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Effect of *APOE* ε4 Status on Brain Amyloid-β and Cognitive Function in Amnestic and Nonamnestic Mild Cognitive Impairment: A [18F] Florbetapir PET-CT Study

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Mild cognitive impairment (MCI) is recognized as a predementia syndrome caused by multiple etiologies and nonmemory symptoms in MCI have recently gained increasing attention. However, the pattern of Aβ deposition and the effect of APOE (apolipoprotein E, APOE) ϵ4 on cognitive impairment in amnestic MCI (aMCI) and nonamnestic MCI (naMCI) patients has not been demonstrated. In this work, the amyloid-β (Aβ) load by [^{18}F]florbetapir PET imaging and cognitive performance is compared by comprehensive neuropsychological scales in participants with different MCI types or different APOE ϵ4 carriage status. According to the Aβ positivity and results of voxel-wise analysis, higher Aβ loads are observed in aMCI patients than naMCI patients, especially aMCI patients with APOE ϵ4. Additionally, it is observed that memory domain Z scores show a strong negative correlation with global florbetapir SUVR in the aMCI group ($r = -0.352$, $p < 0.001$) but not in the naMCI group ($r = -0.016$, $p = 0.924$). Moreover, this correlation is independent of APOE e4 carriage status. This study aims to identify high-risk groups at an early stage of AD(Alzheimer's Disease, AD) through cognitive performance and APOE ϵ4 carrier status, which can be important for guiding clinical intervention trials.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder clinically characterized by multidomain cognitive impairment, with impaired memory function as the initial symptom.[1] Amyloid-β (Aβ) deposition is acknowledged as a defining pathological biomarker of AD and has been demonstrated to play a crucial role in the decline of memory function.[2] Mild cognitive impairment (MCI) is an intermediate stage between normal cognition and the onset of AD. MCI is further divided into amnestic MCI (aMCI) and nonamnestic MCI (naMCI) based on whether cognitive impairments involve or do not involve memory, respectively.[3] aMCI is at more likely to progress to AD, whereas naMCI is more likely to convert to vascular dementia (VaD), frontotemporal dementia (FTD), or dementia with Lewy bodies (DLB), with various nonamyloid pathologies being observed.[4]

Apolipoprotein-E (*APOE*) ϵ4 has been confirmed as a high-risk gene for sporadic AD, and individuals carrying it exhibit more pronounced Aβ deposition and earlier clinical symptoms, typically manifesting as more severe cognitive impairments, especially in the domain of memory.[5] The potential mechanism may be that APOE ϵ4 disrupts the maintenance of synaptic integrity and plasticity due to its low efficiency in transporting cholesterols, leading to increased Aβ deposition and reduced clearance.[6] Recently, nonmemory symptoms in MCI have gained increasing attention. Utilizing amyloid positron emission tomography (PET), researchers have identified greater Aβ accumulation in individuals with aMCI than in those with naMCI.[7] However, the differences in Aβ deposition patterns between aMCI and naMCI patients, as well as the effect of *APOE* ϵ4 on cognitive impairments and amyloid deposition in naMCI patients, remain unclear.

In this study, we aimed to explore the differences in Aβ deposition between aMCI and naMCI patients and the effect of *APOE* ϵ4 carrier status on Aβ deposition and the correlation between Aβ deposition and various cognitive functions using [^{18}F]florbetapir PET imaging. The aim of our study was to identify high-risk groups at an early stage of AD based on information related to their different cognitive domain impairments

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Table 1. Demographic information and clinical characteristics of participants.

	aMCI participants [n = 118]	naMCI participants [n = 44]	P_1 value	*APOE* ϵ4 carriers [n = 53]	*APOE* ϵ4 noncarriers [n = 109]	P_2 value
Age	66.36 ± 7.08	64.05 ± 5.85	0.057	67.37 ± 6.97	64.97 ± 6.66	**0.037**
Male sex (%)	44.9%	18.2%	**0.002**	34.0%	39.4%	0.499
Education (years)	11.20 ± 3.36	10.61 ± 2.65	0.30	11.19 ± 3.31	10.96 ± 3.14	0.671
Aβ+ (%)	42.4	27.3	0.079	49.1	33.0	**0.049**
MMSE	26.15 ± 2.91	27.09 ± 1.57	0.092	26.00 ± 3.60	26.60 ± 2.05	0.703
MoCA-B	21.97 ± 3.16	21.50 ± 3.71	0.442	21.97 ± 3.07	21.80 ± 3.40	0.776
AVLT-LDR	1.55 ± 1.43	4.33 ± 2.53	**<0.001**	1.58 ± 1.85	2.63 ± 2.23	**0.002**
AVLT-REC	16.64 ± 2.13	21.21 ± 1.81	**<0.001**	17.00 ± 2.88	18.27 ± 2.80	**0.009**
AFT	13.67 ± 3.50	11.00 ± 2.29	**<0.001**	13.54 ± 3.61	12.73 ± 3.35	0.209
BNT	22.21 ± 3.75	18.51 ± 2.85	**<0.001**	22.32 ± 3.80	20.85 ± 3.87	**0.046**
STT-A	57.46 ± 21.10	61.60 ± 23.65	0.360	60.21 ± 23.23	58.0 ± 21.37	0.838
STT-B	155.71 ± 47.40	168.23 ± 55.21	0.288	161.13 ± 40.36	158.37 ± 52.86	0.324

MMSE: Mini Mental State Examination, MoCA-B: Montreal Cognitive Assessment-Basic, AVLT-LDR: long delayed recall of the AVLT, AVLT-REC: recognition portion of the AVLT, AFT: the Animal Fluency Test, BNT: the 30-item Boston Naming Test, STT-A: Shape Trails Test Parts A, STT-B: Shape Trails Test Part B.

and *APOE* ϵ4 carrier statuses, which could be crucial aspects for guiding clinical intervention trials.

2. Results

2.1. Demographics and Clinical Assessments

The study included a total of 118 patients with aMCI (44 *APOE* ϵ4 carriers and 74 *APOE* ϵ4 noncarriers) and 44 patients with naMCI (9 *APOE* ϵ4 carriers and 35 *APOE* ϵ4 noncarriers) patients (**Table 1**). In the analysis stratified by cognitive function, the naMCI group included significantly more female participants and fewer *APOE* ϵ4 noncarriers compared to the aMCI group (male: 44.9% vs 17.8%, $P = 0.002$; *APOE* ϵ4 carrier: 18.6% vs 37.3%, $P = 0.021$). The aMCI group exhibited higher Z scores for language domain but lower Z scores for memory domain compared to the naMCI group ($P < .001$). In the *APOE* status stratified analysis, *APOE* ϵ4 carriers were significantly older than noncarriers ($P = 0.037$) and had a higher Aβ positivity rate (49.1% vs 33.0%, $P = 0.049$). *APOE* ϵ4 carriers manifested lower Z scores for memory domain (AVLT-LDR: 1.58 ± 1.85, $P = 0.002$; AVLT-REC: 17.00 ± 2.88, $P = 0.009$) but higher BNT scores compared to noncarriers (22.32 ± 3.80, $P = 0.046$).

Furthermore, we found that *APOE* ϵ4 carriers had higher Aβ positivity than noncarriers in the aMCI group (56.8% vs 33.8%, $P < 0.05$), while no difference was observed in the naMCI group. No significant difference was observed between *APOE* ϵ4 carriers and noncarriers in memory (AVLT-LDR and AVLT-REC) in either the aMCI or naMCI group. The aMCI group displayed worse memory function (AVLT-LDR and AVLT-REC) than the naMCI group in both *APOE* ϵ4 carriers and noncarriers. Similarly, there was no discrepancy between *APOE* ϵ4 carriers and noncarriers in language and executive function (AFT, BNT, and STT-A/B) in either the aMCI or naMCI groups. Nevertheless, aMCI patients who were *APOE* ϵ4 carriers exhibited higher BNT scores compared to naMCI patients who were *APOE* ϵ4 carriers. Among *APOE* ϵ4 noncarriers, the aMCI group had better language function (AFT and BNT) than the naMCI group. These results are shown in **Table 2**.

2.2. Group Differences in the Level of Amyloid Accumulation

A significant interaction between MCI subtype and *APOE* ϵ4 status was observed in the frontal lobe and parietal lobe (**Figure 1**). Examination simple main effects revealed that the primary effects of MCI subtypes on Aβ deposition were predominantly observed in the frontal lobe, temporal lobe, parietal lobe, occipital lobes, and cingulate gyrus. The primary effects of *APOE* ϵ4 status were predominantly found in the frontal lobe and the cingulate gyrus.

Specifically, the aMCI group exhibited higher Aβ deposition, particularly in the medial and lateral temporal lobes and precuneus, compared to the naMCI group (**Figure 2A**). However, *APOE* ϵ4 carriers had higher global Aβ deposition than *APOE* ϵ4 noncarriers in the overall cohort (Figure 2B). Similarly, in the stratified analysis (Figure 2C), *APOE* ϵ4 carriers in the aMCI group exhibited higher Aβ global deposition than noncarriers, whereas no significant difference was found between the *APOE* ϵ4 carriers and noncarriers in the naMCI group.

Among *APOE* ϵ4 carriers, the aMCI group exhibited higher Aβ deposition in the frontal lobe, temporal lobe, occipital lobe, precuneus and cingulate gyrus compared to the naMCI group. However, among *APOE* ϵ4 noncarriers, the aMCI group exhibited higher Aβ deposition in a small region of the right lateral temporal lobe than the naMCI group (Figure 2D,E).

2.3. Correlation Analysis

Memory domain Z scores (AVLT-LDT and AVLT-REC) exhibited a robust negative correlation with Aβ deposition in the whole cortex in the MCI and aMCI groups, as demonstrated by voxel-wise and region-of-interest (ROI)-based analyses. However, the Z scores of AVLT-LDT and AVLT-REC were not correlated with

Table 2. Demographic information and clinical characteristics of participants.

	aMCI *APOE* ϵ4 carrier [$n = 44$]	aMCI *APOE* ϵ4 noncarrier [$n = 74$]	naMCI *APOE* ϵ4 carrier [$n = 9$]	naMCI *APOE* ϵ4 noncarrier [$n = 35$]	*P* value
Age	67.41 ± 7.39	65.75 ± 6.87	67.13 ± 4.32	63.34 ± 5.97	0.062
Male sex (%)	40.9%[b*]	47.3%[d**e*]	0[b*d**]	22.9%[e*]	**0.005**
Education (years)	11.41 ± 3.29	11.07 ± 3.42	10.0 ± 3.42	10.74 ±2.48	0.630
Aβ+ (%)	56.8%[a*b*c*]	33.8%[a*]	11.1%[b*]	31.4%[c*]	**0.016**
MMSE	25.64 ± 3.77	26.46 ± 2.23	28.00 ± 1.31	26.89±1.57	0.110
MoCA-B	22.06 ± 3.21	21.93 ± 3.15	21.40 ± 2.07	21.51 ± 3.91	0.891
AVLT-LDR	1.14 ± 1.46[b**c***]	1.80 ± 1.37[e***]	4.00 ±2.00[b**]	4.40 ± 2.66[c***e***]	**<0.001**
AVLT-REC	16.34 ± 2.46[b***c***]	16.81±1.90[d***e***]	20.63 ± 2.33[b***d***]	21.34 ± 1.68[c***e***]	**<0.001**
AFT	13.91 ± 3.60[c**]	13.55 ± 3.47[e***]	11.0 ± 2.74	11.0 ± 2.95[c**e***]	**<0.001**
BNT	22.88 ± 3.57[b*c***]	21.91 ± 3.82[e***]	17.50 ± 1.73[b*]	18.63 ± 2.95[c***e***]	**<0.001**
STT-A	58.12 ± 21.94	57.16 ± 20.85	74.40 ± 29.38	59.77 ± 22.63	0.585
STT-B	156.56 ± 36.02	155.32 ± 52.02	192.2 ± 58.17	165.80 ± 54.78	0.339

MMSE: Mini Mental State Examination, MoCA-B: the Montreal Cognitive Assessment-Basic, AVLT-LDR: long delayed recall of the AVLT, AVLT-REC: recognition portion of the AVLT, AFT: the Animal Fluency Test, BNT: the 30-item Boston Naming Test, STT-A: Shape Trails Test Part A, STT-B: Shape Trails Test Part B. There was a significant difference between [a)] aMCI patients with *APOE* ϵ4 gene versus aMCI patients without *APOE* ϵ4 gene; [b)] aMCI patients with *APOE* ϵ4 gene versus naMCI patients with *APOE* ϵ4 gene; [c)] aMCI patients with *APOE* ϵ4 gene versus naMCI patients without *APOE* ϵ4 gene; [d)] aMCI patients without *APOE* ϵ4 gene versus naMCI patients with *APOE* ϵ4 gene and; [e)] aMCI patients without *APOE* ϵ4 gene versus naMCI patients without *APOE* ϵ4 gene. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

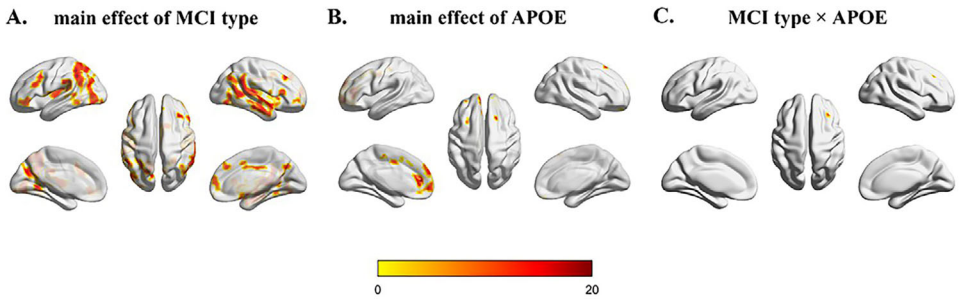

Figure 1. Interaction effect of MCI subtype and *APOE* ϵ4 carrier status on Aβ deposition. A) The main effects of MCI subtype on Aβ deposition were mainly in the parietal lobe, frontal lobe, medial and lateral temporal lobes, occipital lobes, precuneus, and cingulate gyrus. B) The main effects of *APOE* ϵ4 genotypes were mainly in the frontal lobe and the cingulate gyrus. C) Interaction effects of *APOE* ϵ4 genotypes and MCI subtype were mainly in the frontal and parietal lobes.

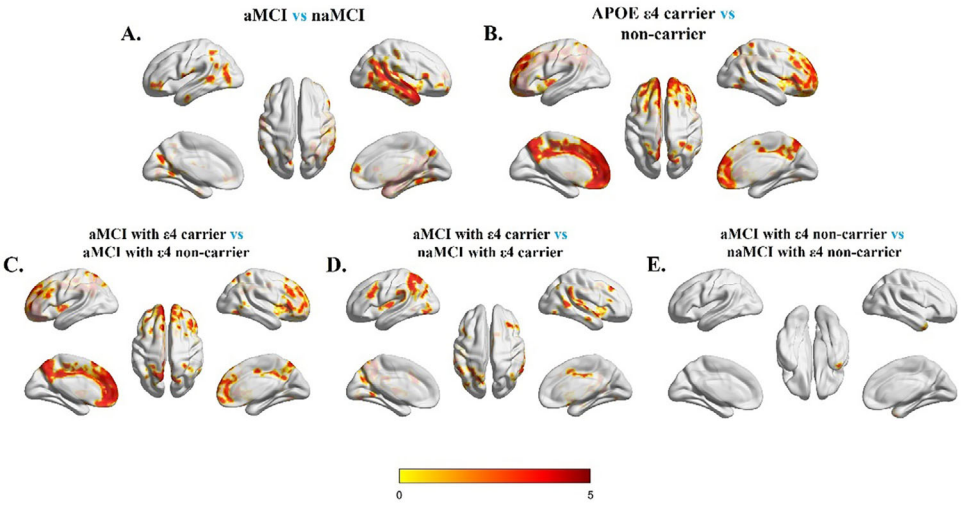

Figure 2. Comparison of Aβ deposition differences in different MCI groups with different *APOE* ϵ4 carrier statuses. A) aMCI versus naMCI; B) *APOE* ϵ4 carriers versus ϵ4 noncarriers; C) *APOE* ϵ4 carriers versus ϵ4 noncarriers in the aMCI group; D) aMCI versus naMCI among *APOE* ϵ4 carriers; E) aMCI versus naMCI among *APOE* ϵ4 noncarriers.

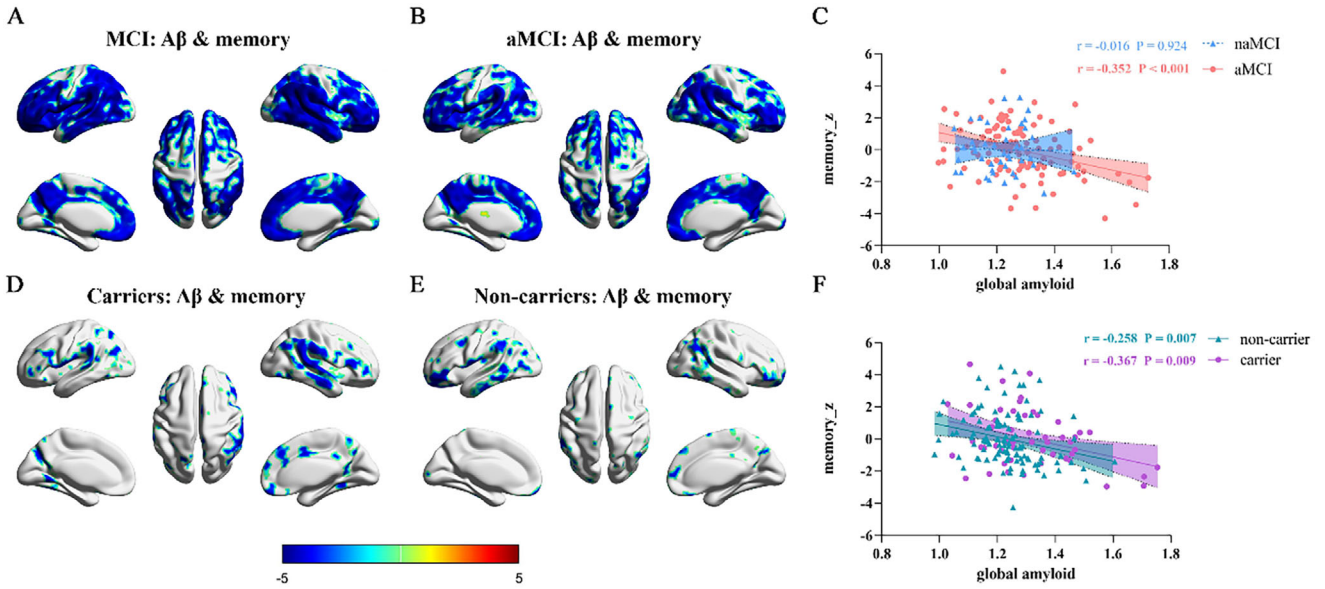

Figure 3. Correlation between Aβ deposition and Z scores of neuropsychological tests in the memory domain in MCI patients. The correlation between Aβ deposition and memory functions A) in the overall MCI cohort, B) in the aMCI group by voxelwise analysis, and C) in the overall MCI cohort by ROI-based analysis. The correlation between Aβ deposition and memory functions D) in *APOE* ϵ4 carriers, E) in *APOE* ϵ4 noncarriers by voxelwise analysis, and F) in the overall cohort by ROI-based analysis.

SUVRs in the naMCI group, indicating that memory was not correlated with Aβ deposition (**Figure** 3A–C). In the stratified analysis of *APOE* ϵ4 status (Figure 3D–F), the Z scores of AVLT-LDT and AVLT-REC were associated with SUVRs in the frontal lobe, temporal lobe, precuneus and posterior cingulate gyrus in *APOE* ϵ4 carriers, and a similar relation in smaller regions was observed in *APOE* ϵ4 noncarriers. In the ROI-based analysis, we found that the Z scores of AVLT-LDT and AVLT-REC showed a significant negative correlation with global florbetapir SUVR in the aMCI group ($r = -0.352$, $p < 0.001$) but not in the naMCI group ($r = -0.016$, $p = 0.924$). However, the Z scores of AVLT-LDT and AVLT-REC displayed a significant inverse correlation with global florbetapir SUVR in both *APOE* ϵ4 carriers ($r = -0.367$, $P = 0.009$) and *APOE* ϵ4 noncarriers ($r = -0.258$, $P = 0.007$).

Regarding nonmemory cognitive domains (AFT, BNT and STT-A/B) (**Figure** 4), we found that only the Z scores of AFT and BNT were positively correlated with global [^{18}F]florbetapir SUVR in *APOE* carriers ($r = 0.362$, $P = 0.030$). Nevertheless, no significant correlation was found between SUVRs and the Z scores of STT-A/B in the stratified analysis of MCI subtypes or *APOE* ϵ4 status.

3. Discussion

The study evaluated the interaction between *APOE* genotype and MCI subtype, revealing that the aMCI group displayed higher Aβ deposition positivity and a broader range of deposited brain regions compared to the naMCI group. *APOE* ϵ4 carriers showed a higher Aβ-positive rate and amyloid deposition in the MCI population, with the dosage effect being prominent in the aMCI group but not in the naMCI group. Furthermore, Aβ deposition was associated with more severe memory impairment in aMCI but not in naMCI. Amyloid deposition also had no or a weak association with nonmemory function in the analyses stratified by MCI subtypes or *APOE* status. These results indicated that memory impairment and *APOE* genotypes played significant roles in MCI patients.

The *APOE* × MCI subtype interaction was observed in small regions of the frontal lobe and parietal lobe, while the main-effect analysis indicated that MCI subtype had a significant effect on amyloid deposition in a wide range of cortical regions. A difference in amyloid deposition between the aMCI and naMCI groups has not previously been shown. We found that the aMCI group displayed higher amyloid deposition primarily in the medial and lateral temporal lobes than the naMCI group. This result is consistent with the conclusions of previous studies that amyloid deposition in the temporal lobe is considered one of the key signs of AD. Some studies also have indicated that aMCI patients exhibit gray matter loss in the medial and inferior temporal lobes, whereas naMCI patients, who are more likely to progress to non-AD dementia, present a different pattern.[4b,8] The causes of this progression may be more heterogeneous than in our study, but our results suggest that Aβ deposition in the aMCI population aligns more closely with the typical pathological features of AD. Follow-up studies are needed to further confirm that Aβ deposition is a key factor in the progression of aMCI to AD.

The *APOE* ϵ4 could be another risk factor for the progression from aMCI to AD. As previously reported, *APOE* ϵ4 carriers displayed higher amyloid deposition than noncarriers among individuals with MCI.[5b,9] In this study, we found that *APOE* ϵ4 carriers in the aMCI group, but not in the naMCI group, showed considerable amyloid deposition, suggesting that memory function, instead of nonmemory function, could be influenced by the *APOE* ϵ4 genotype. *APOE* ϵ4 may directly affect cognition through multiple pathways, including facilitated Aβ deposition, increased tangle formation, and neuroinflammation.[10]

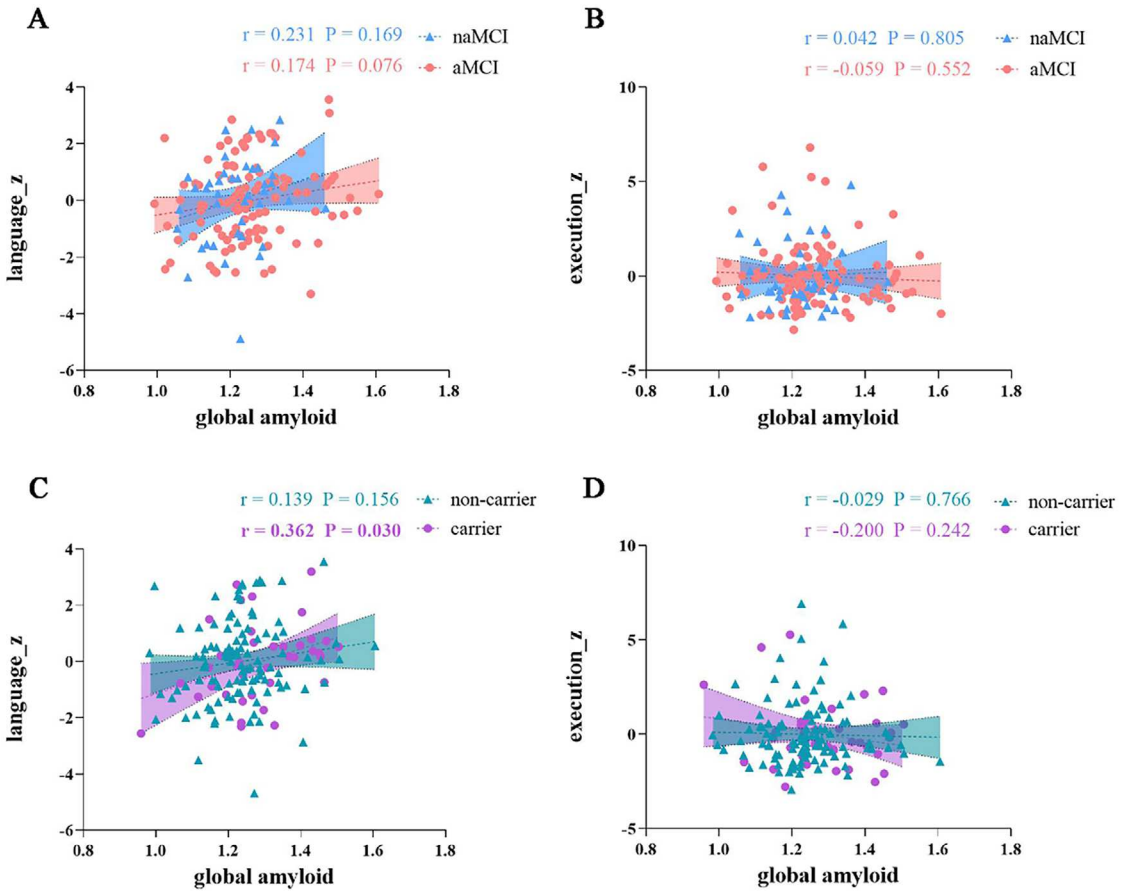

Figure 4. Correlation between Aβ deposition and Z scores of neuropsychological tests in the nonmemory domain. Scatterplots showing no correlation between Aβ deposition and Z scores A) in the language domain or B) in the executive domain in the aMCI and naMCI groups. C) Significant correlation between Aβ deposition and Z scores in the language domain in *APOE* ϵ4 carriers; no correlation was found in *APOE* ϵ4 noncarriers. D) No correlation between Aβ deposition and Z scores in the executive domain was found in *APOE* ϵ4 carriers or *APOE* ϵ4 noncarriers.

However, a longitudinal study is necessary to investigate the conversion of naMCI among *APOE* ϵ4 carriers to confirm that *APOE* ϵ4 can potentially accelerate amyloid deposition in naMCI patients.

Furthermore, both *APOE* ϵ4 carriers and noncarriers in the aMCI group exhibited higher amyloid deposition than their respective counterparts in the naMCI group, indicating that aMCI individuals could be more vulnerable to amyloid deposition than naMCI individuals regardless of *APOE* status. These results demonstrated that memory impairment is a important sign of amyloid deposition and for conversion to AD. Previous studies have also shown that the etiology of cognitive impairment in Aβ-negative MCI patients may be related to nonamyloid pathological changes, such as age-related cerebrovascular disease and hippocampal sclerosis, DLB or Parkinson's disease associated with Lewy bodies.[11] Atypical AD patients, for example, the healthy aging population, usually do not have significant medial temporal lobe atrophy or amyloid deposition.[12] The change in clinical symptoms of these patients with atypical AD may be more related to pathological tau protein, glucose metabolism or neuroinflammation.[13] Therefore, an analysis of amyloid deposition-related memory impairments and their underlying *APOE* genotypes is important for the development of related therapies.

Correlation analysis further confirmed that Aβ deposition was significantly negatively correlated with memory function in patients with aMCI, rather than naMCI. However, no significant correlation between amyloid deposition and nonmemory function was observed. The findings are consistent with previous studies demonstrating that the MCI patients with higher amyloid deposition perform worse on episodic memory tests and have a faster functional decline.[14] These results are also in line with previous neuroimaging studies, in which the most extreme cortical atrophy was observed in the medial temporal lobe (especially the hippocampus) in MCI patients, particularly in aMCI patients.[8b,15] A recent study showed that aMCI patients had higher Aβ deposition in the bilateral temporal lobe and other neocortices, which further confirmed that Aβ deposition in the temporal-parietal lobe is important for cognitive decline. Our results indicated that amyloid deposition is closely associated with memory decline in MCI.

Notably, Aβ deposition is associated with impaired memory function in both *APOE* ϵ4 carriers and *APOE* ϵ4 noncarriers. Previous studies have shown that Aβ deposition in aMCI occurred

earlier and progressed more rapidly in *APOE* ϵ4 carriers. Aβ deposition also showed a stronger correlation with memory impairment from onset and reached a plateau earlier.[16] At this stage, the progression rate of Aβ deposition decreases significantly, but the clinical symptoms continue to deteriorate, so the correlation between Aβ deposition and cognitive impairment is present in *APOE* ϵ4 carriers.[17] However, in *APOE* ϵ4 noncarriers, memory decline could also be induced by amyloid deposition. Here, we observed a correlation between Aβ deposition and memory in *APOE* ϵ4 noncarriers.

There are some limitations of this study. Only 9 naMCI patients who were *APOE* ϵ4 carriers were included, which limited the analytical power of this study. We will continue to increase the sample size to further confirm the stability of these findings. Furthermore, this study was only a cross-sectional observational study, and longitudinal studies are necessary to investigate the relationships among *APOE* genotype, cognitive impairment progression, and different MCI outcomes in the future.

4. Conclusion

In conclusion, the study identified that both aMCI and *APOE* ϵ4 carriers had higher Aβ deposition and that the role of *APOE* in promoting Aβ deposition was more significant in aMCI. We also found that amyloid deposition was positively correlated with impaired memory function in aMCI but not in naMCI, independent of *APOE* ϵ4 status. In addition, although individuals with naMCI also have cognitive impairment, this impairment may be associated with non-AD diseases, which may convert to various non-AD dementias. Therefore, the development of specific early preventions for cognitive impairments and therapeutic approaches targeting memory/nonmemory function and *APOE* ϵ4 status is necessary in the future.

5. Experimental Section

Participants: This study adopted a cross-sectional design, enrolling a total of 162 participants from the memory clinic or communities in Shanghai as detailed in the previous report.[18] All participants underwent a battery of neuropsychological tests, MRI examinations, and *APOE* genotyping at Shanghai Jiao Tong University Affiliated Sixth People's Hospital from December 2018 to October 2022. The [^{18}F]-florbetapir PET scans were performed in the PET Center of Fudan University Affiliated Huashan Hospital. This study received approval from the Institutional Ethics Reviewing Board of Huashan Hospital and Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Signed informed consent forms from all participants or their guardians were obtained prior to the research.

The inclusion criteria for all participants were as follows: 1) Age over 50 years, regardless of gender or years of education; 2) All patients are matched with one caregiver and willing to complete the questionnaire assessment; 3) Age- and education-corrected Mini-Mental State Examination (MMSE) scores $\geq$ 21; 4) Diagnoses of aMCI and naMCI were diagnosed according to Jak and Bondi's revised criteria[19]: Participants were included in the aMCI group if both of their neuropsychological scale scores in the memory cognitive domain indicated impairment (defined as scores below 1 standard deviation (SD) of the age-corrected mean). The participants were included in the naMCI group if both neuropsychological scale scores in the nonmemory cognitive domains (language or executive domains) indicated impairment and no more than 1 scale score in the memory cognitive domain indicated impairment; 5) Do not have serious comorbidities, such as psychiatric disorders, neurological malignancies, history of severe stroke or trauma, etc.

Neuropsychological Assessments: All participants underwent a comprehensive neuropsychological assessment with the following tests, which were revised based on the Chinese background of the patients[20]: the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment-Basic (MoCA-B) for general global cognition; the 30-min-long delayed recall (LDR) and the recognition (REC) portion of the auditory verbal learning test (AVLT) for the memory domain; the animal fluency test (AFT) and Boston naming test (BNT) for the language domain; and parts A and B of the shape trails test (STT-A/B) for the executive function domain.[21]

For all patients, the diagnosis was made on clinical grounds according to corresponding international criteria. All neuropsychological tests were administered by professional neurologists.

APOE Genotyping: The APOE genotype was determined by ligase detection reaction (LDR) method. To investigate the effect of the *APOE* ϵ4 allele on Aβ deposition and cognitive impairment specifically, participants carrying the *APOE* ϵ2 allele, which may have a protective effect against AD,[22] were excluded. Approximately 2 mL of fasting peripheral venous blood was collected from the participants for DNA extraction using the blood DNA extraction kit manufactured by Shanghai Generay Biotech Co., Ltd., China. In addition, participants were excluded from this study when they met any of the following criteria: memory impairment complicated with intracranial organic lesions, other psychoneurological diseases, or severe medical diseases (such as heart, lung, liver, or kidney failure); an allergy to radiographic agents; an inability to cooperate with the examination or refusal to sign the informed consent; pregnancy or lactation; and the presence of metallic foreign body implants.

Imaging Acquisition and Processing: The [^{18}F] florbetapir imaging agent was prepared in the Department of Nuclear Medicine & PET Center, Huashan Hospital, Fudan University, as described in the previous report.[18] PET/CT imaging was acquired by PET/CT scanners (Biograph mCT Flow PET/CT, Siemens, Germany). Participants were intravenously injected with a dose of 0.37–0.55 MBq kg^{-1} of [^{18}F] florbetapir. Then, the participants rested for 50 min before undergoing a 20-min PET/CT scan of the brain. The images were acquired by a 10-s low-dose head CT scan (120 kV, 150 mA) followed by a 20-min PET scan of the brain in 3D mode. The images were reconstructed by a reconstructed image matrix size of 168 × 168 × 148 and a voxel size of 2.04 × 2.04 × 1.50 mm.

Magnetic resonance (MR) scans were performed on a 3.0 T MRI scanner (Prisma 3.0T, Siemens, Germany) at Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China. T1-weighted image data were acquired in the sagittal position by a magnetization-prepared rapid gradient echo (MRI) sequence with the following parameters: matrix size = 320 × 320, field of view (FOV) = 256 × 256 mm3, layer thickness = 0.8 mm, voxel size = 0.8 × 0.8 × 0.8 mm3, repetition time (TR) = 3000 ms, echo time (TE) = 2.56 ms, inversion time (TI) = 900 ms, tilt angle = 7°, and number of layers = 208.

The binary visual reading method was used by three experienced PET diagnosticians to qualitatively analyze Aβ PET images in an independent manner.[18a] MATLAB R2018b software and Statistical Parametric Mapping (SPM) 12 were used for imaging preprocessing and extracting the mean [^{18}F] florbetapir standard uptake value (SUV) from the global cortical SUV. The preprocessing steps included image format conversions, the fusion of individual PET images with their own T1-weighted images, the segmentation of the individual T1-weighted images, the partial volume effect correction (PVC) of the PET-T1 fused images using a tissue probability map (TPM), and normalization and smoothing to obtain standard spatial images for quantitative analysis. All PET imaging variables were computed in the standard space. The PET images were spatially normalized and intensity normalized without smoothing in ROI analysis, while were spatially normalized and smoothed in voxel-wise analysis.

Seven ROIs were defined, including gray matter areas in the frontal, parietal, lateral temporal, medial temporal, occipital, posterior cingulate gyrus, and precuneus lobes, and the whole-brain ROIs consisted of the aforementioned seven ROIs. The mean global cortical SUV ratio (SUVR) was calculated with cerebellar gray matter. The [^{18}F] florbetapir images

were qualitatively analyzed for Aβ deposition by a visual assessment method by at least two full-senior level nuclear medicine physicians.

Statistical Analysis: Two independent-sample t tests or Mann-Whitney U tests were used to compare the demographic information and clinical scale scores between different MCI types or *APOE* ϵ4 carrier statuses. One-way analysis of variance (ANOVA) or the Kruskal-Wallis test was further utilized to evaluate the differences among the four subgroups (participants with aMCI with who were *APOE* ϵ4 carriers, participants with aMCI who were APOE ϵ4 noncarriers, participants with naMCI who were *APOE* ϵ4 carriers and participants with naMCI who were *APOE* ϵ4 noncarriers).

Scores for each neuropsychological scale were converted into standard scores and then summed in the respective cognitive domain to derive the Z scores for each domain. These Z scores were utilized for subsequent between group comparisons and correlation analyses. The scores for each neuropsychological scale were converted into standard scores and summed the standard scores in the same cognitive domain to obtain the Z score of each domain, which was used for subsequent between-group comparisons and correlation analyses. Partial correlation was applied to explore the correlation between the mean global cortical [18F]florbetapir SUVR and the Z scores of each cognitive domain, with age, sex and years of education as covariates. Then, Fisher's Z test was employed to compare the correlation coefficients. Statistically significant was considered when $P < 0.05$. A scatter plot was created to represent the results of the partial correlation analysis. All the above statistical analyses were conducted with IBM SPSS Statistics (version 26.0) software.

For voxelwise analysis, multivariate ANOVA was applied to assess the effects of different MCI types and ϵ4 carrier status on Aβ deposition, and multiple linear regression was applied to analyze the correlation between Aβ deposition and Z scores for each cognitive domain, with age, sex and years of education as covariates. None of the results of voxelwise analysis underwent false discovery rate (FDR) or familywise error (PWE) correction. The difference was statistically significant when $P < 0.001$ and Kep $\geq$ 100 voxels. All the above statistical analyses were conducted by SPM12.

Ethical Approval and Informed Consent: This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.W., Z.Z., and Y.W. contributed equally to this work. F.X., Q.G., Z.Z., and M.W. designed this study and organized the data collection. J.W., Y.W., L.W., and Q.H. processed and analyzed the data. R.N. and Y.G. reviewed the study design and helped to refine it. W.M. and F.X. led the manuscript writing, and all authors reviewed and revised the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

amyloid beta-peptides, apolipoprotein E4, mild cognitive impairment, positron-emission tomography

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