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ORIGINAL ARTICLE

Beta-amyloid deposition and cognitive function in patients with major depressive disorder with different subtypes of mild cognitive impairment: ^{18}F-florbetapir (AV-45/Amyvid) PET study

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Abstract

Purpose The objective of this study was to evaluate the amyloid burden, as assessed by ^{18}F-florbetapir (AV-45/Amyvid) positron emission tomography PET, in patients with major depressive disorder (MDD) with different subtypes of mild cognitive impairment (MCI) and the relationship between amyloid burden and cognition in MDD patients.

Methods The study included 55 MDD patients without dementia and 21 healthy control subjects (HCs) who were assessed using a comprehensive cognitive test battery and ^{18}F-florbetapir PET imaging. The standardized uptake value ratios (SUVR) in eight cortical regions using the whole cerebellum as reference region were determined and voxel-wise comparisons between the HC and MDD groups were performed. Vascular risk factors, serum homocysteine level and the apolipoprotein E (ApoE) genotype were also determined.

Results Among the 55 MDD patients, 22 (40.0 %) had MCI, 12 (21.8 %) non-amnestic MCI (naMCI) and 10 (18.2 %) amnestic MCI (aMCI). The MDD patients with aMCI had the highest relative ^{18}F-florbetapir uptake in all cortical regions, and a significant difference in relative ^{18}F-florbetapir uptake was found in the parietal region as compared with that in naMCI subjects ($P<0.05$) and HCs ($P<0.01$). Voxel-wise analyses revealed significantly increased relative ^{18}F-florbetapir uptake in the MDD patients with aMCI and naMCI in the frontal, parietal, temporal and occipital areas ($P<0.005$). The global cortical SUVR was significantly negatively correlated with MMSE score ($r=-0.342$, $P=0.010$) and memory function ($r=-0.328$, $P=0.015$). The negative correlation between the global SUVR and memory in the MDD patients remained significant in multiple regression analyses that included age, educational level, ApoE genotype, and depression severity ($\beta=-3.607$, $t=-2.874$, $P=0.006$).

Conclusion We found preliminary evidence of brain beta-amyloid deposition in MDD patients with different subtypes of MCI. Our findings in MDD patients support the hypothesis that a higher amyloid burden is associated with a poorer memory performance. We also observed a high prevalence of MCI among elderly depressed patients, and depressed patients with MCI exhibited heterogeneously elevated ^{18}F-florbetapir retention as compared with depressed patients without MCI. The higher amyloid burden in the aMCI patients suggests that these patients may also be more likely to develop Alzheimer's disease than other patients diagnosed with major depression.

Keywords Major depressive disorder · Amyloid · ^{18}F-Florbetapir (AV-45/Amyvid) · Alzheimer's disease · Dementia · Mild cognitive impairment

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Introduction

Converging evidence from meta-analyses [1–3] suggests that a history of depression approximately doubles an individual's risk of developing dementia later in life. Mild cognitive impairment (MCI) is considered a transitional stage between normal aging and dementia. Different subtypes of MCI have been proposed based on clinical consensus [4]: amnestic MCI (aMCI) is defined as the presence of significant memory impairment, while non-amnestic MCI (naMCI) is defined as impairment in cognitive domains other than memory. The prevalence of MCI in elderly depressed patients is approximately 50 %, which is substantially higher than the reported 3 % to 19 % prevalence of MCI in individuals who are not depressed [5–8]. Therefore, late-life depression, MCI, and dementia may represent a clinical continuum.

Beta-amyloid (Aβ) deposition in the brain is one of the hallmarks of pathological changes and is implicated in the pathogenesis of Alzheimer's disease (AD). One post-mortem study in patients with AD [9] has shown that amyloid plaque is more pronounced in patients who have a life-time history of major depression as compared with patients without a history of depression. This implies an underlying relationship between depressive syndromes and incipient AD dementia in later life. Recent advances in noninvasive PET imaging of amyloid [10–12] that permit direct assessment of the brain AD pathology in vivo have shown promise in terms of detecting groups of individuals at risk of AD. At present, a limited number of studies have used amyloid PET to examine the brain Aβ burden in patients with major depressive disorder (MDD) [13–16], although late-life depression is known to be related to cognitive impairment, and a large proportion of elderly MDD patients meet the criteria for MCI. Butters et al. [13] and Wu et al. [15] have found that depressed patients without dementia have a heterogeneously elevated Aβ radiotracer retention as compared with healthy controls. However, Madsen et al., [14] did not find this difference among depressed individuals. Only one of these studies [13] compared the Aβ deposition in depressed patients with different subtypes of MCI. That study showed a variably elevated ^{11}C-Pittsburgh compound B (PIB) retention across all MCI subtypes, but the number of patients was small (two without MCI, three with naMCI and three with aMCI). Besides, consensus regarding the relationship between Aβ burden and cognition in clinically nondepressed normal older individuals has not been reached, as a number of studies have yielded variable results [17–20]. Therefore, among patients with late-life depression, the differences in AD pathology in patients with different MCI subtypes remain largely unclear, and the relationship between Aβ burden and cognition in MDD is also not well understood.

^{18}F-Florbetapir (AV-45/Amyvid) is a novel PET tracer for selective imaging of Aβ pathology in the brain. Recent studies have demonstrated that ^{18}F-florbetapir PET can differentiate patients with AD, and even those with MCI, from cognitively normal older adults [10]. We hypothesized that the degree of Aβ deposition in depressed patients with different subtypes of MCI is variable. In the current study we used ^{18}F-florbetapir PET to investigate (1) brain Aβ deposition in MDD patients without dementia with different MCI subtypes, and (2) the relationship between Aβ burden and cognitive performance to determine whether amyloid deposition plays a role in cognitive dysfunction in MDD patients without dementia.

Materials and methods

Subjects and protocol

The study included 55 MDD patients without dementia and 21 healthy controls (HCs). The MDD patients were recruited consecutively from among geriatric psychiatric outpatients at Chang Gung Memorial Hospital (CGMH). All enrolled subjects were aged >50 years. Patients were diagnosed with MDD according to the DSM-IV criteria, and were required to have a clinical dementia rating score of 0 or 0.5 and to be functioning well in activities of daily living. Subjects were excluded if they had clinically significant medical diseases or neurological diseases, or had abused alcohol or other substances within the past year. Patients with a history of psychotic depression or at risk of suicide were also excluded from the study. None of the participants met the NINCDS-ADRDA criteria for probable AD or the DSM-IV criteria for dementia. All subjects were evaluated by the same board-certified geriatric psychiatrist to examine their clinical characteristics. The depressed patients were evaluated in terms of the life-time presence and course of DSM-IV major depressive episodes, and the nondepressed HC subjects were confirmed to have a life-time absence of psychiatric illness. Diagnosis and a life-time history of MDD were also verified from the available medical information, including charts and information obtained from the treating physician. The life-time MDD course, including MDD onset age, number of major depressive episodes, late-onset MDD (cut-off age 60 years) and time since the first MDD, was recorded for further analysis. All eligible subjects were administered a comprehensive battery of neuropsychological tests and underwent ^{18}F-florbetapir PET imaging.

The apolipoprotein-E (ApoE) genotype, serum homocysteine level and vascular risk factors as defined by the Framingham stroke risk score (FSRS) were determined. The ApoE genotype was determined by PCR (polymerase chain reaction) amplification of genomic DNA. At the time of the imaging study, 52 patients (94.5 %) were taking antidepressants and other psychiatric medications. Serotonin norepinephrine reuptake inhibitors were the most frequently used

drugs (52.7 %), followed by selective serotonin reuptake inhibitors (20.0 %), mirtazapine (18.2 %) and bupropion (14.5 %). Nine patients (16.4 %) were receiving two antidepressants combined, and 25 patients (45.5 %) were receiving low-dose antipsychotics. Quetiapine was the most frequently used antipsychotic (23.6 %), followed by sulpiride (10.9 %), olanzapine (7.3 %) and aripiprazole (3.6 %). The protocol was approved by the institutional review board of CGMH. Written informed consent was obtained for all subjects.

Neuropsychological assessments and subtypes of MCI among MDD patients

To include patients with varying levels of cognitive function and to exclude patients potentially with dementia, we used three cut-off values of the Mini Mental Status Examination (MMSE) for different educational levels based on previous MMSE studies in Taiwan [21, 22], i.e. less than 16 for illiterate subjects, less than 21 for grade-school literate subjects, and less than 24 for junior-high-school and higher education literate subjects. These cut-off values have a validated sensitivity of 100 % for dementia [22].

All eligible subjects were scored in a total of six domains of cognitive function assessment: information processing speed, executive function, memory, language, visuospatial function, and attention. The tests used to assess information processing speed were the Wechsler Adult Intelligence Scale – third edition (WAIS-III) digit symbol test [23] and the Trail-making A test [24]; those used for executive function were the Controlled Oral Word Association (COWA) test [25], the Frontal Assessment Battery (FAB) test [26], the Trail-making B test [27], and the WAIS-III similarity test [23]; those used for memory were the 12-item, six-trial selective reminding test (SRT) [28], the total number of words learned in six trials, and delayed recall following a 15-minute delay; that used for language was the WAIS-III language test [23]; that used for visuospatial function was the Visual Discrimination Test (VDT) [29]; and that used for attention was the WAIS-III digit span test [23].

The original score value of each neuropsychological test was transformed into a standardized z score, which was generated using regression-based norms and adjusted for age and educational level. For cognitive domains examined using more than one test, a composite score was calculated by taking the average of the z scores for each neuropsychological test within the same domain. Details of the methods used in this study have been described elsewhere [15].

According to the consensus in previous studies [4, 30], we defined the subtypes of MCI based on the demographically-corrected z scores of each cognitive domain. Amnestic MCI (aMCI) was diagnosed if the memory z score was ≤1.5, while naMCI was diagnosed if there was impairment in cognitive domains other than memory with a z score ≤1.5. Therefore, we subdivided the MDD patients into three groups: MDD without MCI, MDD with naMCI, and MDD with aMCI.

Amyloid PET acquisition

The radiosynthesis of ^{18}F-florbetapir [31] and acquisition of amyloid PET data [32] have been described previously by our group. Briefly, each subject underwent a ^{18}F-florbetapir PET scan using a Biograph mCT PET/CT system (Siemens Medical Solutions, Malvern, PA) in a three-dimensional acquisition mode. A 10-min PET scan was acquired starting approximately 50 min after injection of 378 ± 18 MBq of ^{18}F-florbetapir. All PET images were reconstructed using the 3-D OSEM algorithm (four iterations, 24 subsets; Gaussian filter 2 mm, zoom 3) with CT-based attenuation correction, and scatter and random corrections. The reconstructed images had a matrix size of 400 × 400 × 148 and a voxel size of 0.68 × 0.68 × 1.5 mm.

Image analysis

All image data were processed and analysed using PMOD image analysis software (version 3.3; PMOD Technologies Ltd, Zurich, Switzerland). Each PET image was coregistered to the corresponding T1-weighted MR image, and the individual T1-weighted MR images were spatially normalized to the Montreal Neurological Institute (MNI) MRI template. The resulting transformed parameters from spatial normalization were then applied to the MRI-matched PET images. A total of eight volumes of interest (VOIs), including the whole cerebellum, frontal, anterior cingulate, posterior cingulate, precuneus, parietal, occipital, and temporal areas, were selected based on the modified automated anatomic labelling (AAL) atlas (full details of the VOI definition are provided in the Supplementary material) [33, 34]. The whole cerebellum was used as the reference region for calculating the standardized uptake value ratios (SUVR) to obtain the final spatially normalized PET SUVR image for each subject. The average SUVR from seven cerebral cortical VOIs was computed as the global cortical SUVR for further analysis.

Voxel-wise analysis

Voxel-wise analysis was performed using SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) in Matlab 2010a (MathWorks Inc., Natick, MA). Spatially normalized SUVR images of ^{18}F-florbetapir were smoothed using an isotropic Gaussian kernel of 8 mm FWHM. Note that the SUVR images for voxel analysis are same as those normalized by the mean value of the whole cerebellum as in previous VOI quantitation. Voxel-wise two-sample t tests were used to compare the HCs and the three

MDD subgroups using the amyloid SUVR images. SPM t-maps were examined using an uncorrected threshold of $P<0.005$ and an extent threshold of 100 voxels.

Statistical analysis

Data are expressed as means ± SD or as absolute numbers with proportion for descriptive statistics. The regional SUVRs of the ^{18}F-florbetapir PET images were compared using the non-parametric Kruskal-Wallis test with Dunn's multiple comparison post-hoc analysis for group comparisons among the HCs, and the MDD patients without MCI, with naMCI and with aMCI. Pearson's correlation was used to evaluate the correlations between the global ^{18}F-florbetapir SUVR and each parameter of the clinical characteristics (MMSE, six cognitive domains, age at onset of MDD, number of major depressive episodes, time since onset of MDD, and late-onset MDD) in the MDD patients and all subjects (including the HCs). Multiple linear regression analysis was used to further evaluate the associations between ^{18}F-florbetapir binding and cognitive function in MDD patients after controlling for age, educational level, ApoE ε4 genotype, and Hamilton depression rating (HAM-D) score. A P value of 0.05 was taken as the threshold for statistical significance in each test.

Results

Subtypes of MCI and clinical characteristics of each group

Among the 55 MDD patients, 22 (40.0 %) met the definition of MCI, and of these 12 (21.8 %) were classified as having naMCI and 10 (18.2 %) aMCI. Table 1 shows the demographic and clinical characteristics of each group. The groups did not differ significantly in terms of age, sex, MMSE score, frequency of ApoE ε4 genotype, serum homocysteine level or vascular risk factors. However, the MDD patients with naMCI had a lower educational level than the HCs, and had experienced more major depressive episodes than the MDD patients without MCI. In terms of cognition, there were significant differences among the groups for all cognitive domains (Table 1). The MDD patients without MCI had significantly poorer scores for executive function and information-processing speed than the HCs. The MDD patients with naMCI showed poorer functioning in the domains of executive function, information processing speed and language than the MDD patients without MCI. As expected, the aMCI group showed the poorest memory function among all the groups.

Beta-amyloid burden

Average ^{18}F-florbetapir SUVR images are shown in Fig. 1. The MDD patients with aMCI had higher ^{18}F-florbetapir SUVR in all regions. Comparing the four groups, Table 2 shows significant differences in ^{18}F-florbetapir SUVR in the parietal cortex ($P=0.003$), and trends in the occipital ($P=0.077$), precuneus ($P=0.081$) and posterior cingulate regions ($P=0.066$). The post-hoc analysis showed significant differences in ^{18}F-florbetapir SUVR in the parietal region between the MDD patients with aMCI and the HCs ($P<0.01$). Significant differences were also seen between the MDD patients with aMCI and those with naMCI ($P<0.05$). The mean values of SUVR within each region in the MDD patients and the HCs are plotted in Fig. 2.

The SPM analysis showed that the MDD patients with aMCI had the highest amyloid burden among all groups, those with naMCI had a moderate burden, and there was no difference in amyloid burden between the MDD patients without MCI and the HCs (Fig. 3). With a stringent threshold of $P<0.005$ (uncorrected, $T=2.76$, minimum cluster size 100 voxels), the MDD patients with aMCI had significantly higher ^{18}F-florbetapir binding of various degrees than the HCs in the frontal, parietal, temporal and occipital areas. The MDD patients with naMCI had significantly higher ^{18}F-florbetapir binding than the HCs in the frontal, parietal and occipital areas. The most prominent differences in ^{18}F-florbetapir SUVR were observed in the bilateral precuneus and middle temporal cortex between the MDD patients with aMCI and the HCs.

Beta-amyloid burden and cognition in MDD

To assess the relationship between Aβ burden and cognitive performance, we first calculated the correlations between the global cortical SUVR and MMSE score, as well as each neuropsychological test score across the whole group of MDD patients. The global cortical SUVR was negatively correlated with MMSE score ($r=-0.342$, $P=0.010$). For each cognitive domain, only the memory score ($r=-0.328$, $P=0.015$) was significantly negatively correlated with the global cortical SUVR (Fig. 4). The global SUVR was significantly negatively correlated with memory only when all subjects (MDD and HCs) were included ($r=-0.373$, $P=0.001$), but not in the MDD patients when the aMCI patients were excluded ($r=0.126$, $P=0.411$). As age, educational level, ApoE ε4 status and depression severity are also known to have effects on cognitive performance, we further conducted a series of multiple linear regression analyses to examine the association between amyloid deposition and memory function in the MDD patients. After controlling for age, educational level, ApoE ε4 genotype and HAM-D score, the Aβ burden remained significantly and negatively correlated with memory ($\beta=-3.607$, $t=-2.874$, $P=0.006$).

The global SUVR was not significantly correlated with serum homocysteine level ($r=0.118$, $P=0.311$), vascular risk factors measured by the FSRS ($r=0.068$, $P=0.558$),

Table 1 Demographic and clinical characteristics of the healthy controls (HC) and patients with major depressive disorder (MDD) and different subtypes of MCI

Characteristic	HC	MDD			*P* value
		Without MCI	With naMCI	With aMCI	
No. of patients	21	33	12	10	
Age (years), mean ± SD	66.5 ± 7.1	65.9 ± 6.5	67.3 ± 5.7	66.9 ± 5.9	0.9321
Gender (M/F), *n*	9/12	10/23	0/12	4/6	0.0783
Education (years), mean ± SD	11.0 ± 4.1	8.4 ± 4.5	5.9 ± 3.9**[a]	7.9 ± 3.5	0.0080
Age at onset (years), mean ± SD	–	55.0 ± 13.0	58.8 ± 7.7	56.9 ± 9.8	0.6380
Duration (years), mean ± SD	–	10.9 ± 11.2	8.6 ± 4.0	10.5 ± 7.2	0.6935
Late-onset MDD, *n* (%)	–	15 (45.5)	5 (41.7)	3 (30.0)	0.6908
Episodes, mean ± SD	–	1.7 ± 0.9	2.6 ± 1.3	2.1 ± 1.3	0.0375
Homocysteine (μmol/l), mean ± SD	8.9 ± 2.1	9.3 ± 2.7	8.8 ± 1.6	9.0 ± 2.6	0.8874
ApoE ε4 carrier, *n* (%)	4 (19.0)	6 (18.2)	1 (8.3)	3 (30.0)	0.6394
FSRS, mean ± SD	7.3 ± 3.1	9.1 ± 4.6	7.8 ± 2.8	9.7 ± 4.5	0.2715
HAM-D score, mean ± SD	2.0 ± 1.5	7.3 ± 6.7***[a]	7.3 ± 3.8***[a]	9.4 ± 5.6***[a]	<0.0001
MMSE score, mean ± SD	27.5 ± 1.8	25.6 ± 2.4*[a]	23.8 ± 2.9***[a]	22.8 ± 3.0***[a]	<0.0001
Cognitive domain scores, mean ± SD					
Executive function	0.7 ± 0.5	0.1 ± 0.6**[a]	−0.8 ± 0.8***[a],*[b]	−0.7 ± 0.8***[a]	<0.0001
Memory	0.4 ± 0.6	−0.1 ± 0.8	−0.6 ± 0.6*[a]	−2.3 ± 0.6***[a],***[b]	<0.0001
Processing speed	0.7 ± 1.0	−0.4 ± 0.7**[a]	−1.6 ± 0.6***[a],**[b]	−0.7 ± 1.0**[a]	<0.0001
Language	1.8 ± 0.7	1.3 ± 0.8	0.4 ± 0.8***[a],*[b]	1.0 ± 0.9*[a]	0.0003
Visuospatial function	0.6 ± 0.7	0.2 ± 0.8	−0.8 ± 1.4*[a]	−0.2 ± 1.4	0.0115
Attention	0.7 ± 0.9	0.5 ± 0.9	−0.2 ± 1.2	−0.2 ± 0.7*[a]	0.0112

HAM-D 17-item Hamilton depression rating Scale, *FSRS* Framingham stroke risk score, *MCI* mild cognitive impairment, *naMCI* non-amnestic mild cognitive impairment, *aMCI* amnestic mild cognitive impairment

[a] Significant difference compared with HC: *$P<0.05$, **$P<0.01$, ***$P<0.001$

[b] Significant difference as compared with MDD patients without MCI: *$P<0.05$, **$P<0.01$, ***$P<0.001$

age at onset of depression ($r=0.154$, $P=0.266$), number of major depressive episodes ($r=-0.113$, $P=0.418$), time since onset of depression ($r=-0.157$, $P=0.256$), or late-onset major depression ($r=-0.043$, $P=0.753$). Further analysis also indicated that regional ^{18}F-florbetapir SUVRs were not significantly correlated with serum homocysteine, FSRS or the clinical characteristics of depression (data not shown).

Discussion

We first classified the MDD patients according to MCI subtype. The rate of MCI was 40 % in our study, which was lower than the 52.3 % found in a previous study in Taiwan [6]. Meanwhile, the rate was also much lower than the 61 % for any cognitive deficit at the acute stage found by Butters et al. [5]. This may be explained in part by the somewhat different

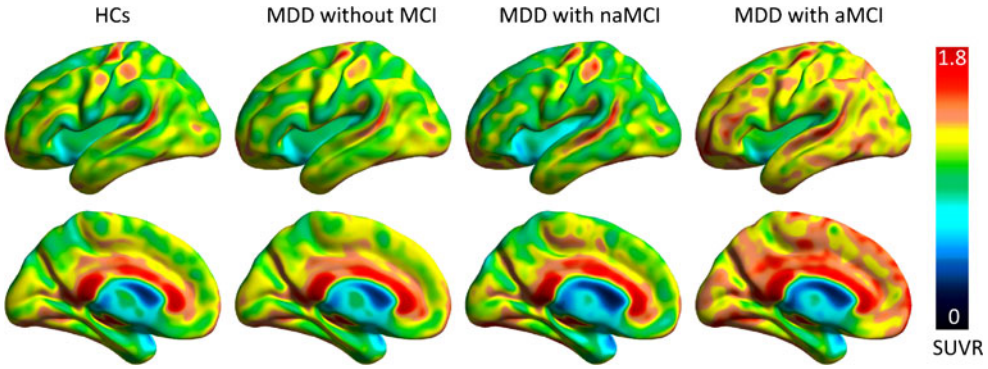

Fig. 1 Average ^{18}F-florbetapir SUVR images among the healthy controls (HCs) and the MDD patients with different subtypes of MCI (*naMCI* non-amnestic MCI, *aMCI* amnestic MCI)

Table 2 ^{18}F-florbetapir SUVRs in healthy controls (HC) and patients with major depressive disorder (MDD) and different subtypes of MCI in seven cortical VOIs and the global cortex

Region	HC	MDD			*P* value
		Without MCI	With naMCI	With aMCI	
Frontal	1.08 ± 0.09	1.10 ± 0.06	1.10 ± 0.09	1.25 ± 0.23	0.3115
Parietal	1.03 ± 0.08	1.08 ± 0.09	1.03 ± 0.08	1.23 ± 0.21*,**	0.0032
Temporal	1.02 ± 0.06	1.02 ± 0.06	1.02 ± 0.06	1.12 ± 0.16	0.3902
Occipital	1.15 ± 0.08	1.18 ± 0.08	1.19 ± 0.08	1.28 ± 0.18	0.0767
Anterior cingulate	1.20 ± 0.11	1.21 ± 0.10	1.24 ± 0.10	1.29 ± 0.22	0.3448
Posterior cingulate	1.32 ± 0.11	1.31 ± 0.13	1.34 ± 0.10	1.48 ± 0.18	0.0662
Precuneus	1.03 ± 0.07	1.06 ± 0.08	1.05 ± 0.09	1.22 ± 0.25	0.0807
Global	1.12 ± 0.07	1.14 ± 0.06	1.15 ± 0.07	1.28 ± 0.20	0.1496

naMCI non-amnestic mild cognitive impairment, *aMCI* amnestic mild cognitive impairment

*$P < 0.01$ vs. HC, **$P < 0.01$ vs. MDD patients with naMCI

populations, particularly in terms of the inclusion of younger subjects and subjects with a higher educational level in the present study. Omitting the five MDD patients without MCI aged under 60 years, the rate of MCI increased to 44 % (22/50), which was closer to the rate found in the previous study in Taiwan. Despite differences in methodology and the definition of cognitive impairment, several previous studies have found that approximately 50 % of depressed elderly patients meet the criteria for the diagnosis of MCI [8, 35, 36], This rate is far higher than the prevalence of MCI reported in the general population, which ranges from 3 % to 19 % [37]. This implies that depressed elderly people very often have MCI regardless of remission of depression.

In this study MDD patients, both those with naMCI and those with aMCI, showed cognitive dysfunction in all domains. However, the information processing speed and executive function in the MDD patients, even those without MCI, were significantly poorer than in HCs. This finding is in accordance with those of previous studies [5, 38] demonstrating that slowing of information processing might mediate other cognitive deficits in late-life depression during the acute depressive stage. However, cognitive impairment persists even after acute depression has subsided, which implies the possibility of a neurobiological mechanism being involved in the association between depression and dementia [38, 39].

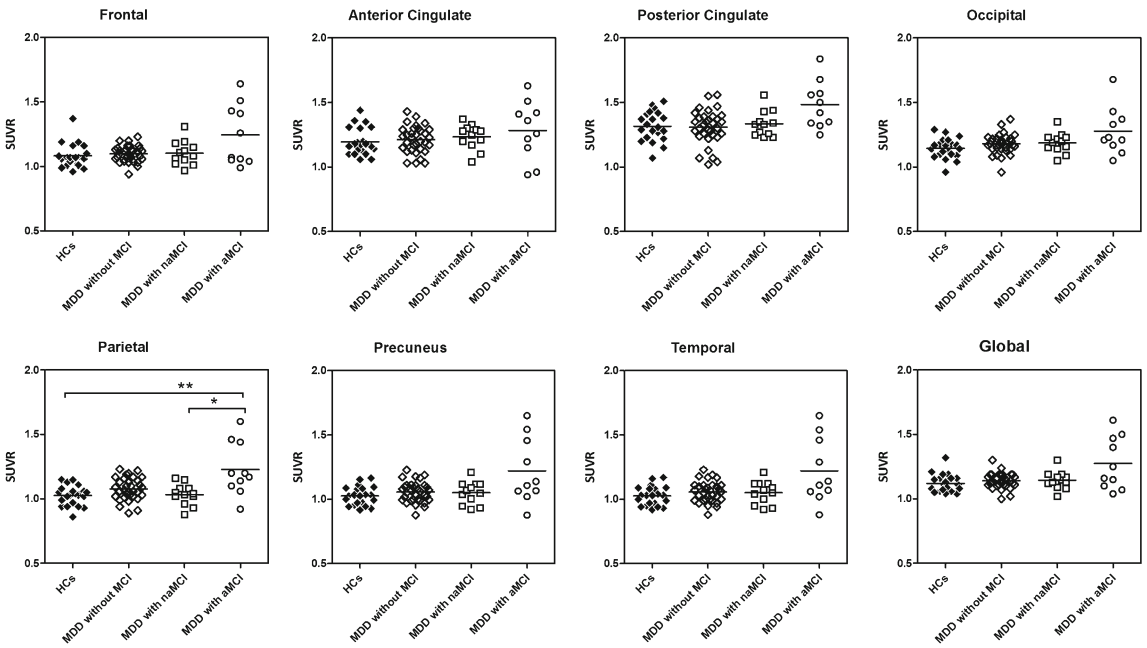

Fig. 2 Regional SUVR values of ^{18}F-florbetapir in healthy controls (HCs) and the MDD patients with different subtypes of MCI in seven cortical VOIs and the global cortex (*naMCI* non-amnestic mild cognitive impairment, *aMCI* amnestic mild cognitive impairment). *$P < 0.01$, **$P < 0.01$

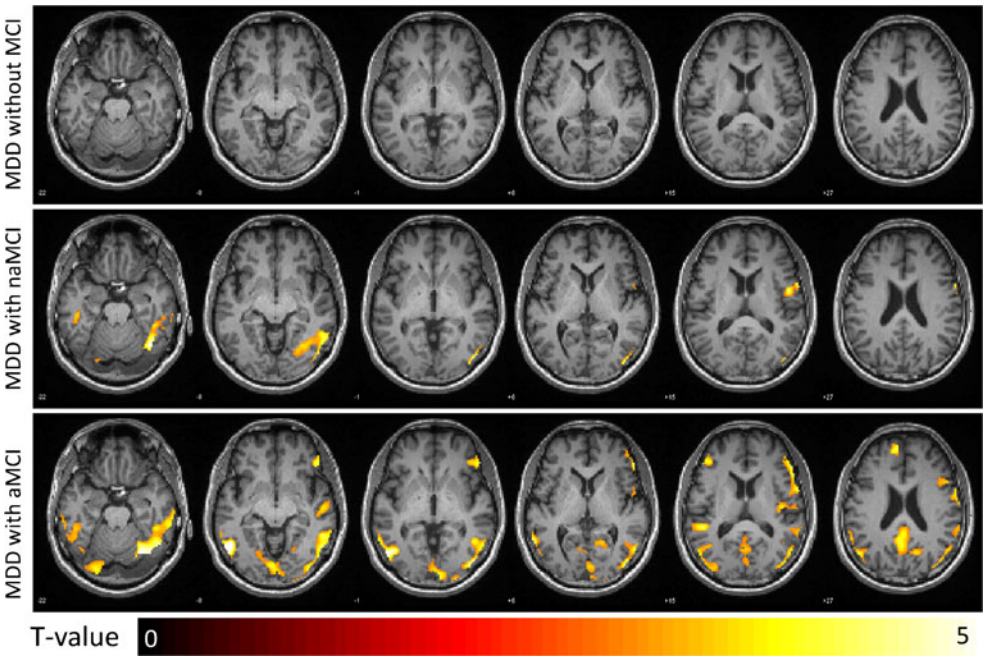

Fig. 3 Spatial distribution of increased ^{18}F-florbetapir SUVR in the MDD patients with different subtypes of MCI as compared with the healthy controls (HCs) as examined by SPM analysis, with an uncorrected $P < 0.005$ and clusters consisting of a minimum of 100 contiguous voxels, which were considered to indicate a significant difference (*naMCI* non-amnestic mild cognitive impairment, *aMCI* amnestic mild cognitive impairment)

In our previous study [15] patients without dementia with life-time major depression had regionally higher ^{18}F-florbetapir SUVRs in the parietal and precuneus cortex areas, but there was no difference in the global cortical ^{18}F-florbetapir SUVR between the depressed patients and the comparison subjects. In the present study, we further found that the MDD patients with aMCI carried a greater Aβ burden in comparison with the depressed patients with other subtypes of MCI. An initial pilot study using ^{18}F-PIB in elderly patients with treated major depression [13] recruited nine patients, and eight completed amyloid imaging (two no MCI, three naMCI, three aMCI). The regions with amyloid retention in the depressed patients were highly variable in the frontal, temporal, parietal and precuneus areas. Another study [14] showed that depressed patients did not have increased levels of ^{18}F-PIB binding as compared with healthy subjects, neither globally nor in the subregions. In the present study in MDD patients with differing MCI status, the most prominent ^{18}F-florbetapir SUVR was found in the bilateral precuneus and middle temporal cortex in those with aMCI. The regional patterns of cortical ^{18}F-florbetapir SUVR found in the present study would be expected to be associated with high amyloid deposition in patients with early AD [40, 41]. The regional patterns in the depressed patients with aMCI also closely corresponds with stage B according to the amyloid deposition category of Braak and Braak, which recognizes three stages (A, B, C) in the gradual evolution of cortical amyloid deposition [42, 43]. Taken together, these characteristics suggest that MDD with aMCI may represent preclinical AD and thus is indicative of early AD.

In this study, the Aβ burden, measured in vivo by ^{18}F-florbetapir PET imaging, was only related to memory

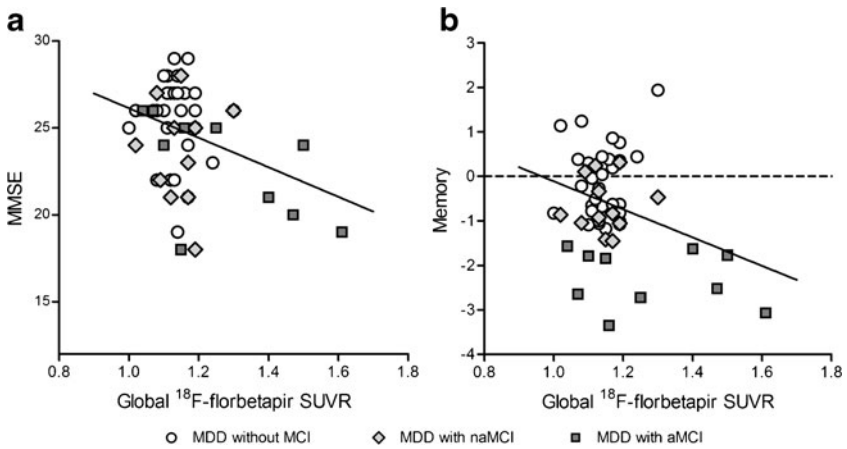

Fig. 4 Relationship between the global cortical ^{18}F-florbetapir SUVR and (**a**) MMSE score ($r = -0.34$, $P = 0.01$), and (**b**) memory z score ($r = -0.32$, $P = 0.019$) in the MDD patients

dysfunction. Previous studies have shown that non-memory cognitive functions have either a weak or even no relationship with Aβ deposition [17, 44]. Our results are consistent with previous findings. To reduce the potential interference, we further conducted multiple regression analyses, and the results remained significant when controlling for the effects of age, educational level, depression and ApoE ε4 status. Although the relationship between amyloid burden and memory dysfunction was modest, our findings in MDD patients suggest that the presence of occult Aβ deposition is associated with reduced memory performance. Our findings could be placed in the context of the growing body of literature regarding the relationship between amyloid burden and cognition in clinically normal older individuals and those with MCI. Some studies have shown no relationship between Aβ deposition, as estimated by PET imaging, and cognitive performance [45, 46], whereas several others have shown significant inverse correlations between amyloid burden and baseline memory performance, as well as a longitudinal decline in cognition [17, 20, 47, 48].

The relationship between amyloid and memory in MDD patients in this study was based mainly on the results in the aMCI group. Not surprisingly, patients with late-life depression are an aetiologically heterogeneous group (i.e. different ages at illness onset, different numbers of acute relapses, and different medical comorbidities, etc.). These various presentations probably reflect the differential involvement of factors or mechanisms bringing about a change in cognition, such as the presence of other non-AD pathologies (vascular burden or neurofibrillary tangles) in addition to Aβ burden, particularly in elderly depressed patients with naMCI and without MCI. Besides, a recent study by Chung et al. [49] found that patients with aMCI and life-time MDD have a significantly higher Aβ deposition in the bilateral frontal lobes than patients with aMCI without life-time MDD. This finding suggests differential features of Aβ deposition for depressive symptomology in aMCI patients. Potential relationships between amyloid accumulation and cognitive functions in major depression need to be assessed with larger sample sizes where more specific relationships between Aβ burden and specific cognitive domains could be assessed.

This study had several limitations. First, the sample sizes, particularly the number of subjects with aMCI and naMCI, were relatively small, which would have influenced the statistical power. The depressed patients with MCI could not be further subdivided into a single domain or multiple domains of cognitive deficit. Another limitation was possible selection bias. However, the ranges of global ^{18}F-florbetapir SUVR values among the HCs and non-MCI subjects in this study were comparable to those among cognitively healthy controls in previous ^{18}F-florbetapir PET studies [41, 50]. Third, in this study, the depressed patients had received various antidepressant and other psychotropic treatments over their life-time before they were recruited into this cross-sectional imaging study. Detailed information on life-time medications was unavailable. Therefore, we were unable to precisely estimate the life-time dosages of all psychotropic medications they received and the cumulative effects on brain amyloid accumulation. The potential effects of antidepressant treatment on Aβ burden and regional distribution are unknown. Future studies should be carefully designed to assess the effects of medications on amyloid binding through longitudinal follow-up. Fourth, there was no association between the cortical SUVR and the clinical characteristics of depression so no evidence was provided suggesting that life-time depression is associated with the risk of amyloid pathology. However, potential recall bias regarding life-time MDD history could not be ruled out, because most patients were able to recall their clinical course over recent years. Fifth, although we divided the MDD patients into groups with different subtypes of MCI based on the currently-published consensus, the cut-off value was arbitrary. Some depressed patients without MCI had cognitive domain scores close to the threshold limit values, which might have influenced the group comparisons. Finally, most PET tracers for amyloid detection bind mainly to fibrillar forms of Aβ, but laboratory data suggest that oligomeric forms may be more toxic to neurons [51]. In other words, memory impairment may be more related to the presence of soluble Aβ oligomers, which might not be detected accurately by current amyloid PET imaging techniques [52]. Nevertheless, fibrillar forms of Aβ are thought to be in equilibrium with oligomeric forms, and they can still serve as a proxy for the presence of other soluble oligomers [53].

The pathophysiological process in AD is believed to begin many years before the diagnosis of dementia. The long preclinical phase of AD provides a critical opportunity to modify the disease process. It is important, therefore, to further elucidate the underlying mechanism(s) and causal relationship linking depression and dementia. Long-term studies with large sample sizes and repeated follow-up amyloid imaging studies in elderly depressed patients without dementia are required to identify the emergence of key pathological events in the transition from depression to MCI and AD.

Conclusion

We observed a high prevalence of MCI among elderly depressed patients, as found in prior studies. We found that MDD patients with aMCI and naMCI have heterogeneously elevated ^{18}F-florbetapir retention as compared with HCs, while depressed patients without MCI do not show such a difference. In addition, the higher amyloid burden in the aMCI patients suggests that these patients may also be more likely to develop AD than other patients

diagnosed with major depression. Longitudinal follow-up of the present and other cohorts is warranted in order to determine whether these MDD patients will demonstrate cognitive decline towards dementia.

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Compliance with ethical standards

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Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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