



The effect of ApoE ϵ 4 on clinical and structural MRI markers in prodromal Alzheimer's disease

Chunhua Zhang^{1#}, Min Kong^{2#}, Hongchun Wei¹, Hua Zhang³, Guozhao Ma⁴, Maowen Ba¹; for the Alzheimer's Disease Neuroimaging Initiative

¹Department of Neurology, the Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, China; ²Department of Neurology, Yantaishan Hospital, Yantai 264000, China; ³Department of Neurology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China; ⁴Department of Neurology, East Hospital, Tongji University School of Medicine, Shanghai 200120, China

[#]These authors contributed equally to this work.

Correspondence to: Maowen Ba. Department of Neurology, the Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, China. Email: bamaowen@163.com; Guozhao Ma. Department of Neurology, East Hospital, Tongji University School of Medicine, Shanghai 200120, China. Email: maguozhao@163.com.

Background: Apolipoprotein E (ApoE) ϵ 4 has been identified as the strongest genetic risk factor for Alzheimer's disease (AD). However, the importance of ApoE ϵ 4 on clinical and biological heterogeneity of AD is still to be determined, particularly at the prodromal stage. Here, we evaluate the association of ApoE ϵ 4 with clinical cognition and neuroimaging regions in mild cognitive impairment (MCI) participants based on the AT (N) system, which is increasingly essential for developing a precise assessment of AD.

Methods: We stratified 178 A+T+MCI participants (prodromal AD) into ApoE ϵ 4 (+) and ApoE ϵ 4 (-) according to ApoE genotype from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We determined A β -positivity (A+) by the standardized uptake values ratios (SUVR) means of florbetapir-PET-AV45 (the cut-off value of 1.1) and fibrillar tau-positivity (T+) by cerebrospinal fluid (CSF) phosphorylated-tau at threonine 181 position (p-Tau) (cut-off value of 23 pg/mL). We evaluated the effect of ApoE ϵ 4 status on cognitive conditions and brain atrophy from structural magnetic resonance imaging (MRI) scans. A multivariate analysis of variance was used to compare the differences of cognitive scores and brain atrophy from structural MRI regions of interest (ROIs) between both groups. Furthermore, we performed a linear regression model to assess the correlation between signature ROIs of structural MRI and cognitive scores in the prodromal AD participants.

Results: ApoE ϵ 4 (+) prodromal AD participants had lower levels of CSF A β 1-42, higher levels of t-Tau, more memory and global cognitive impairment, and faster decline of global cognition, compared to ApoE ϵ 4 (-) prodromal AD. ApoE ϵ 4 (+) prodromal AD participants had a thinner cortical thickness of bilateral entorhinal, smaller subcortical volume of the left amygdala, bilateral hippocampus, and left ventral diencephalon (DC) relative to ApoE ϵ 4 (-) prodromal AD. Furthermore, the cortical thickness average of bilateral entorhinal was highly correlated with memory and global cognition.

Conclusions: ApoE ϵ 4 status in prodromal AD participants has an important effect on clinical cognitive domains. After ascertaining the ApoE ϵ 4 status, specific MRI regions can be correlated to the cognitive domain and will be helpful for precise assessment in prodromal AD.

Keywords: Alzheimer's disease (AD); apolipoprotein E (ApoE); structural MRI; cognition; prodromal AD

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Introduction

Alzheimer's disease (AD) is a common progressive neurodegenerative disorder characterized by distinct brain pathological changes, including amyloid β ($A\beta$) accumulation, neurofibrillary tangle deposition, synaptic dysfunction, and neuronal death with gross brain atrophy (1,2). Mild cognitive impairment (MCI) is conceptualized as an intermediate state (3) between healthy aging and clinical dementia. Individuals with MCI are often at an increased risk of developing dementia (4). MCI is regarded as a prodromal stage of AD (5) and a better therapeutic time window for AD clinical trials. Furthermore, diagnoses of AD and MCI based on clinical criteria have limited sensitivity and specificity compared with autopsy (6). Approximately 50% of subjects with clinically diagnosed MCI show amyloid-negative ($A\beta^-$) which is insufficient to represent prodromal AD (7). Prodromal AD requires $A\beta$ plaques and fibrillar tau.

The ϵ 4 allele of apolipoprotein E (ApoE) is the most significant genetic risk factor for sporadic AD (8,9). Some studies have demonstrated that carriers of the ApoE ϵ 4 allele who have AD dementia or amnesic MCI predominantly show memory impairment and medial temporal lobe atrophy, particularly involving the hippocampus compared with non-carriers (10-16). However, previous research on ApoE ϵ 4 of AD has been limited by the absence of biomarker-based confirmation of AD diagnosis, which makes it possible that subjects have been included in research with false-positive diagnoses of AD.

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed a new research framework focusing on diagnoses of AD with biomarkers for living persons (17). The scheme [which is labeled AT (N)] is based on grouping biomarkers into 3 categories: β amyloid deposition (A), pathologic tau (T), and neurodegeneration (N) (17). $A\beta$ biomarkers can determine whether an individual is in the Alzheimer's continuum or not. Pathologic tau biomarkers can determine whether someone in the Alzheimer's continuum has AD, as deposits of both $A\beta$ and paired helical filament (PHF) tau are required to fulfill neuropathologic criteria for AD (18,19). With AT (N) biomarkers playing a vital role in AD research, we focused on biologically diagnosed prodromal AD. Our main goal was, therefore, to evaluate the impacts of ApoE ϵ 4 on clinical cognition, cerebrospinal fluid (CSF) biomarkers, and neuroimaging regions in prodromal AD. We hypothesized that ApoE ϵ 4 carriers would be associated with differences in cognitive profiles and cerebral atrophy patterns.

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI) and study participants

Data were downloaded from the ADNI in August 2016 (adni.loni.usc.edu). The ADNI database was launched in 2003 as a public-private partnership, led by its principal investigator, Michael W. Weiner, MD. The primary goal of ADNI was to identify the optimal combinations of serial magnetic resonance imaging (MRI), positron emission tomography (PET), CSF, and neuropsychological assessment to test the progression of MCI and early AD. For more up-to-date information, see www.adni-info.org. For the present study, we selected 780 ADNI-GO/2 participants meeting the criteria for MCI who had Mini-Mental State Examination (MMSE) scores of 24–30, a clinical dementia rating score of 0.5, subjective memory complaint and objective memory loss, and the absence of other neuropsychiatric disorders (20). More specifically, all selected participants had undergone lumbar puncture, ^{18}F -fluorodeoxyglucose PET (FDG-PET), Flortetapir-PET-AV45, structural MRI scanning, and neuropsychological assessments. We excluded MCI cases attributed to non-AD, such as medication and demyelination disease, unknown or uncertain etiology, aging, small vessel disease, stress, depression, and subjects without complete information. In total, we included only 178 A+T+MCI participants with positive biomarkers of $A\beta$ plaques and fibrillar tau, as described above.

Ethics approval and consent to participate

The ADNI study ethical approval was given by the institutional review boards of all participating institutions. All participants or authorized representatives provided written informed consent.

Neuropsychological assessment

Neuropsychological tests were performed by certified raters using standardized ADNI protocols (www.adni-info.org). The Rey Auditory Verbal Learning Test (RAVLT) (21) and the ADNI composite scores for memory (ADNI-MEM) (22) were used to measure memory. For evaluation of executive function, Trail Making Test (TMT) parts A and B (23) were used. For language function, Category Fluency Tests (24) and the Boston Naming Test (BNT) were conducted; to assess global cognition, the MMSE (21), Clinical

Dementia Rating Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) consisting of 11 (ADAS-Cog11) and 13 items (ADAS-Cog13), Montreal Cognitive Assessment (MoCA) (25), and the Functional Assessment Questionnaire (FAQ) were used. Clock tests were included to evaluate visuospatial ability.

ApoE genotyping

ApoE genotypes were determined using standard polymerase chain reaction methods, which have been described previously (26). Individuals with 1 or 2 copies of allele 4 were designated as ϵ 4-carriers (ϵ 4 +); individuals with no allele 4 were designated as non-carriers (ϵ 4 -). ApoE ϵ 4 genotyping methods are described at <http://www.adni-info.org>.

CSF data

As previously mentioned, CSF A β 1-42, total tau (t-Tau), and p-Tau were measured using the multiplex xMAPLuminex platform (Luminex) with Innogenetics (INNO-BIA AlzBio3) immunoassay kit-based reagents (27). The CSF data used in this article were obtained from the ADNI files "UPENNBBIOMK5-8.csv". Further details of ADNI methods for CSF acquisition, measurements, and quality control procedures are available online (<http://adni.loni.usc.edu/>). To select subjects with fibrillar tau (T+), we set the CSF cut-off point at 23 pg/mL for p-Tau181p, as previous studies described (27).

FDG data

FDG-PET was determined as a sum of mean glucose metabolism averaged across 5 regions of interest (ROIs) (i.e., right and left angular gyri, bilateral posterior cingulate, right and left inferior temporal gyri) (28). In addition to the composite FDG-PET, we also considered measurements for separate FDG-ROIs labeled as an "AD signature meta-ROI" (i.e., right and left angular, right and left temporal, bilateral cingulum post) (29). The FDG data used in this study were obtained from the ADNI file "UCBERKELEYFDG_07_30_15.csv".

Florbetapir-PET-AV45

To calculate the amyloid burden, we analyzed SUVR means of Florbetapir-PET-AV45 (anterior and posterior

cingulate, precuneus, prefrontal, orbitofrontal, parietal, temporal cortices) (30). Previous studies have proven that PET quantitation might be preferable for accurate selection and therapeutic monitoring of individuals in clinical trials (31,32). Participants were classified as A β -positive (A+) or A β -negative (A-) according to the SUVR cutoff of 1.1 for amyloid positivity. Data on cortical amyloid burden were obtained from the ADNI file "UCBERKELEYAV45_06_15_16.csv". Further details of ADNI methods for image acquisition and processing can be found at www.adni-info.org/methods.

Structural MRI

All ADNI MRI scans in this study were acquired at multiple sites using GE, Philips, and Siemens. All 3 available T MRI scans were collected for each subject using a sagittal MPRAGE sequence, and the raw DICOM images were obtained from the public ADNI site. Parameter values may vary depending on the scanning site, which can be downloaded at <http://www.loni.ucla.edu/ADNI/Research/Cores>. All MRI scans were processed, with little to no manual intervention using the segmentation module of the FreeSurfer software, as described in previous reports (33-35).

In the present study, we used ROIs analysis to calculate differences between ApoE ϵ 4-carriers and non-carriers. In total, 107 ROIs were automatically segmented according to the label on the Jacob atlas defined by FreeSurfer (36), and then non-carriers and ϵ 4-carriers groups were compared. At last, 7 ROIs that could significantly influence MCI progression were selected. The 7 ROIs included the average cortical thickness of the right rostral anterior cingulate and bilateral entorhinal, subcortical volume of the left amygdala, bilateral hippocampus, and left ventral diencephalon (DC). The structural MRI neuroimaging data were downloaded from the ADNI file "UCSFFSL_11_02_15" and "UCSFFSX51_11_02_15_V2".

Statistical analysis

Continuous variables are shown as mean \pm SD, and categorical variables are represented as frequencies (percentages). Comparisons between the two groups on continuous variables were performed with independent-samples *t*-tests, and categorical variables were analyzed with chi-squared tests. Wilcoxon rank-sum test was used when the variance did not satisfy the normality or homogeneity.

A multivariate analysis of variance was separately used to

Table 1 Baseline demographics and sample characteristics in prodromal AD participants

Demographics	ApoE ϵ 4- (n=53)	ApoE ϵ 4+ (n=125)	P value
Age, years	75.18 \pm 7.41	72.05 \pm 6.19	0.004*
Education, years	16.28 \pm 2.7	16.04 \pm 2.9	0.603
Male, n (%)	32 (60.38)	67 (53.60)	0.416
CSF A β 1-42	149.46 \pm 32.44	133.15 \pm 23.92	<0.001*
CSF total tau	99.09 \pm 51.48	123.47 \pm 55.64	0.007*
CSF P-tau _{181P}	51.44 \pm 19.67	57.88 \pm 25.05	0.098
Florbetapir-PET global SUVR	1.36 \pm 0.16	1.41 \pm 0.16	0.09

Data are the mean \pm standard deviation or number (%).*, statistically significant. AD, Alzheimer's disease; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; A β , β -amyloid; P-tau_{181P}, tau phosphorylated at threonine 181; florbetapir-PET global SUVR, uptake values ratios (SUVR) means of florbetapir-PET-AV45.

assess differences in cognitive scores and ROIs of structural MRI between study groups. The effects of age, gender, and years of education were adjusted for all analyses of covariance (ANCOVAs). ROIs of structural MRI and cognitive measures that statistically differed between both groups were further explored with linear regression models, adjusted for age, gender, education, and ApoE ϵ 4 status.

Furthermore, longitudinal associations between ApoE ϵ 4 status and cognitive measures were assessed by linear mixed models using the lme4 package of R software. Separate models were fitted for ApoE ϵ 4 status in relation to each dependent cognitive assessment. The longitudinal effect of ApoE ϵ 4 status on cognitive performance was estimated by the two-way interaction between time and ApoE ϵ 4 status, with adjustment for confounders (age, gender, and education).

All statistical analyses were conducted with IBM SPSS and R software. The analysis of variance with $P < 0.05$ was considered statistically significant.

Results

Subject demographics and sample characteristics

Demographics and sample characteristics of the study population, including age, gender, educational level, SUVR means of Florbetapir-PET-AV45, and CSF biomarker

values (A β 1-42, t-Tau, and p-Tau) are presented in *Table 1*.

ApoE ϵ 4 (+) prodromal AD participants were slightly younger (72.05 \pm 6.19 versus 75.18 \pm 7.41, $P = 0.004$), with significantly lower levels of CSF A β 1-42 ($P < 0.001$) and higher levels of t-Tau ($P = 0.007$), compared to ApoE ϵ 4 (-) prodromal AD subjects. The CSF concentration of p-Tau was numerically higher in ApoE ϵ 4 (+) prodromal AD participants, but the difference was not significant. There were no significant differences in gender, year of education, and amyloid burden measured by Florbetapir-PET-AV45.

Effects of ApoE ϵ 4 on FDG data

There were no differences in glucose metabolism measured by FDG-PET between ApoE ϵ 4 carriers and non-carriers, adjusted for age, sex, and year of education. FDG-PET in regional brain regions (the right and left angular gyri, bilateral posterior cingulate, and right and left inferior temporal gyri) also did not differ by ApoE ϵ 4 status (data not shown).

Effects of ApoE ϵ 4 on cognition

ApoE ϵ 4 status showed significant differences in cognitive assessments, as highlighted in *Table 2*.

We found that ApoE ϵ 4 (+) prodromal AD participants had worse results on global cognition and memory-related tasks. ApoE ϵ 4 was not associated with differences in executive function, visuospatial ability, and language domains.

More specifically, ApoE ϵ 4 (+) prodromal AD participants had higher mean RAVLT-perc-forgetting score (71.98 \pm 28.28 versus 59.79 \pm 31.82, $P = 0.015$), lower mean ADNI-MEM score (-0.03 \pm 0.6 versus 0.21 \pm 0.66, $P = 0.006$), higher mean ADAS-Cog11 score (11.22 \pm 4.77 versus 10.08 \pm 5.04, $P = 0.048$), and higher mean ADAS-Cog13 score (18.49 \pm 7.01 versus 16.08 \pm 7.26, $P = 0.008$). These analyses were adjusted for age, sex, and year of education.

Longitudinal FAQ data were available in a subset of the subjects (*Figure 1*). Significant interactions between ApoE ϵ 4 allele status and time were identified for the FAQ score. Possession of the ApoE ϵ 4 allele was accompanied by an added annual increase of 1.5796 points on the FAQ score.

Effects of ApoE ϵ 4 on brain structure

We evaluated differences in 107 ROIs obtained from structural MRI between the ApoE ϵ 4 carriers and non-

Table 2 Effects of ApoE ϵ 4 on cognitive assessments

Cognitive assessments	ApoE ϵ 4- (n=53)	ApoE ϵ 4+ (n=125)	P value	Adjusted P
CDR-SB	1.51±0.85	1.74±0.99	0.134	0.102
ADAS-Cog11	10.08±5.04	11.22±4.77	0.154	0.048*
ADAS-Cog13	16.08±7.26	18.49±7.01	0.039	0.008*
MMSE	27.76±1.79	27.39±1.94	0.245	0.198
RAVLT-immediate	33.64±10.28	32.62±9.29	0.518	0.208
RAVLT-learning	4.26±2.6	3.82±2.43	0.271	0.257
RAVLT-forgetting	4.64±2.35	5.42±2.22	0.036	0.075
RAVLT-perc-forgetting	59.79±31.82	71.98±28.28	0.012	0.015*
FAQ	3.7±3.86	3.66±4.47	0.961	0.799
MOCA	22.96±3.04	22.55±3.02	0.409	0.212
ADNI-MEM	0.21±0.66	-0.03±0.6	0.021	0.006*
Clock test	4.23±1.07	4.44±0.82	0.149	0.309
BNT	26.19±3.75	25.74±3.68	0.465	0.161
Category fluency tests	18.19±5.36	17.07±5.46	0.211	0.083
TMT-A	39.76±17.12	42.62±20.36	0.371	0.079
TMT-B	116.57±71.41	119.27±65.34	0.806	0.147

Data are the mean \pm standard deviation. Adjusted P was adjusted for age, sex, and education. *, statistically significant. ApoE, apolipoprotein E; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; ADAS-Cog11 or 13, Alzheimer's Disease Assessment Scale-11 or 13-Item Subscale; MMSE, Mini-Mental State Examination; FAQ, Functional Assessment Questionnaire; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; BNT, Boston Naming Test; TMT-A,B, Trail Making Test A,B.

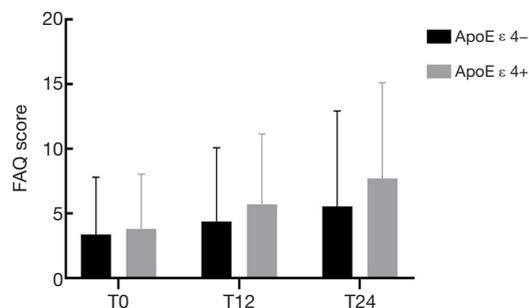


Figure 1 Longitudinal FAQ. The longitudinal associations between ApoE ϵ 4 status and cognitive performance were assessed by linear mixed models using the lme4 package of R software. The longitudinal effect of ApoE ϵ 4 status on FAQ score was estimated by the two-way interaction between time and ApoE ϵ 4 status, with adjustment for confounders (age, sex, and education). T0 = baseline; T12 = 12-month follow-up time; T24 = 24-month follow-up time. FAQ, Functional Assessment Questionnaire; ApoE, apolipoprotein E.

carriers, and 7 of them had significant differences. ApoE ϵ 4 (+) prodromal AD participants showed thinner cortical thickness in the bilateral entorhinal, along with smaller subcortical volume of the left amygdala, bilateral hippocampus and left ventral DC, while ApoE ϵ 4 (-) prodromal AD participants showed thinner cortical thickness in the right rostral anterior cingulate (2.74±0.25 versus 2.87±0.3, P=0.006). Details of these findings are provided in Table 3. These analyses were adjusted for age, sex, and year of education.

Regional atrophy-cognition relationships

To better understand how cognitive differences relate to underlying neuroanatomy, linear regression models were created. We evaluated independent effects of ROIs in structural MRI (cortical thickness average of the right rostral anterior cingulate and bilateral entorhinal; the subcortical volume of the left amygdala, bilateral hippocampus, and left ventral DC) on cognitive assessments (ADAS-Cog11,

Table 3 Comparison of ROIs from structural MRI

Regions	ApoE ϵ 4- (n=53)	ApoE ϵ 4+ (n=125)	P value	Adjusted P
Thickness average of the right rostral anterior cingulate	2.74±0.25	2.87±0.3	0.006	0.006*
Subcortical volume of the left amygdala	1,318.55±244.71	1,279.19±245.04	0.328	0.042*
Thickness average of the left entorhinal	3.25±0.5	3.14±0.49	0.186	0.03*
Subcortical volume of the left hippocampus	3,437.68±578.13	3,281.66±548.6	0.09	0.004*
Subcortical volume of the left ventral DC	3,706.51±410.39	3,586.15±359.67	0.052	0.011*
Thickness average of the right entorhinal	3.37±0.53	3.26±0.54	0.188	0.012*
Subcortical volume of the right hippocampus	3,495.09±598.62	3,364.48±561.47	0.166	0.011*

Data are the mean \pm standard deviation. Adjusted P was adjusted for age, sex, and education. *, statistically significant. ROI, region of interest; MRI, magnetic resonance imaging; ApoE, apolipoprotein E; DC, diencephalon.

Table 4 Associations between ROIs in structural MRI and cognitive assessments

Regions	Subgroup	ADAS-Cog11	ADAS-Cog13	RAVLT-perc-forgetting	ADNI-MEM
Subcortical volume of the left amygdala	B	-0.005	-0.011	-0.042	0.001
	P	0.001**	<0.001**	<0.001**	<0.001**
Subcortical volume of the left hippocampus	B	-0.003	-0.006	-0.021	0.001
	P	<0.001**	<0.001**	<0.001**	<0.001**
Subcortical volume of the left ventral DC	B	0	-0.001	-0.006	0
	P	0.681	0.379	0.343	0.327
Subcortical volume of the right hippocampus	B	-0.003	-0.005	-0.014	0
	P	<0.001**	<0.001**	0.001**	<0.001**
Thickness average of the left entorhinal	B	-2.99	-5.709	-16.337	0.462
	P	<0.001**	<0.001**	0.001	<0.001**
Thickness average of the right entorhinal	B	-3.053	-5.375	-14.029	0.414
	P	<0.001**	<0.001**	0.002	<0.001**
Thickness average of the right rostral anterior cingulate	B	-0.375	-0.527	5.62	-0.006
	P	0.77	0.778	0.478	0.97

Data are the mean \pm standard deviation. *P<0.05; **, P<0.001. Regression coefficients (B) and level of significance (P) for Linear regression models, adjusted for age, gender, education, and ApoE ϵ 4 status. ROI, region of interest; MRI, magnetic resonance imaging; ADAS-Cog11 or 13, Alzheimer's Disease Assessment Scale-11 or 13-Item Subscale; DC, diencephalon.

ADAS-Cog13, RAVLT-perc-forgetting, and ADNI-MEM). The ApoE ϵ 4 status, age, sex, and years of education were included in models to avoid the effect of ApoE ϵ 4 group differences driving these correlations. These results are shown in *Table 4*. The results indicate that the subcortical volumes of the left amygdala and bilateral hippocampus, along with

the cortical thickness average of the bilateral entorhinal, were highly correlated with global cognition (ADAS-Cog11, ADAS-Cog13) and memory measures (RAVLT-perc-forgetting, ADNI-MEM). The cortical thickness average of the bilateral entorhinal had the most significant effect on global cognition and memory performance.

Discussion

Our goal was to provide a comprehensive evaluation of the effects of ApoE ϵ 4 carrier status on CSF biomarkers (A β 1-42, t-Tau, and p-Tau levels), glucose metabolism measured by FDG-PET, clinical cognitive performances, and neurodegeneration (atrophy on structural MRI) in prodromal AD participants. The major findings regarding effects of the ApoE ϵ 4 genotype in MCI individuals with A β plaques and fibrillar tau biomarkers were as follows: (I) ApoE ϵ 4 (+) prodromal AD participants had lower CSF A β 1-42 levels and higher t-Tau levels, compared with ApoE ϵ 4 (-) participants; (II) ApoE ϵ 4 (+) prodromal AD participants had worse global cognition and memory performance, more rapid progression of global cognitive decline, and thinner cortical thickness in the bilateral entorhinal, along with smaller subcortical volume of the left amygdala, bilateral hippocampus, and left ventral DC, compared to ApoE ϵ 4 (-) prodromal AD subjects; (III) significant associations among memory, global cognition, and cortical thickness in bilateral entorhinal were found. In line with previous findings on ApoE ϵ 4 (37-39), our results indicate a significant ApoE ϵ 4-dependent heterogeneity in AD, with differences in clinical characteristics, biochemistry, and brain structure. Importantly, we showed that specific MRI regions have correlated cognitive domains which will be helpful for precise assessment in prodromal AD.

The most important advance relative to prior studies was that we conducted the current study in MCI participants with A β plaques and fibrillar tau biomarkers based on the AT (N) system from the 2018 NIA-AA research framework. Although many previous studies have detected the effects of ApoE ϵ 4 in AD, their diagnostic criteria were based on clinical classification, which ignored the pathologic changes of AD at autopsy (40,41). Around 10–30% of clinically diagnosed AD patients did not show any AD neuropathologic changes at autopsy (40). In the current study, only MCI participants with A β plaques and fibrillar tau biomarkers were included in order to significantly mitigate the concern of misdiagnosis that might occur in samples defined on the clinical basis. In this way, it was hoped that the conclusion made concerning the clinical characteristics of the MCI individuals would be more accurate.

Previous research has shown that the ApoE ϵ 4 genotype plays an important role in A β metabolism (42). In the present study, we demonstrated that prodromal AD participants carrying the ApoE ϵ 4 allele had lower CSF A β 1-42

levels than those without the ϵ 4 allele, despite having an amyloid burden with similar levels to those measured by Florbetapir-PET-AV45. ApoE ϵ 4-associated cerebral A β deposition might be illustrated by the ApoE ϵ 4 allele being associated with enhanced A β deposition into plaques and the differentially regulated clearance of A β from the brain (43-46).

Many studies have associated the presence of the ApoE ϵ 4 allele with both reduced cognitive performance and accelerated cognitive decline in AD, MCI, and cognitively healthy subjects (16,47,48). Memory deficits were often considered to be a major cognitive impairment in AD, and the ApoE ϵ 4 genotype might modify the clinical phenotype of AD. In the present study, we found that prodromal AD participants carrying the ApoE ϵ 4 allele had inferior performance in global cognition and memory. This finding confirms a previous study on clinically diagnosed MCI subjects, seemingly resembling subjects in the early stages of AD in terms of cognition and memory (16). Furthermore, longitudinal studies revealed that the ApoE ϵ 4 genotype is related to a more rapid decline in global cognition.

Cerebral atrophy is one of the gross pathologic features of AD. Structural imaging based on MRI has been widely used for the prediction of patients with AD or MCI. Medial temporal lobe substructures, which include the entorhinal cortex, amygdala, and hippocampus, are the earliest regions of the brain to show AD-related neurodegeneration. Atrophy later spreads to the temporal lobe, and the parietal and frontal cortices. Several studies have shown important associations between brain atrophy measured using MRI and cognitive impairments in people with MCI and AD. MR volumetric studies have indicated that the memory impairment in subjects with MCI and AD have demonstrated a close relation to the degeneration of the medial temporal lobe, especially in the entorhinal cortex and hippocampus (49-51). By studying the relationship between structural MRI and cognitive impairment, we found that the bilateral entorhinal region was most significantly associated with cognitive function. An earlier study showed extended associations between verbal episodic memory and diencephalon shrinkage in AD, while our results also showed a smaller subcortical volume of left ventral DC in ApoE ϵ 4 (+) prodromal AD participants. Yet, an association between the left ventral DC and memory has not been observed, at least in the present prodromal AD participants (52). Thus, our results confirm the complexity of the relationship between the ApoE ϵ 4 genotype and MRI markers of neurodegeneration, and future studies should further clarify the effects of ApoE ϵ 4 and other candidate gene variants on MRI biomarkers, which

in turn may help elucidate the roles of genetic factors in the neuropathology of AD.

There are several potential limitations to this study. First, only baseline MRI scans were analyzed in the current study. Future investigation on the association of longitudinal measures of cognitive decline and brain atrophy is warranted. Second, a small sample size had amyloid PET scans, and this might have affected the accuracy. Third, we specifically limited our study to those subjects who had already been clinically diagnosed as MCI. Thus, the study group might not be generalizable to all settings or populations. Finally, there was insufficient β -amyloid plaque density in some AD clinical phenotypes. The cause of their dementia is not investigated as a part of this research, but may be clarified in later research. Further studies are needed to support the present findings with larger sample sizes.

Conclusions

In summary, we found that ApoE ϵ 4 (+) prodromal AD participants had more memory and global cognitive impairment, more rapid memory decline, and greater brain atrophy. The findings highlight the heterogeneity in prodromal AD and the need for molecular diagnostics of the disease. ApoE ϵ 4 genotypes seem to be an important contributor to the heterogeneity of AD, and this may have implications on therapeutic targets for AD prevention.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies involving the ADNI participants were conducted following the Helsinki declaration. The ADNI study was approved by the institutional review boards of all of the participating institutions. Informed written consent was obtained from all participants and their legal representatives at each site before the collection of clinical, genetic, and imaging data.

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