is low in CN (29.5%) [28], whereas high in AD dementia (61.1%) [29]. On the contrary, MCI group showed a relatively even distribution for both factors (52.9% for Aβ-positive; 47.1% for APOE ε4 carrier) [28]. This differential distribution of APOE ε4 status and Aβ burden level across groups could potentially contribute to the statistical results. For example, when Aβ-independent APOE ε4 effects on rCMglc was investigated, controlling for Aβ burden levels may be far less effective for individuals with CN because of disproportionally low Aβ burden. On the other hand, differential effects of APOE ε4 on rCMglc according to Aβ-dependent and Aβ-independent process can be large in MCI. Nevertheless, no studies have investigated the influence of APOE *ε4* on rCMglc after controlling for Aβ burden levels in MCI. The biological underlying mechanism for the association between APOE ε4 and brain metabolism could be more clearly understood in the context of a continuum of AD, particularly in MCI.

Therefore, this study aims to investigate the effects of APOE ε4 on rCMglc in the continuum of AD. We further examined these effects after controlling for Aβ burden levels.

METHODS

Participants

Participants were selected from the ADNI database (http://adni.loni.usc.edu). For a detailed explanation

and up-to-date information on ADNI, please see http://www.adni-info.org. We included participants from all phases of ADNI only if [^{18}F] florbetapir PET and FDG-PET had been conducted within 3 months from a clinical and cognitive assessment visit, and their APOE genotype was available. Subjects with the APOE 2/4 genotype were excluded due to the unclear effects of these alleles. The final analysis included 318 CN elderly participants, 498 individuals with MCI, and 178 patients with AD dementia who underwent clinical evaluations and florbetapir PET scans (Table 1). Detailed eligibility criteria for each study group has been described elsewhere [30]. Briefly, CN subjects had a Clinical Dementia Rating (CDR) of 0 and Mini-Mental State Examination (MMSE) scores between 24 and 30. These subjects were non-depressed, non-demented, and had not been diagnosed with MCI. Subjects with MCI had a CDR of 0.5 and MMSE scores between 24 and 30, they complained of objective memory loss but showed no impairment in other cognitive domains, demonstrated preserved activities of daily living, and were non-demented. AD dementia subjects had a CDR of 0.5 or 1.0 and MMSE scores between 20 and 26 and met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [31].

Clinical and neuropsychological assessment

We included the CDR sum of boxes (CDR SOB) as a clinical severity measure. This measure covers six domains of cognitive and daily functioning with a score ranging from 0 to18. This is a tool commonly used for staging clinical severity. For everyday functioning, we included the functional assessment questionnaire (FAQ). This questionnaire assesses the instrumental activities of daily living with a score ranging from 0 to 30 [32]. We included MMSE score for assessing the global cognitive function.

APOE genotyping

APOE genotyping was performed at the time of participant enrollment in the ADNI study. APOE genotypes were determined using standard polymerase chain reaction methods, which have been described previously [33]. Individuals with one or two copies of ε4 allele were designated as APOE ε4 carriers (ε4+); individuals with no ε4 allele were designated as APOE ε4 non-carriers (ε4–).

Florbetapir PET

We collected the mean florbetapir standard uptake value ratio (SUVR) for each participant. A detailed description of florbetapir PET acquisition and processing can be found on the ADNI website (https://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_PET_Tech_Manual_0142011.pdf) or in previously published reports [34]. Briefly, the subject's first florbetapir image was coregistered to their magnetic resonance image and segmented into cortical regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal) defined using Freesurfer (version 4.5.0). The mean florbetapir uptake from those gray matter regions was extracted relative to uptake in the whole cerebellum. The SUVR cutoff of 1.11 was applied to determine amyloid positivity [34].

FDG-PET and image preprocessing

To investigate APOE effects, we collected the most preprocessed form of FDG-PET data from the ADNI. The ADNI preprocessing steps of FDG-PET data were previously described [35]. A quality control process was applied to all scans. To reduce inter-scanner differences (17 different scanner models from three vendors), images were smoothed with a scanner-specific filter derived from each site's Hoffman phantom [36], and then provided a common isotropic resolution of 8 mm full width at half of the maximum resolution [35]. We applied a further preprocessing for the group-level analysis. These scans were adjusted for their origin and spatially normalized to the Montreal Neurological Institute (MNI, McGill University, Montreal, Que., Canada) space using Statistical Parametric Mapping 8 (SPM8) (Institute of Neurology, University College of London, UK) implemented on Matlab. Then the scans were smoothed with a Gaussian kernel of 8 mm full width at half of the maximum resolution. Since we investigated the APOE effects separately within each diagnostic group, intensity normalization to pons or cerebellum was not performed. Instead, global normalization using proportional scaling was performed because it shows a higher signal-to-noise ratio compared to the cerebellar count normalization [37]. For the global FDG index, we downloaded the values from ADNI. The

Table 1
Demographic and clinical characteristics of the participants

	CN	MCI	AD	*p*
N	318	498	178	
Age, y	74.53(6.52)	72.43(7.82)	74.99(7.87)	<0.001
Education, y	16.46(2.65)	16.12(2.70)	15.94(2.70)	0.083
Female, *n* (%)	171(53.8)	217(43.6)	74(41.6)	0.006
APOE ε4 carriers, *n* (%)	82(25.8)	227(45.6)	117(65.7)	<0.001
Aβ	1.11(0.18)	1.20(0.22)	1.37(0.22)	<0.001
Aβ positive, *n* (%)	99(31.1)	268(53.8)	149(83.7)	<0.001
CDR SOB	0.06(0.24)	1.49(0.92)	4.90(2.06)	<0.001
FAQ	0.33(1.21)	2.68(3.74)	14.07(6.96)	<0.001
MMSE	28.98(1.29)	28.05(1.73)	22.51(3.22)	<0.001

Values are mean (standard deviation) for continuous variables or frequency (percentage) for categorical variables such as gender, APOE, and Aβ positive. CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE, Apolipoprotein E; Aβ, average Florbetapir mean standard uptake value ratio of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum; Aβ positive, amyloid positive according to florbetapir standard uptake value ratio cutoff 1.11; CDR SOB, sum of boxes of the clinical dementia rating; FAQ, Functional Assessment Questionnaire; MMSE, Mini-Mental Status Examination.

mean FDG uptake was determined by the mean uptake of in the bilateral inferior temporal and lateral parietal regions and the bilateral posterior cingulate cortex region. The details were previously described [34].

Statistical analysis

Demographic and clinical data were compared between groups using separate one-way analysis of variance (ANOVA) and χ^2 test for continuous and categorical variables, respectively. These analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL); *p*-values less than 0.05 were considered significant.

The difference of rCMglc between ε4+ and ε4–were estimated on a voxel-by-voxel basis using a 'two-sample *t*-test' design with age, gender, and education as covariates. To control for Aβ burden level, florbetapir SUVR was further added as a covariate. We applied $p < 0.001$ (two-tailed, uncorrected for multiple comparisons) as a significance height threshold at the voxel-level across the whole brain, with an extent threshold of greater than 20 contiguous voxels. These analyses were performed using SPM8.

Ethics statement

Study procedures were approved by the institutional review boards of 55 research centers in the United States and Canada participating in ADNI. Written informed consent to share data for scientific research purposes was obtained from each participant.

RESULTS

Participant characteristics

The demographic and clinical characteristics of the 994 individuals are presented in Table 1. No group differences in education were detected. Participants with MCI were younger than CN and AD dementia participants ($p < 0.001$). The CN group included significantly more women than the other two study groups. The frequencies of ε4+ and Aβ positive were lowest in CN group and highest in AD dementia group. MCI group showed relatively an even distribution in the positivity for both ε4+ and Aβ. As expected, subsequent comparisons of Aβ, CDR SOB, FAQ, and MMSE revealed significant differences between groups (Table 1). Global Aβ levels were significantly higher in ε4+ than in ε4–within each group (all $p < 0.001$).

Effect of APOE ε4 on rCMglc

In the CN group, ε4+ showed reduced rCMglc in the bilateral frontal and temporal regions, and the left parietal regions compared to ε4–. When Aβ was adjusted, significant reductions in the bilateral frontal and parietal regions were remained, whereas the difference in the bilateral temporal regions were no longer statistically significant. In the MCI group, the pattern was largely similar to the result of the CN group but were found to be more robust. ε4+ showed reduced rCMglc mainly in the bilateral parietal regions, bilateral temporal regions and left frontal gyrus compared to ε4–. After Aβ was adjusted, significant rCMglc reductions in the bilateral precuneus

and left frontal gyrus were remained, whereas the bilateral temporal regions were no longer statistically significant (Fig. 1 and Table 2). In the AD group, ε4+ showed reduced rCMglc in the left hippocampus, right insular, and right temporal regions. However, these difference were no longer statistically significant after Aβ adjustment (Fig. 1 and Table 2). No increased regions were emerged from the analysis in ε4+ compared with ε4–for all groups.

DISCUSSION

We investigated the effects of *APOE ε4* on rCMglc after adjusting for Aβ burden in a large group of CN elderly, individuals with MCI, and AD. Our findings suggest that Aβ-independent APOE ε4-related hypometabolism was limited in the parietal and frontal lobe in the CN and MCI groups, whereas no significant differences between ε4+ and ε4–were observed in the AD group. The APOE ε4-related temporal lobe dysfunctions, commonly reported in previous studies might be mediated by Aβ-dependent pathway.

In agreement with previous reports [15, 16, 18, 25, 26], our analysis highlighted an AD-related regional hypometabolism in ε4+ than ε4– in the CN and MCI groups. Regional areas of APOE ε4– related reductions in the MCI group were much larger than the areas observed in the CN group. This may be partly due to the reported difference in ε4+ frequency in the two groups. Frequency of MCI with ε4+ were approximately twice than that of CN with ε4+ (e.g., 45.6% in MCI versus 25.8% in CN). This difference in ε4+ distribution may lead to statistically more

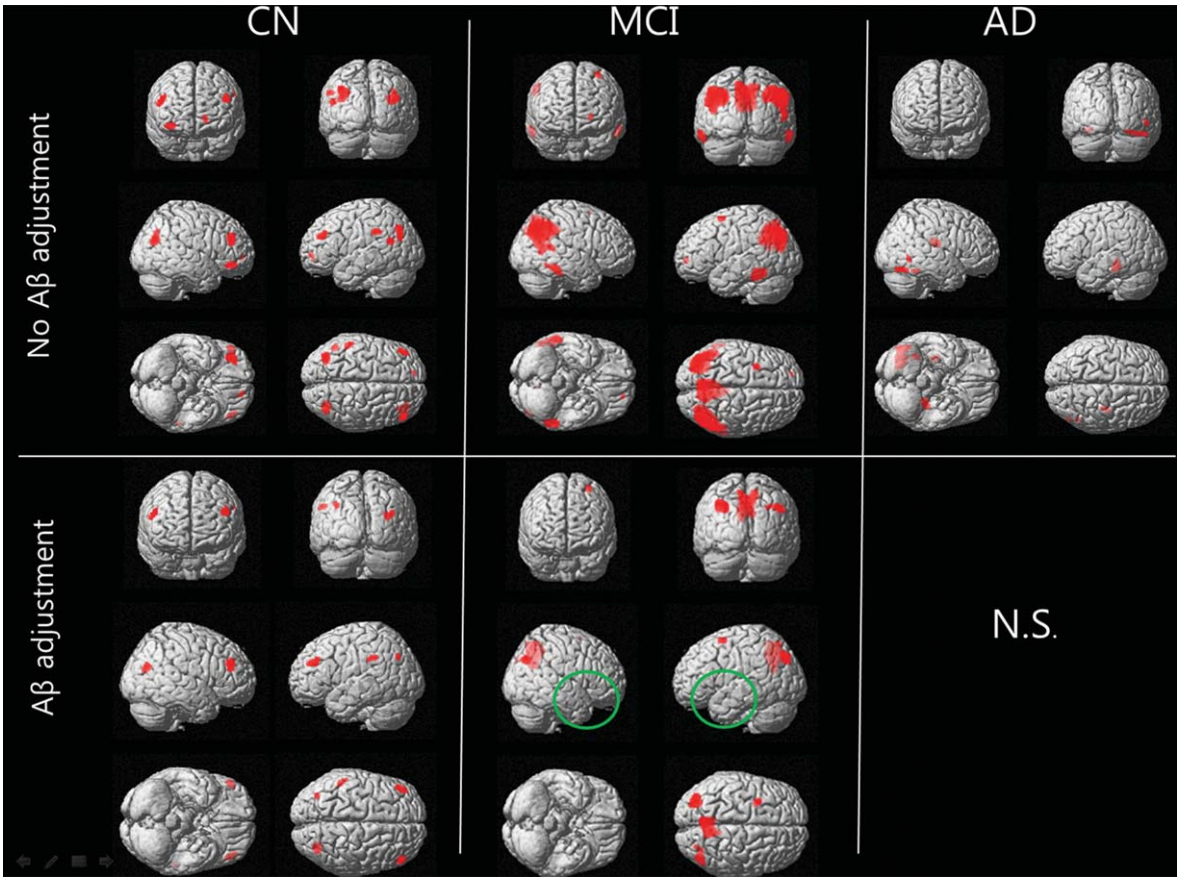

Fig. 1. Brain areas showing APOE ε4-related hypometabolism. No Aβ adjustment: decreased metabolism in APOE ε4 carriers compared with non-carriers controlling for age, gender, and education within each study group. Aβ adjustment: decreased metabolism in APOE ε4 carriers compared with non-carriers controlling for age, gender, education, and florbetapir SUVR within each study group. The green circles in the bottom panel indicate the lack of temporal hypometabolism after Aβ adjustment in mild cognitive impairment group. Significant regions are at $p < 0.001$ (two-tailed, uncorrected for multiple comparisons) with an extent threshold of greater than 20 contiguous voxels. The significant peak voxels of clusters are presented in Table 2. CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease.

Table 2
Brain regions showing APOE ε4-related hypometabolism

Brain regions	BA	Voxel number	MNI coordinates			T	p (unc)
			x	Y	z		
CN							
With no Aβ adjustment							
R. Middle frontal gyrus	46	112	50	40	28	4.547	<0.001
L. Middle frontal gyrus	46	76	–44	40	28	4.363	<0.001
L. Precuneus	19	279	–34	–72	34	4.140	<0.001
R. Middle temporal gyrus	39	240	40	–70	26	4.093	<0.001
R. Middle frontal gyrus	11	154	38	40	–10	4.050	<0.001
L. Superior temporal gyrus	39	60	–50	–58	20	3.763	<0.001
L. Inferior parietal lobule	40	74	–54	–38	34	3.632	<0.001
L. Superior frontal gyrus	10	36	–12	56	0	3.439	<0.001
With Aβ adjustment							
L. Middle frontal gyrus	46	77	–46	38	28	4.279	<0.001
R. Middle frontal gyrus	46	82	52	40	26	4.277	<0.001
R. Precuneus	31	109	32	–72	20	3.600	<0.001
L. precuneus	19	28	–34	–72	36	3.394	<0.001
L. Supramarginal gyrus	40	48	–52	–40	34	3.386	<0.001
MCI							
With no Aβ adjustment							
L. Precuneus	19	1856	–36	–78	40	6.216	<0.001
R. Supramarginal gyrus	40		–50	–56	32	4.202	<0.001
L. Precuneus	7	3357	–4	–64	34	6.009	<0.001
R. Cingulate gyrus	31		8	–58	30	5.403	<0.001
R. Angular gyrus	39	2415	46	–70	36	5.282	<0.001
R. Superior temporal gyrus	22		56	–46	12	3.849	<0.001
R. Middle temporal gyrus	39		56	–60	10	3.552	<0.001
L. Inferior temporal gyrus	20	248	–60	–48	–18	4.272	<0.001
L. middle frontal gyrus	6	64	–30	6	62	3.672	<0.001
L. superior frontal gyrus	10	27	–20	56	2	3.511	<0.001
With Aβ adjustment							
L. Precuneus	7/19	1328	–6	–64	34	4.357	<0.001
R. Precuneus	7/39	166	44	–72	36	3.676	<0.001
L. middle frontal gyrus	6	63	–30	6	62	3.587	<0.001
AD*							
With no Aβ adjustment							
L. Hippocampus	–	153	–28	–34	–12	3.751	<0.001
R. Inferior temporal gyrus	19	36	50	–58	–4	3.527	<0.001
R. Insular	13	75	34	–20	20	3.454	<0.001
R. Fusiform gyrus	37	37	36	–46	–22	3.417	<0.001

CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease; APOE, Apolipoprotein; Aβ, average Florbetapir mean standard uptake value ratio of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum; BA, Brodmann Area; L, left; R, right. *no areas showed significance after Aβ adjustment.

robust differences at the regional level. The AD group displayed APOE ε4-related reductions mainly in temporal lobe.

When we statistically adjusted the Aβ burden effect, the significant effect previously detected in the temporal region hypometabolism was no longer present in all three groups. This result suggests that the temporal region function in the AD continuum is mediated by the Aβ burden rather than by a direct APOE ε4 effect. On the other hand, hypometabolism in the bilateral precuneus and middle frontal gyrus in ε4+ groups in CN and MCI remained significant even after adjusting for Aβ burden, indicating that those regions are affected by Aβ-independent APOE ε4 process. These results were largely supported by the additional analysis performed separately for those participants with low and high Aβ burden. Especially for MCI group, ε4-related bilateral precuneus and right temporal hypometabolism was observed in Aβ burden positive group. However, the significant effect previously detected in the temporal region hypometabolism was no longer present but bilateral precuneus hypometabolism remained in Aβ burden negative group (Supplementary Figure 1). It has been suggested that APOE ε4 may contribute to the AD pathogenesis through two distinct pathways: Aβ-dependent and -independent processes [3–6]. The Aβ-dependent process includes production,

aggregation, and clearance of Aβ, while the Aβ-independent process includes tau pathology, synaptic dysfunction, brain metabolic alterations, and mitochondrial dysfunction. Our results also support the idea that APOE ε4 associated brain functions are mediated by those two pathophysiological processes.

One possible interpretation of the present results is that APOE ε4 may predispose for regional vulnerability differently according to Aβ-independent and Aβ-dependent processes, although further studies are needed to confirm this interpretation. In other words, APOE ε4 may predispose for a preferential vulnerability of the posterior parietal and frontal lobe that is independent of Aβ burden. On the contrary, APOE ε4 influence on temporal lobe vulnerability may be mediated by the Aβ burden. The posterior parietal lobe, particularly the precuneus/posterior cingulate cortex is the most commonly affected area in the very early course of AD. One postmortem brain study reported that ε4+ young adults with no evidence of Aβ pathology showed lower mitochondrial activity in posterior cingulate regions than ε4–individuals [38]. Accordingly, one study performed on a large sample of cognitively healthy young individuals reported that APOE ε4-related effects on the posterior parietal regions were the most prominent [16]. Another study also reported that CN elderly with ε4+ had significant reductions in functional brain complexity in the precuneus and posterior cingulate regions, and abnormal frontal-parietal connectivity compared to ε4- individuals [39]. The precuneus and the middle frontal region largely overlap with the default mode network which has been consistently reported as altered in ε4+ individuals [40–42]. The frontal lobe and precuneus both seem to play a critical role in a wide spectrum of highly integrated cognitive tasks such as those measured in executive function tests. In close agreement with our results, APOE ε4 predominantly influenced the performance on frontal executive function tasks that was not explained by Aβ status [43].

On the other hand, the absence of hypometabolism in the temporal region after Aβ adjustment suggests a close association between the Aβ burden and the temporal lobe dysfunction. Our result is consistent with previous studies reporting a significant correlation between Aβ magnitude and medial temporal lobe (MTL) hypometabolism [44] or disrupted MTL connectivity [45]. A convincing hypothesis on the mechanism underlying spatial separation of the site of Aβ and tau pathology postulates that MTL tauopathy is a downstream event of Aβ deposition, the so-called hypothesis of Aβ-facilitated tauopathy in MTL [45, 46]. Based on our analysis, APOE ε4 influence on temporal lobe dysfunction seems to be mediated by Aβ burden.

There are some limitations and future directions to be discussed. First, this study is based on a cross-sectional design. To better understand the predictive value of cerebral metabolic changes related to APOE ε4, longitudinal follow-up studies are needed, particularly for the CN and MCI groups. Second, partial volume correction was not performed during FDG-PET image processing. Therefore, we cannot exclude the possibility that the hypometabolism we have observed may have been biased by the presence of brain atrophy. Future studies controlling partial volume effect are needed to replicate our findings.

In conclusion, we have shown that the Aβ-independent APOE ε4 influence on cerebral metabolism is limited to the parietal and frontal lobe, while it has no effect on the temporal lobe. The present results suggest that APOE ε4 may differentially predispose for regional vulnerability according to Aβ-independent and Aβ-dependent processes. APOE ε4 itself may play a role in the pathogenesis of AD in the precuneus and the middle frontal regions, and it may also modulate Aβ-related pathophysiological processes in the temporal regions.

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Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0395r1.

SUPPLEMENTARY MATERIAL

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