Lifetime History of Depression Predicts Increased Amyloid-β Accumulation in Patients with Mild Cognitive Impairment

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Abstract. Mounting evidence associates a lifetime history of major depression (LMD) with an increased risk for Alzheimer's disease (AD). Studies have shown that major depression (MD) is strongly linked to pathophysiological markers of AD, such as cortical amyloid-β (Aβ) burden. However, no imaging studies have shown *in vivo* whether an LMD is linked to increased Aβ accumulation in patients with mild cognitive impairment (MCI) in four cortical regions that have been highly associated with increased Aβ deposition in previous literature: frontal, cingulate, parietal, and temporal. Drawing from the ADNI database, we found that patients with amnestic MCI (aMCI) and an LMD ($n = 39$) had significantly higher ^{18}F-Florbetapir standardized uptake value ratios, a surrogate measure of Aβ deposition, mainly in the bilateral frontal cortex, compared to patients with aMCI without an LMD ($n = 39$) ($p = 0.02$). This difference was not explained by current depressive symptoms, vascular risk factors, or the use of different PET scanners. The results were reliable employing two independent methods for analysis: region-of-interest and voxel-based analyses. Increased Aβ in the bilateral frontal lobes may be a biomarker of depressive symptomology in aMCI patients. Further studies should test whether higher Aβ predicts future conversion into AD in this population.

Keywords: Alzheimer's disease, amyloid-β, major depression, mild cognitive impairment, positron emission tomography

INTRODUCTION

Several studies link a lifetime history of major depression (LMD) with an increased risk of developing late-onset Alzheimer's disease (AD) [1–4]. Two meta-analyses report that major depression (MD) can almost double the risk of developing dementia [5, 6]. Moreover, a single episode of late-life depression is found to elevate the risk of AD by 4- to 6-fold [7]. Reynolds et al. reported that MCI patients with late-life depression who were on donepezil, which is a treatment for AD, showed decreased conversion rate to dementia, in comparison to those who were on placebo [8].

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Depression is a potentially modifiable risk factor for AD and projections indicate that successful interventions targeting late-life depression might reduce the prevalence of AD by up to 10.6% globally [9].

Mild cognitive impairment (MCI) is thought to be a transitional risk state between normal aging and AD [10]. The conversion rate from MCI to AD varies from as low as 10% to as high as 100%, depending on the follow-up period and controversially, the amnestic, as opposed to the non-amnestic type of MCI [11–13]. Additionally, among patients with MCI, depression is one of the most prevalent neuropsychiatric symptoms with a prevalence rate of up to 20% [14]. Patients with MCI and depressive symptoms are more likely to convert to AD than those without depression [15, 16]. This is supported by an autopsy study, which reported that patients with AD and MD had more hippocampal plaques and neurofibrillary tangles than AD patients without MD [17]. This result suggests that depression adds to the amyloid burden above and beyond the AD itself.

Through the use of positron emission tomography (PET) radiotracers, such as ^{18}F-2-(1-[16]-ethylidene) malononitrile (FDDNP), ^{11}C-Pittsburgh Compound B (PIB), and ^{18}F-Florbetapir (AV-45), it is possible to estimate amyloid-β (Aβ) deposition *in vivo* [18, 19]. A recent study using AV-45 revealed that Aβ accumulation is increased in frontal, temporal, and parietal regions of depressed patients, in comparison to non-depressed patients [20]. Another study reported that current depression scores in patients with MCI are associated with increased lateral temporal FDDNP binding [21]. In addition to frontal, parietal, and temporal regions, the cingulate region has been linked to increased Aβ accumulation [22]. Taken together, current evidence supports the notion that the cortical Aβ burden may be higher in depressed MCI patients within frontal, cingulate, parietal, and temporal regions.

However, to date, no previous PET study has directly tested whether an LMD is linked to Aβ accumulation in these aforementioned regions. Using data from Alzheimer's Disease Neuroimaging Initiative (ADNI) databases [23], we compared the AV-45 standardized uptake value ratio (SUVR) in these four region of interests (ROIs) between amnestic MCI patients with an LMD (aMCI+LMD) and amnestic MCI patients without an LMD (aMCI-LMD). Investigating these *a priori* regions, we hypothesized that the aMCI+LMD group would have higher AV-45 SUVR in frontal, cingulate, parietal, and temporal region in comparison to the aMCI-LMD group.

MATERIALS AND METHODS

Study patients and diagnosis

The entire dataset was downloaded from ADNI-1, ADNI-2, and ADNI Grand Opportunity (ADNI-GO) databases on 29 March 2014 [23]. The ROI-based AV-45 dataset that we used was updated as of 2 May 2014. Briefly, in ADNI-1, 800 participants, including controls, patients with aMCI, and patients with mild AD, were recruited from 50 different sites in Canada and the United States [24]. Each subject was either an English or Spanish speaker, aged between 55 and 90 years, and had a study partner able to provide an independent evaluation of functioning. The key eligibility criteria for aMCI participants were: a Mini–Mental State Examination (MMSE) score [25] of equal or higher than 24 of 30, a memory complaint, having objective memory loss measured by education adjusted scores on the Wechsler Memory Scale [26] Logical Memory II, a Clinical Dementia Rating (CDR) score [27] of 0.5, an absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living and an absence of dementia. In ADNI-2, 100 early-stage aMCI patients and 150 late-stage aMCI patients were recruited from 55 different sites from Canada and the United States [28]. In ADNI-GO, 200 participants, including patients with mild AD and early aMCI were recruited. Eligibility criteria in ADNI-2 and ADNI-GO were identical to those in ADNI [29]. Scores on the Functional activities questionnaire (FAQ) [30], Geriatric Depression Scale (GDS) [31] and Neuropsychiatric Inventory (NPI) [32], Modified Hachinski Ischemic scores [33], which assesses vascular dementia, history of cardiovascular disease (CVD), systolic blood pressure and current smoking status, were obtained from ADNI-1, ADNI-2, and ADNI-GO. For our current study, we only included patients with aMCI who had both a T1-weighted magnetic resonance imaging (MRI) scan and a AV-45 PET scan completed within a 6-month interval between each scan (68 patients completed within a month interval between each scan, 5 patients within a 2-month interval, 3 patients within a 3-month interval and 2 patients within a 6-month interval).

aMCI-LMD patients were matched to aMCI+LMD patients based on following conditions. Discrete factors such as gender, apolipoprotein E4 (apoE4) genotype, race, ethnicity, and marital status were matched between the two groups; continuous factors, including age, education years, and scores on MMSE, FAQ, and CDR were also matched. The exclusion

criteria included missing covariates, missing information about PET scans, ambiguous descriptions about depression, temporal gap between medical assessments and the scans. As a result, this study included 39 aMCI+LMD patients and 39 matched aMCI-LMD patients.

Lifetime history of major depression

The presence of an LMD was determined using patients' medical history from ADNI-1, ADNI-GO, and ADNI-2. Medical history was obtained by trained research assistants from aMCI patients, their caretakers or informants during ADNI screening and follow-up visits [34]. Using the keyword "depress†" in the medical history database, LMD was defined as having at least one major depressive episode prior to the PET scan. Patients who were actively depressed were also included. For this study, the definition of major depression excluded the following types of depression: mild depression, postpartum depression, situational or reactive depression, bipolar/depression type, and depression/anxiety type, as recorded in the ADNI medical history.

Cortical Aβ deposition

Data for AV-45 imaging were available from ADNI-2 and ADNI-GO. AV-45 data were acquired from PET scanners located at 59 different acquisition sites. The detailed information about the technical scan procedure is described online [35]. Each of the two ADNI initiatives reported ROI-based AV-45 SUVR. ROIs included bilateral frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices. ROI-based AV-45 SUVR was calculated by dividing the AV-45 mean from one of the ROIs into the AV-45 mean of a composite reference region (average of whole cerebellum, brainstems/pons, and eroded subcortical white matter). More details about the PET analysis are described online [36].

Scanning and imaging procedure

AV-45 was prepared by ADNI study coordinators, after referencing Avid Radiopharmaceuticals, Inc. Clinical Supplies Guidance Document for the necessary steps prior to radiotracer injection [37, 38]. With participants' informed consent, a 370 MBq (10 mCi ± 10%) bolus injection of AV-45 was administered. A continuous 20-min PET scan occurred 50-min post-injection and was reconstructed

in 4 frames of 5-min each. Scans were acquired from different PET scanners depending on the site ($n = 13$): Siemens/CTI, Model = HR+ ($n = 19$); Philips Medical Systems, Model = GEMINI TF series ($n = 14$); GE Medical System, Model = Discovery ST series ($n = 13$); CPS, Model = LSO PET/CT HI-REZ ($n = 2$); SIEMENS, Model = 1094 ($n = 6$); GE MEDICAL SYSTEMS, Model = Discovery LS series ($n = 8$); Philips Medical Systems, Model = Guardian Body(C) ($n = 4$); Philips Medical Systems, Model = Allegro Body(C) ($n = 3$); GEMS, Model = Advance ($n = 3$); SIEMENS, Model = Biograph64 ($n = 2$); Siemens/CTI, Model = ACCEL ($n = 2$); GE MEDICAL SYSTEMS, Model = Discovery 600 ($n = 1$); and SIEMENS, Model = SOMATOM Definition AS_mCT ($n = 1$). Each subject also had an MRI scan session, including a T1-weighted scan, which was employed for spatial normalization during voxel-based analysis. All patients' PET-AV-45 scans and last clinical assessment of their diagnostic status were completed approximately at the same time.

Positron emission tomography analysis

PET analysis was performed using Analyze 6.0 software and Statistical Parametric Mapping 2.0 (SPM2, http://www.fil.ion.ucl.ac.uk/spm/) running on Matlab 6.5. Using Analyze 6.0 software, an average PET scan was constructed using the four frames of PET-AV-45 scans for each subject. Consequently, each subject's T1-weighted MRI scan was coregistered to average PET images into native PET space. Next, the coregistered T1-weighted MRI scan and the average PET scan were normalized into Montreal Neurological Institute (MNI) space using the T1-weighted MRI template provided by SPM2 as the target. The MNI normalized average PET images of the radiotracer uptake were converted to SUVR images. The SUVR images were generated by dividing the average PET image into the mean radioactivity extracted from the cerebellar gray matter. The cerebellar grey matter radioactivity was defined using the Automated Anatomical Labeling template [39], avoiding cerebellar white matter. SUVR images were smoothed with a Gaussian filter in each coordinate direction with a kernel of 8-mm for the voxel-based analysis. The ROI analysis was performed using region-specific SUVRs from frontal, anterior/posterior cingulate, lateral parietal and lateral temporal cortices, as reported by the ADNI database (updated on 2 May 2014).

Statistical analysis

The demographic and clinical characteristics between aMCI+LMD and aMCI-LMD groups were compared by independent *t*-tests.

The ROI analysis was performed using univariate analyses of covariance (ANCOVA) to investigate whether differences existed in region-specific AV-45 SUVR between the two groups, controlling for potential confounds such as: GDS score at time of scanning; Modified Hachinski Ischemic score at the screening visit; current smoking status; NPI total score at time of scanning; medical history of CVD; apoE4 genotype; FAQ score at the time of scanning; systolic blood pressure at the time of scanning, and PET scanner models. Medical assessments and PET scans occurred within a maximum of a year interval between each other. Any participants with missing information regarding these covariates were excluded from the study (Fig. 1). The statistical tests were performed using Statistical Package for the Social Sciences Version 21.0 (IBM, New York, US). Based on our *a priori* hypotheses, the statistical significance was assumed at $p < 0.05$.
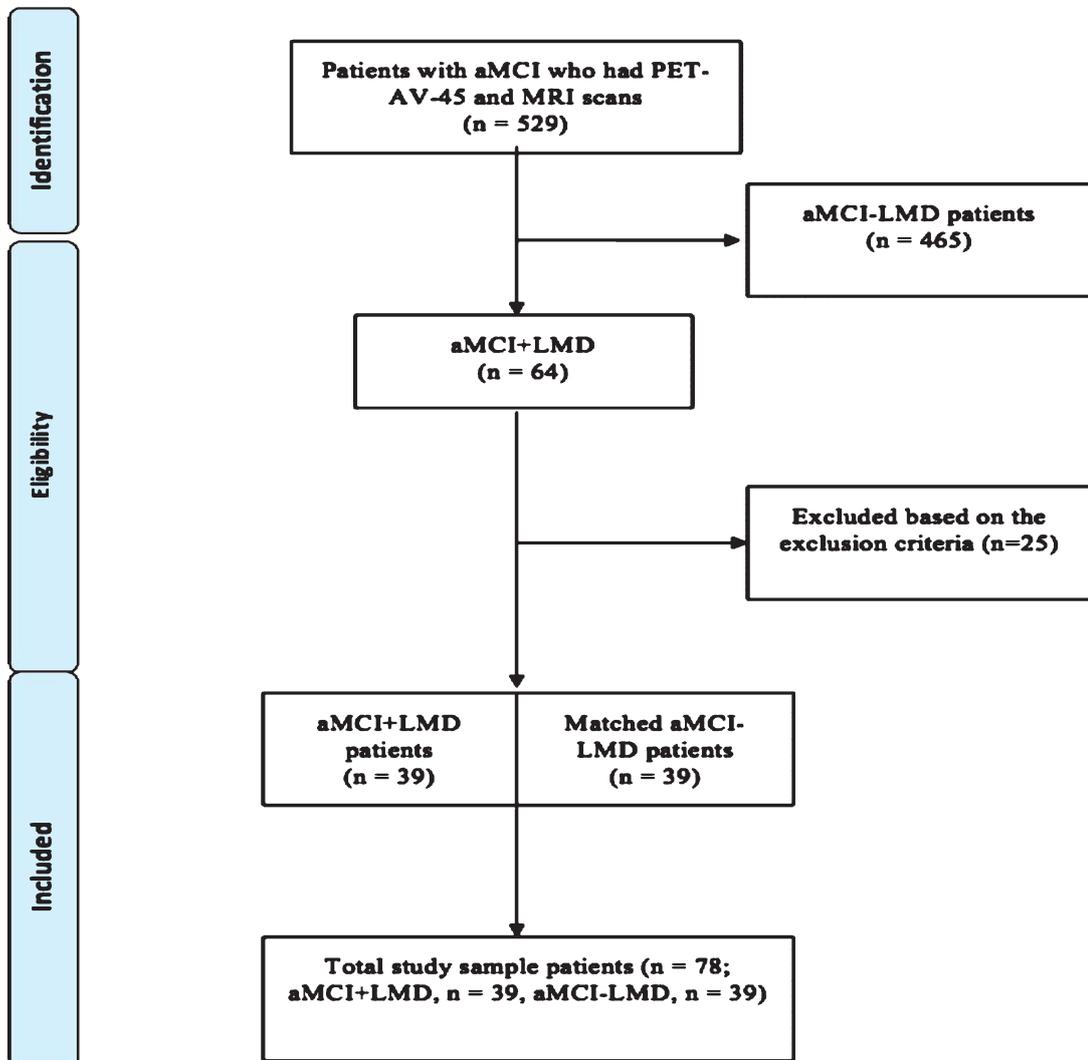
Fig. 1. Flow chart showing the selection of aMCI patients with a lifetime history of depression and aMCI patients without a lifetime history of depression from ADNI database. aMCI, amnestic mild cognitive impairment; aMCI+LMD, aMCI with a lifetime history of major depression; aMCI-LMD, aMCI without a lifetime history of major depression; AV-45, ^{18}F-Florbetapir; MRI, magnetic resonance imaging; PET, positron emission tomography.

Voxel-based PET analysis

Voxel-based analysis was performed using SPM2. A general linear model analysis for two-independent samples was performed to compare AV-45 SUVR images between aMCI+LMD and aMCI-LMD groups used in the ROI analysis. We reported areas only if they met the joint criteria of *p*-uncorrected <0.01 and an arbitrary cluster size of more than 12 voxels (~3.75 the isotropic kernel used for smoothing with a voxel size of 2 mm) in the *a priori* regions defined in the ADNI study: frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices. No *a priori* regions were considered significant if p-FDR corrected <0.05.

RESULTS

Demographic and clinical profile

Matching variables were similar in aMCI+LMD and aMCI-LMD groups including age, education years, MMSE score, CDR score, gender, apoE4 genotype, race, ethnicity, and marital status. Confounding factors, such as current GDS score, modified Hachinski Ischemic score, current smoking status, NPI total score, medical history of CVD, FAQ score, and systolic blood pressure were similar between groups (Table 1).

Comparison of AV-45 SUVR between aMCI-LMD and aMCI+LMD

Figures 2 and 3 show that the aMCI+LMD group had higher frontal AV-45 SUVR than the aMCI-LMD group. The univariate ANCOVA (Table 2), controlling for current GDS score, modified Hachinski ischemic scale score, current smoking status, medical history of CVD, apoE4 genotype, FAQ score, systolic blood pressure, and the different PET scanners, showed that the aMCI+LMD group had higher frontal AV-45 SUVR than the aMCI-LMD group (F (76) = 5.62 p = 0.02). The univariate ANCOVA for the cingulate, parietal and temporal regions showed that there were no differences in AV-45 SUVR within these areas (F (76) = 0.14,

Table 1

Comparison of demographic and clinical variables between aMCI patients with a lifetime history of major depression and aMCI patients without a lifetime history of major depression

Demographic variables	aMCI-LMD (n = 39)		aMCI+LMD (n = 39)		p-value
	mean	SD	mean	SD	
Age, years	71.39	6.86	68.90	6.86	0.11
Education years	16.38	2.74	15.79	2.85	0.35
MMSE score	27.10	4.05	27.92	1.58	0.24
CDR score	2.01	2.58	2.00	1.18	0.98
Modified Hachinski	0.51	0.56	0.49	0.64	0.68
GDS score	1.72	1.36	2.51	2.27	0.07
Systolic blood pressure	133.72	16.28	128.18	16.35	0.14
NPI total score	3.09	4.02	5.57	9.16	0.20
FAQ	3.38	5.04	4.05	4.80	0.55
Demographic variables	Number (frequency [%])		Number (frequency [%])		p-value (two-tailed)
CVD+	24 (61.54)		23 (58.97)		1.00
Smoking+	2 (5.13)		3 (7.69)		1.00
White	37 (94.87)		39 (100.00)		0.24
Hispanic/Latino	2 (5.13)		1 (2.56)		1.00
Married	33 (84.62)		33 (84.62)		1.00
Females	18(46.15)		22(56.41)		0.50
0 ApoE4	19 (48.72)		20 (51.28)		0.86
1 ApoE4	17 (43.59)		15 (38.46)		0.86
2 ApoE4	3 (7.69)		4 (10.26)		0.86

aMCI-LMD and aMCI+LMD groups were matched in all the demographic variables listed above (*t*-test, two-tailed for the continuous demographic variables; χ^2-test, two-tailed for the discrete demographic variables). aMCI, amnestic mild cognitive impairment; aMCI+LMD, aMCI with a lifetime history of major depression; aMCI-LMD, aMCI without any lifetime history of major depression; ApoE4, apolipoprotein E4; 0 ApoE4, number of 0 ApoE4 allele holders; 1 ApoE4, number of 1 ApoE4 allele holders; 2 ApoE4, number of 2 ApoE4 alleles holders; CDR, the Clinical Dementia Rating; CVD+, presence of history of cardiovascular disease; FAQ, the Functional Activities Questionnaire score; GDS, the Geriatric Depression Scale score; MMSE, the Mini-Mental state examination score; Modified Hachinski, the Modified Hachinski Ischemic scale score; NPI, the Neuropsychiatric Inventory total score; Smoking+, currently smoking; χ^2-test, Chi-squared test/Fischer's Exact test.
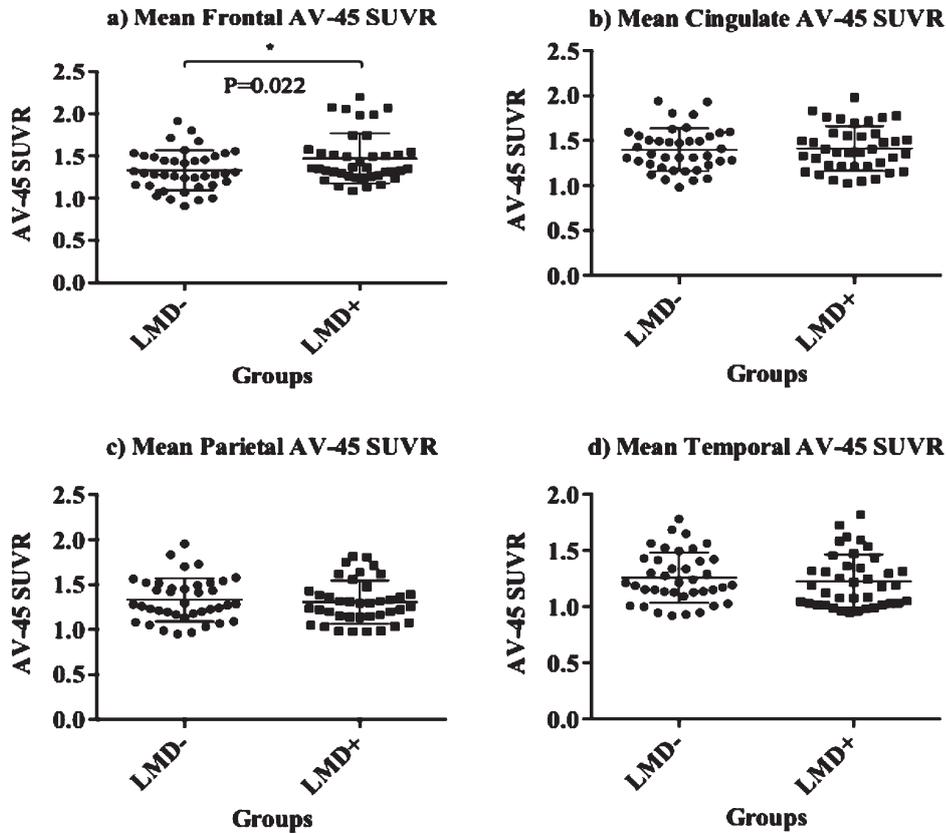
Fig. 2. Scatterplots representing the AV-45 SUVR between aMCI patients with a lifetime history of major depression and aMCI patients without a lifetime history of major depression. a) Mean frontal AV-45 SUVR; b) Mean Cingulate AV-45 SUVR; c) Mean parietal AV-45 SUVR; d) Mean temporal AV-45 SUVR. The LMD+ group showed significantly higher AV-45 SUVR in the frontal region than the LMD+ group. There is no significant difference in other regions between two groups. *indicates statistical significance at $p < 0.05$, two-tailed. Error bars represent SD. aMCI, amnestic mild cognitive impairment; AV-45 SUVR, ^{18}F-Florbetapir standardized uptake value ratio; LMD-, aMCI patients without a lifetime history of major depression; LMD+, aMCI patients with a lifetime history of major depression.

$p = 0.71$; F $(76) = 0.45$, $p = 0.50$ and F $(76) = 0.76$, $p = 0.39$, respectively). There was no difference in global AV-45 SUVR, which is the average AV-45 SUVR of the frontal, anterior cingulate, precuneus, and parietal cortex AV-45 SUVR uptake relative to the cerebellum reference region, between two groups (F $(76) = -1.02$; $p = 0.31$).

Voxel-based analysis

The brain areas with higher SUVR in the aMCI+LMD group, in comparison to the aMCI-LMD group, are described in Table 3 and illustrated in Fig. 3. The brain areas with higher SUVR in the aMCI+LMD group, in comparison to the aMCI-LMD group, are described in Table 3 and illustrated in Fig. 3. The regions include: right medial frontal gyrus, right middle frontal gyrus, left superior frontal gyrus, left inferior frontal gyrus, right superior temporal gyrus,

and left anterior cingulate (Cohen's effect size = 0.72, 0.64, 0.65, 0.60, 0.66, and 0.65, respectively).

DISCUSSION

Our study showed higher AV-45 SUVR in the frontal cortex (Cohen's effect size = 0.53) of the aMCI+LMD group, in comparison to the aMCI-LMD group. The increased AV-45 SUVR was found employing a pre-defined set of ROIs informed directly by the ADNI database and confirmed by a voxel-based parametric analysis. The confirmatory voxel-based analysis found that the increased AV-45 SUVR was in the bilateral frontal cortex including the left dorsolateral prefrontal cortex (DLPFC), bilateral orbitofrontal cortex (OFC), and medial prefrontal cortex (mPFC). In addition, the voxel-based analysis reported increased AV-45 SUVR in the superior temporal gyrus and anterior cingulate. The ROI global AV-45 SUVR was no different
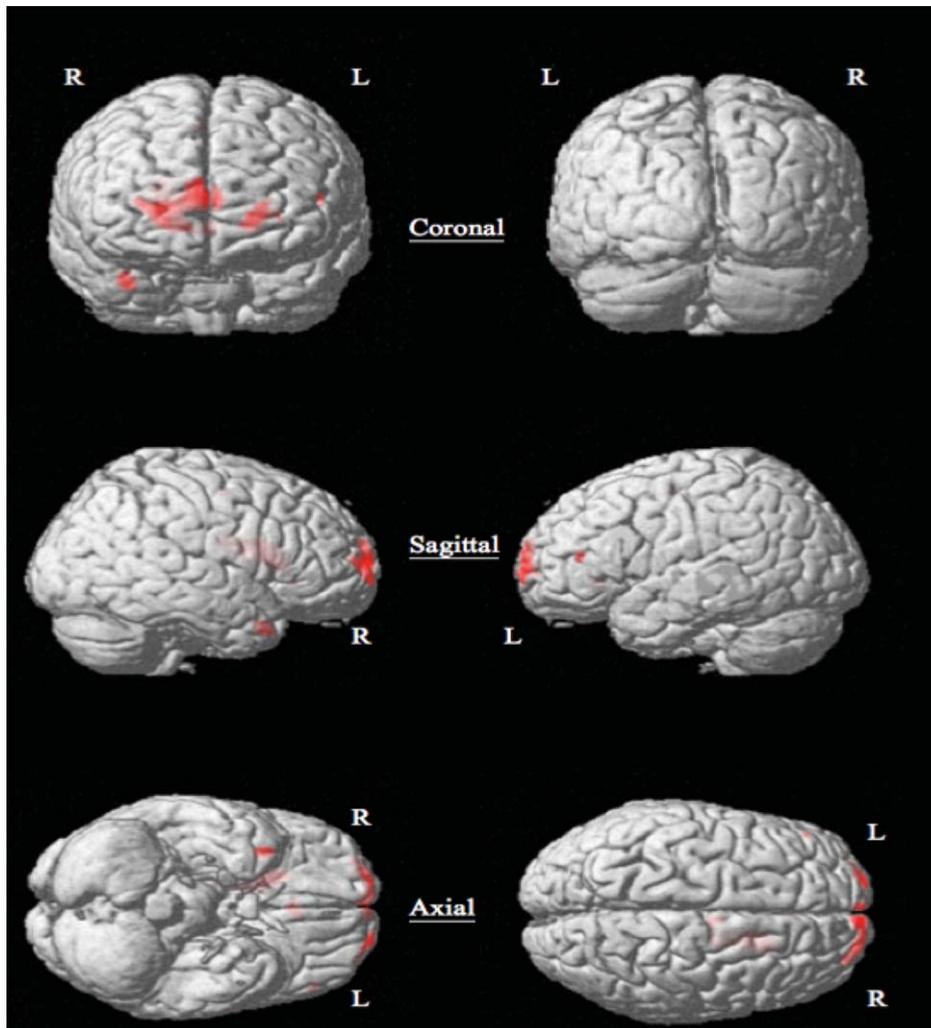
Fig. 3. Cortical render comparing AV-45 SUVR between aMCI patients with a lifetime history of major depression and aMCI patients without a lifetime history of major depression. The regions that show higher AV-45 SUVR in aMCI+LMD mainly include bilateral prefrontal cortex. Few regions in the right temporal region also show higher AV-45 SUVR in aMCI+LMD group. aMCI+LMD, patients with amnestic mild cognitive impairment with a lifetime history of major depression; AV-45 SUVR, ^{18}F-Florbetapir Standardized uptake value ratio.

between the two groups. This is consistent with previous findings that reported no difference in global Aβ deposition between depressed and non-depressed persons [20, 40].

Participants were matched on potential confounding factors, such as age, gender, education years, race, ethnicity, CDR score, FAQ score, MMSE score, NPI score, apoE4 genotype, and marital status. Additional analyses were also conducted, controlling for current GDS score, vascular risk factors, and different PET scanners, to ensure that any difference in AV-45 SUVR was related to an LMD, rather than any other variables. Moreover, according to the vascular depression hypothesis, the central mechanism of depression is disruption of the prefrontal system through accumulation of frontal vascular lesions [41]. As there is high comorbidity among depression, vascular risk factors, and vascular disease, we controlled or matched for vascular risk factors that may contribute to the association between Aβ accumulation and depressive symptoms [42]. This approach reduced the possibility that vascular damage may lead the higher Aβ accumulation in frontal regions showed in the aMCI+LMD group. Additionally, we also observed statistically significant increase of AV-45 SUVR in the frontal region of the aMCI+LMD group without controlling for these covariates (Fig. 2).

Our study identified increased AV-45 in the bilateral frontal cortex of the aMCI+LMD group. The potential mechanisms by which an LMD can elevate the level of Aβ deposition in the frontal region of aMCI patients are currently unclear. Nonetheless, cortisol has been implicated in the pathology of depression and Aβ deposition [43, 44]. Stress-level glucocorticoid administration increases Aβ formation by elevating the levels of amyloid-β precursor protein (AβPP) and AβPP cleaving enzyme, suggesting that cortisol may facilitate the formation of Aβ plaques [45]. According to the glucocorticoid cascade hypothesis of depression, stress elevates glucocorticoid levels, which can in turn have neurotoxic effects in the hippocampus.

Furthermore, neuroinflammation has also been associated with the pathology of depression and Aβ deposition [46]. There is evidence showing that chronic neuroinflammation may explain the structural changes, including the formation of Aβ plaques, in dementia and other types of neurodegenerative disorders [47]. Pro-inflammatory cytokines are thought to regulate a cascade, which ultimately results in over-secretion of cortisol [48]. There are studies suggesting that Aβ deposition in humans occurs early in the prefrontal region [49, 50]. Difference in cortisol response may mechanistically explain the link between an LMD and increased Aβ accumulation in the frontal lobes [51]. Thus, cortisol and neuroinflammation may contribute to the elevation of Aβ deposition levels in the aMCI+LMD group. Further research is needed to elucidate the mechanistic explanation for increased Aβ deposition in this population.

Another explanation that links depression and Aβ deposition is modulation at the level of the N-methyl-D-asparate receptor (NMDAR) [52]. Dysregulation of calcium influx through the NMDAR can increase the level of Aβ by increasing the expression of amyloidogenic isoforms of AβPP [52]. A recent review notes that depression may induce chronic stimulation of the NMDAR, ultimately resulting in elevated levels of Aβ due to increased calcium influx [53]. Thus, cortisol, neuroinflammation, and chronic stimulation of the NMDAR may explain the pathway linking MD and elevated Aβ deposition.

It is widely accepted that frontal dysfunction is implicated in the pathophysiology of depression [54]. Meta-analyses report that MD may be linked to dysfunction of frontal connectivity to other cortical and subcortical regions [55, 56]. Moreover, brain-imaging studies have reported that depressed patients show

Table 2
Comparison of region-of-interest based AV-45 SUVR between aMCI patients with a lifetime history of major depression and aMCI patients without a lifetime history of major depression

Regions of Interest	aMCI-LMD ($n = 39$) SUVR		aMCI+LMD ($n = 39$) SUVR		F-value	p-value
	mean	(SD)	mean	(SD)		
Frontal*	1.33	0.24	1.47	0.29	5.62	0.02*
Cingulate	1.40	0.24	1.39	0.26	0.14	0.71
Parietal	1.33	0.24	1.31	0.24	0.45	0.50
Temporal	1.26	0.22	1.23	0.24	0.76	0.39

The univariate ANCOVA analysis showed that patients with a lifetime history of major depression have significantly higher AV-45 SUVR in the frontal region, but not in other regions, after controlling for the covariates, including current GDS score, current smoking status, modified Hachinski ischemic scale score, FAQ score, apoE4 genotype, systolic blood pressure, medical history of CVD, and the different PET scanners. *indicates statistical significance at $p < 0.05$, two-tailed. aMCI, amnestic mild cognitive impairment; aMCI+LMD, aMCI with a lifetime history of major depression; aMCI-LMD, aMCI without any lifetime history of major depression; ANCOVA, analysis of covariance; AV-45 SUVR, ^{18}F-Florbetapir standardized uptake value ratio.

Table 3
Talaraich coordinates of *a priori* regions that show higher AV-45 SUVR in aMCI patients with a lifetime history of major depression in comparison to aMCI patients without a lifetime history of major depression

Coordinate mm			Regions	Hemisphere	BA	Cluster size	Values	
x	y	z					T	p
4	66	14	Medial frontal gyrus	Right	10	287	3.16	0.003
24	64	6	Middle frontal gyrus	Right	10		2.81	0.003
30	60	10	Middle frontal gyrus	Right	10		2.58	0.006
−20	68	2	Superior frontal gyrus	Left	10	73	2.82	0.003
−30	62	4	Superior frontal gyrus	Left	10		2.43	0.009
−50	38	12	Inferior frontal gyrus	Left	46	15	2.63	0.005
8	−8	52	Medial frontal gyrus	Right	6	28	2.75	0.004
38	14	−32	Superior temporal gyrus	Right	38	63	2.86	0.003
0	30	−2	Anterior cingulate	Left	24	43	2.85	0.003

This table highlights the regions of higher AV-45 SUVR in the aMCI patients with a lifetime history of major depression, in comparison to aMCI patients without a lifetime history of major depression. They were included if they were statistically significant at $p < 0.01$, uncorrected. aMCI, amnestic mild cognitive impairment; AV-45 SUVR, ^{18}F-Florbetapir Standardized uptake value ratio; BA, Brodmann area.

decreased activity in frontal regions during functional imaging tasks [57]. We observed that the aMCI+LMD group had higher AV-45 in the DLPFC than the aMCI-LMD group. The DLPFC is thought to suppress negative affect through top-down inhibition of the amygdala [58], which may be a protective mechanism against depression [59]. A study examining Vietnam veterans showed that DLPFC lesions were positively correlated with current depression scores [60]. Another study reported that DLPFC cerebral blood flow predicts the severity of depressive symptoms in MD patients [61]. DLPFC lesions are also associated with labile affects, poor goal-directed activity, and depression [62–64]. Furthermore, a recent study revealed that the number of depressive episodes, but not the current depressive state, was associated with cortical thinning in the left prefrontal cortex [65]. Therefore, our findings that the aMCI+LMD group had increased Aβ accumulation in the PFC, compared to the aMCI-LMD group, are in keeping with a frontal dysfunction model of depression.

While there is evidence that left frontal lesions are associated with depression [66, 67], the right frontal region has been also implicated in depression [68]. A study suggested a strong link between late-life onset depression and right frontal atrophy, but not with left frontal atrophy [69]. Neurostimulation studies further support the evidence of frontal involvement in MD. Left PFC repetitive transcranial magnetic stimulation (r-TMS) or transcranial direct current stimulation (tDCS), is effective for the treatment of depression [70]. Both high-frequency r-TMS and anodal tDCS to the left PFC resulted in significantly higher antidepressant efficacy compared to sham stimulation [71, 72]. On the other hand, low-frequency r-TMS, which elicits inhibitory action, targeting the right DLPFC, but not the left DLPFC, was shown to be effective in MD patients [73]. Together, these findings suggest that abnormalities in the bilateral PFC may be related to depression symptomatology.

The mechanisms underlying the link between depression and MCI are currently unknown. One study revealed that depression may simply be an early manifestation of AD symptoms prior to cognitive decline [74]. A recent study demonstrated that there was increased Aβ accumulation in patients with an LMD, in comparison to patients without an LMD [20]. Our study focused selectively on aMCI patients, and our findings reinforce the previous literature, which reveals that an LMD may play a significant role in elevating the Aβ accumulation. There are findings suggesting that aMCI+LMD patients are at increased risk of

developing dementia than aMCI-LMD patients by more than two-folds [75]. Furthermore, a study revealed that patients with MCI who are PIB-positive are more likely to convert to AD patients than those who are PIB-negative [13]. All these findings suggest that both MCI patients with an LMD and MCI patients with high Aβ depositions are at a higher risk of developing AD. Thus, future longitudinal studies need to investigate the conversion rate from aMCI+LMD to AD in order to investigate whether LMD may be a strong predictor of AD.

There are limitations to the current investigation. First, the ADNI study did not specifically aim to explore the role of depression on Aβ accumulation, therefore the study did not include several details about depression, such as time since onset of depression, and the duration and number of depressive episodes (i.e., whether participants were continuously depressed, only depressed for a brief period, or if they had recurrent episodes). Another limitation of defining LMD involves underdiagnosis of depression during the time when the participants were diagnosed with depression [76], which may result in insufficient treatment of depression. As a result, these factors may influence the differences between the groups.

Second, the diagnosis of MD was based on clinical interviews with the participants; it was not obtained using a structured psychiatric interview. However, we addressed this issue by excluding participants with unspecified information about whether they met the Diagnostic and Statistical Manual of Mental Disorder criteria of MD. Third, there was a trend level difference in current GDS score between groups. To address this discrepancy, we included current depressive symptoms as a covariate in our analysis. Future studies should examine the relationship between current depressive symptoms and cortical Aβ accumulation using AV-45. Fourth, the study was limited by the use of the radiotracer AV-45 to quantify Aβ accumulation, as AV-45 may not bind to all Aβ plaques [77]. Fifth, the causality between Aβ and depression may be bi-directional. There are few studies showing that injection of Aβ oligomers and Aβ$_{1-42}$ peptide induce depressive-like behaviors in rats [78, 79]. Although these studies were carried out in rodents, findings from these studies suggest that high Aβ deposition may promote depression in humans. Sixth, many of the participants with an LMD were or had been on antidepressant medications for years. There has been one study showing that antidepressant may reduce CSF Aβ production in healthy individuals and transgenic AD mice [80]. However, future studies need to further investigate how

antidepressant usages affect cortical Aβ deposition in aMCI patients. Seventh, cortisol measures were not included as covariates in the analysis. Not every participant had cortisol measures, and among those who had them, there was a temporal discrepancy between cortisol assessments and PET scans. Given that cortisol may increase cortical Aβ formation [45], future studies need to investigate whether current cortisol level mediates the relationship between LMD and cortical Aβ deposition. Lastly, in addition to increased cortical Aβ deposition, other biomarkers of AD, such as hippocampal loss [81] and white matter hyperintensites [82], may be associated with LMD in aMCI population. A recent meta-analysis highlighted that late-life depression increases the risk of subsequent onset of both vascular dementia and AD, but the risk was higher for subsequent vascular dementia [83]. This finding suggests the importance of future studies investigating the relationship between LMD and different biomarkers for various types of dementia.

In conclusion, we found that the aMCI+LMD group had significantly higher AV-45 SUVR in the frontal region, in comparison to the aMCI-LMD group, controlling for current depressive symptoms, vascular risk factors, and the use of different PET scanners. Voxel-based analysis revealed that the difference was present mainly in the bilateral frontal regions. With two independent methods, we obtained consistent findings, which was higher frontal AV-45 SUVR in the aMCI+LMD group. We also observed in the voxel-based analysis a higher AV-45 SUVR in the right temporal region and left anterior cingulate, which was not observed in the ROI analysis. The voxel-based analysis may be a more sensitive method for small regions within larger ROIs. To sum up, our finding suggests that a region-specific frontal Aβ accumulation is associated with the occurrence of past depressive episodes in aMCI patients. Future prospective studies with larger sample sizes are necessary to replicate these findings and to further explore the mechanistic underpinnings of this relationship.

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the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2.

To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see http://www.adni-info.org

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