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Cortical Amyloid β Deposition and Current Depressive Symptoms in Alzheimer Disease and Mild Cognitive Impairment

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Abstract

Depressive symptoms are frequently seen in patients with dementia and mild cognitive impairment (MCI). Evidence suggests that there may be a link between current depressive symptoms and Alzheimer disease (AD)-associated pathological changes, such as an increase in cortical amyloid- β (A β). However, limited in vivo studies have explored the relationship between current depressive symptoms and cortical A β in patients with MCI and AD. Our study, using a large sample of 455 patients with MCI and 153 patients with AD from the Alzheimer's disease Neuroimaging Initiatives, investigated whether current depressive symptoms are related to cortical A β deposition. Depressive symptoms were assessed using the Geriatric Depression Scale and Neuropsychiatric

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Declaration of Conflicting Interests

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Supplemental Material

The online supplement tables are available at <http://jgpn.sagepub.com/supplemental>

Inventory-depression/dysphoria. Cortical A β was quantified using positron emission tomography with the A β probe ¹⁸F-florbetapir (AV-45). ¹⁸F-florbetapir standardized uptake value ratio (AV-45 SUVR) from the frontal, cingulate, parietal, and temporal regions was estimated. A global AV-45 SUVR, defined as the average of frontal, cingulate, precuneus, and parietal cortex, was also used. We observed that current depressive symptoms were not related to cortical A β , after controlling for potential confounds, including history of major depression. We also observed that there was no difference in cortical A β between matched participants with high and low depressive symptoms, as well as no difference between matched participants with the presence and absence of depressive symptoms. The association between depression and cortical A β deposition does not exist, but the relationship is highly influenced by stressful events in the past, such as previous depressive episodes, and complex interactions of different pathways underlying both depression and dementia.

Keywords

dementia; depression; beta-amyloid

Introduction

There is mounting evidence in support of a link among depression, mild cognitive impairment (MCI), and Alzheimer disease (AD).¹⁻⁴ Depressive symptoms occur very commonly in patients with MCI,⁵ with previous findings reporting that the comorbidity rate is approximately 44%.⁶ Current literature suggests that depression in MCI is a strong risk factor for AD.^{7,8} A lifetime history of depression (LMD) confers an increased risk of developing AD, and a single episode of late-life depression increases the risk of developing AD by 4- to 5-fold.⁹ Studies have shown that patients with MCI having depressive symptoms are more likely to develop AD than those without depression.^{10,11} A recent study noted that currently patients with depression having MCI, who have elevated amyloid- β (A β) in the frontotemporal region, are more likely to convert to AD than nondepressed patients.¹² These aforementioned findings suggest a complex relationship among depression, MCI, and AD.

Further, depression is strongly linked with the pathophysiology of neurodegenerative disorders.^{13,14} One study demonstrated that patients with AD having an LMD have higher hippocampal deposits of A β than those without an LMD.¹⁵ In addition, our group recently showed that patients with MCI having an LMD had higher A β accumulation mainly in the bilateral frontal region in comparison to those without an LMD.¹⁶ Therefore, the literature suggests that past depressive episodes are associated with elevated A β level in patients with MCI and AD.

Nevertheless, the relationship between current depressive symptoms and A β deposition in MCI remains to be characterized. Although several studies of peripheral A β levels in the elderly patients have not demonstrated an association between A β and current depressive symptoms,¹⁷⁻²¹ there are others suggesting a positive relationship.²²⁻²⁴ Moreover, there are no studies that have examined the relationship between symptoms of depression and cortical

A β levels. It is also important to note that previous studies did not clearly distinguish LMD from the current depressive symptoms. At least 50% of patients who recover from their first depressive episode will have additional episodes, and approximately 80% of those with LMD will have recurrent episodes.^{25,26} These inconsistent findings suggest that the association between current depressive episode and A β level may be attributable to past depressive episodes rather than current depressive symptoms. Therefore, it is critically important to investigate the association between cortical A β accumulation and current depressive symptoms while controlling for the confounding effect of LMD to understand the role of AD pathology in patients with MCI and AD who have comorbid depression.

Presently, cortical A β deposition can be measured with positron emission tomography (PET) using radiotracers such as 18F-florbetapir (AV-45).²⁷ A recent finding using PET-AV-45 demonstrated that in patients with depression, A β accumulation is increased in frontal, temporal, and parietal regions, in comparison to nondepressed patients.²⁸ In addition, there is evidence of elevated A β accumulation in the cingulate region in patients with depression.²⁹ In this study, investigating these 4 a priori regions—frontal, temporal, parietal, and cingulate— we examined cortical A β deposition in 455 patients with MCI and 153 patients with AD from Alzheimer's Disease Neuroimaging Initiatives (ADNI)³⁰ databases. The primary objective was to assess the relationship between cortical A β deposition in the 4 aforementioned regions of interests (ROIs) and current depressive symptoms, controlling for LMD in vivo. Findings from this study will further characterize the relationship between current depressive symptoms and cortical A β deposition in patients with MCI and AD. Negative results would suggest that current depressive symptoms in MCI and AD might be explained by multiple factors independent of A β pathology.

Method

Study Patients and Diagnosis

The entire data set was downloaded from ADNI-1, ADNI-2, and ADNI Grand Opportunity (ADNI-GO) databases on March 29, 2014.³⁰ The ROI-based AV-45 data set that we used was updated as of May 2, 2014. Briefly, in ADNI-1, 800 participants, including controls, patients with amnesic MCI, and patients with mild AD, were recruited from 50 different sites in Canada and the United States.³¹ More details about participant recruitment procedure are described in the previous study.¹⁶

Eligibility criteria in ADNI-2 and ADNI-GO were identical to those in ADNI.³² For our current study, we only included patients with MCI who had both a T1-weighted magnetic resonance imaging (MRI) scan and an AV-45 PET scan completed approximately at the same time. The diagnostic inclusion criteria of MCI were early MCI, late MCI, normal-to-MCI, and dementia-to-MCI. The diagnostic inclusion criteria of AD were dementia, MCI-to-dementia, and normal-to-dementia.

Depressive Symptoms

Depressive symptoms were assessed using 2 different measures: Geriatric Depression Scale (GDS) Short-Form score and Neuropsychiatric Inventory depression/dysphoria (NPI-D)

score. The GDS³³ and NPI³⁴ were obtained from ADNI-1, ADNI-2, and ADNI-GO. The GDS Short-Form is a 15-item self-assessment addressing depressive symptoms in elderly individuals.³⁵ Its score ranges from 0 to 15, 15 referring to the most severe depressive symptoms, scores 5 or above are suggestive of depression, and scores 10 or above almost always indicate depression.³⁶ The GDS is a valid and reliable way of measuring depressive symptoms in patients with MCI.³⁷ For our study, the cutoff score used to distinguish between “low depressed” and “high depressed” was 5. The NPI-D was assessed using information from primary caretakers or informants of the participants. The severity score of NPI-D is classified into “mild,” “moderate,” or “severe” (score 1–3), and the frequency into “less than once a week,” “once a week,” “most days but not every day,” and “every day” (score 1–4).³⁸ The score of NPI-D is the product of severity and frequency of the depressive symptoms and has a range from 0 to 12. The NPI-D also has high validity and good reliability in measuring depressive symptoms in elderly individuals.³⁹ For our study, the definition of “absence of depressive symptoms” was having a score of 0 in both GDS and NPI-D scores and “presence of depressive symptom” as having a score 1 or above in both GDS and NPI-D scores. Participants who showed inconsistency in their scores were excluded. Medical history of cardiovascular diseases (CVDs), psychiatric disorders (PDs), neurological disorders (NDs), metabolic disorders (MDs), smoking, and alcohol and drug abuse was obtained by trained research assistants from patients with MCI and AD, their caretakers or informants during ADNI screening, and during follow-up visits.⁴⁰ This was similarly done for ADNI-1, ADNI-GO, and ADNI-2. The presence of an LMD was determined using patients’ self-reported medical history from ADNI-1, ADNI-GO, and ADNI-2. Lifetime history of depression was defined using the procedure used in the previous study.¹⁶

The GDS assessment took place within a maximum of 6-month interval from the PET scan, and the NPI assessment took place within a maximum of 1-year interval from the scan.

Cortical A β Deposition

Data for AV-45 imaging were acquired from ADNI-2 and ADNI-GO. The detailed information about the technical scan procedure is described online.⁴¹ Each of the 2 ADNI initiatives reported ROI-based AV-45 standardized uptake value ratio (SUVR), which included bilateral frontal, anterior/posterior cingulate, lateral parietal and lateral temporal cortices, and global AV-45 SUVR, which is the average AV-45 of frontal, cingulate, precuneus, and parietal cortex regions, relative to the cerebellum. Region of interest-based AV-45 SUVR was estimated by dividing the average 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 was also used). The SUVR (ratio of SUV-specific or interest region to SUV reference region) was the outcome measure in order to reduce, as much as possible, any bias or error associated with differences in nonspecific binding between groups.⁴² More details about the PET analysis are described online.⁴³

Scanning and Imaging Procedure

The ADNI study coordinators prepared AV-45, after referencing Avid Radiopharmaceuticals (Philadelphia, Pennsylvania, United States), Inc Clinical Supplies Guidance Document for

the necessary steps prior to radiotracer injection.^{44,45} More details about AV-45 preparation and PET scanning are described in the previous study.¹⁶ Each participant also had an MRI scan session, including a T1-weighted scan. All patients' PET AV-45 scans and the last clinical assessment of their diagnostic status were completed approximately at the same time.

Statistical Analysis

Each participant had assessments of depressive symptoms (GDS and NPI-D scores) and a PET AV-45 scan. Every participant had records of age, education years, gender, race, ethnicity, marital status, apolipoprotein (apoE4) genotype, Mini-Mental State Examination (MMSE) score, Clinical Dementia Rating score, NPI total score, Functional Activities Questionnaire (FAQ) score, Montreal Cognitive Assessment (MOCA) score, and medical history, which include history of LMD, CVD, ND, and PD, MD, history of drug abuse, history of alcohol abuse, history of smoking, current smoking status, years of smoking, and packs of cigarettes smoked during smoking years. Medical assessments were collected from ADNI-1, ADNI-2, and ADNI-GO database. Medical assessments and PET scans occurred within a maximum of a year interval between each other. Any participant with missing information of aforementioned records was excluded from the analyses.

First, partial Pearson correlations between A β deposition and depressive symptoms were performed for each group of patients with MCI and AD: (1) AV-45 SUVR and GDS score and (2) AV-45 SUVR and NPI-D score. Analyses were performed after controlling for aforementioned demographic and clinical factors.

Additionally, analyses of covariance (ANCOVAs) were performed for each group of patients with MCI and AD. We used 2 different approaches for ANCOVA. For the first approach, we separated participants based on low depressive symptom and high depressive symptom based on their GDS score. Then, participants with low depressive symptom were matched to those with high depressive symptom based on their demographic and clinical profiles. The 2 groups were matched for ApoE4 genotype, gender, race, ethnicity, marital status, MMSE score, and education years. For each participant with high depressive symptoms, 3 matched participants with low depressive symptoms were selectively found, and an ANCOVA was carried out controlling for any factor that was significantly different ($P < .05$) or at a trend level of difference between the 2 groups ($P < .10$). This process allowed 3 comparisons of AV-45 SUVR between the 2 groups.

For the second approach, we separated participants based on the presence and absence of depressive symptom based on their GDS and NPI-D scores. Participants without depressive symptoms were matched to those with depressive symptoms, based on their demographic and clinical profiles using the aforementioned variables. Then, we carried out an ANCOVA comparing the AV-45 SUVR between matched participants without depressive symptom and those with depressive symptoms, controlling for any factor significantly different or at a trend level of difference between the 2 groups. The statistical tests were performed using Statistical Package for the Social Sciences Version 21.0 (IBM, New York). The statistical significance was set at $P < .05$.

Results

Clinical and Demographic Profile

The clinical profile of patients with MCI (n = 455) and AD (n = 153) is shown in Supplementary Table 1a. The comparison of ROI-based cortical A β deposition between the 2 groups is shown in Supplementary Table 1b.

Clinical Assessments

Mild cognitive impairment—In patients with MCI (n = 455), among 361 (79.34%) of those with score of 1 or above, 28 (6.15%) of them were suggestive of depression (GDS score of 5 or above). There was no patient with MCI having GDS scores of 10 or above (Supplementary Table 1c). One hundred thirty-seven (30.11%) of the 455 patients had a NPI-D score of 1 or above (Supplementary Table 1d).

Alzheimer disease—In patients with AD (n = 153), among 124 (81.05%) of those with score of 1 or above, 17 (11.11%) of them were suggestive of depression (GDS score of 5 or above) and 3 (1.96%) of them had scores of 10 or above (Supplementary Table 1c). Fifty-seven of the 153 patients (37.25%) had a NPI-D score of 1 or above (Supplementary Table 1d).

Statistical Analyses

The summary of statistical analyses looking at cortical A β deposition and depressive symptoms within the 2 groups is shown in Table 1.

Relationship Between GDS Score Versus AV-45 SUVR

A partial Pearson correlation controlling for aforementioned covariates showed that no correlation existed between GDS score and AV-45 SUVR in frontal, cingulate, parietal, and temporal regions. There was no correlation between GDS score and global AV-45 SUVR both in patients with MCI and AD. A scatter graph illustrating the relationship between GDS score and global AV-45 SUVR is shown in Figure 1A. After excluding participants with GDS score of 0, no correlation was found between GDS score and frontal, cingulate, parietal, temporal, and global AV-45 SUVR in both groups.

Relationship Between NPI-D Score Versus AV-45 SUVR

A partial Pearson correlation controlling for aforementioned covariates identified no correlation between NPI-D score and AV-45 SUVR in frontal, cingulate, parietal, and temporal regions. There was no correlation between NPI-D score and global AV-45 SUVR both in patients with MCI and AD. A scatter graph illustrating the relationship between NPI-D score and global AV-45 SUVR is shown in Figure 1B. After excluding participants with NPI-D score of 0, no correlation was found between NPI-D score and frontal, cingulate, parietal, temporal, and global AV-45 SUVR.

Severity of Depressive Symptom Versus A β Deposition

Mild Cognitive Impairment—In the first pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with MCI having low depressive symptoms (GDS score <5) and high depressive symptoms (GDS score >5), except for NPI, Clinical Dementia Rating Scale Sum of Boxes (CDRSB), and FAQ score (Supplementary Table 2a). The ANCOVA between the first pair of matched participants (n = 28 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between the 2 groups (Table 2A), after controlling for NPI, CDRSB, and FAQ score. In the second pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with MCI having low depressive symptoms and high depressive symptoms (Supplementary Table 2b), except for CDRSB score and history of PD. The ANCOVA between the second pair of matched participants (n = 28 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between groups (Table 2B), after controlling for CDRSB score and history of PD. In the third pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with MCI having low depressive symptoms and high depressive symptoms (Supplementary Table 2c), except for MOCA, CDRSB, and NPI score. The ANCOVA between the third pair of matched participants (n = 28 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between groups (Table 2C), after controlling for MOCA, CDRSB, and NPI score.

Alzheimer disease—In the first pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with AD having low depressive symptoms (GDS score <5) and high depressive symptoms (GDS score >5), except for NPI score (Supplementary Table 3a). The ANCOVA between the first pair of matched patients with MCI having low depressive symptoms and high depressive symptoms (n = 17 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between the 2 groups (Table 3A), after controlling for NPI score. In the second pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with AD having low depressive symptoms and high depressive symptoms (Supplementary Table 3b), except for CDRSB score. The ANCOVA between the second pair of matched participants (n = 17 each) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between groups (Table 3B), after controlling for CDRSB score. In the third pair of matched samples, there was no difference in demographic and clinical profiles between matched patients with AD having low depressive symptoms and high depressive symptoms (Supplementary Table 3c), except for the history of MD. The ANCOVA between the third pair of matched participants (n = 17 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between groups (Table 3C), after controlling for the history of MD.

Presence of Depressive Symptom Versus A β Deposition

Mild cognitive impairment—There was no difference in demographic and clinical profiles between matched patients with MCI having depressive symptoms (presence) and

those without depressive symptoms (absence), except for history of LMD, PD, smoking, NPI total score, CDRSB, and FAQ score (Supplementary Table 4a). The ANCOVA between a pair of matched patients having MCI without depressive symptoms and with depressive symptoms (n = 80 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between groups (Table 4A), after controlling for history of LMD, PD, smoking, NPI total score, CDRSB, and FAQ score.

Alzheimer disease—There was no difference in demographic and clinical profiles between matched patients having AD without depressive symptoms and with depressive symptoms (Supplementary Table 4b), except for NPI total score and history of PD. An ANCOVA between a pair of matched patients having AD without depressive symptoms and with depressive symptoms (n = 22 in each group) showed that there was no difference in frontal, cingulate, parietal, temporal, and global AV-45 SUVR between the 2 groups (Table 4B), after controlling for NPI total score and history of PD.

Discussion

In this study, we demonstrated in a large sample (455 patients with MCI and 153 patients with AD) that current depressive symptoms were not linked to cortical A β deposition in patients with MCI and AD. Symptoms of depression were assessed with the GDS and NPI-D, 2 instruments widely used in the elderly, and AV-45 SUVR was used as a surrogate measure of cortical A β deposition in 4 ROIs: frontal, cingulate, parietal, and temporal regions. There was no association between current depressive symptoms and cortical A β levels, after controlling for multiple confounding factors, such as age and gender. Current literature highlights that there is a link between depression and atrophies in several cortical regions,^{46,47} such as hippocampus and orbitofrontal cortex. In order to account for potential atrophies in patients with depressive symptoms, controlling for total brain volume in the Pearson partial correlation did not influence the relationship between current depressive symptoms and cortical A β levels.

The A β protein hypothesis of AD states that increased production of A β plaques is the first step in the molecular cascade, ultimately leading to the impaired functions that manifest in dementia.⁴⁸ This hypothesis proposes that amyloid accumulation in the brain occurs before the clinical symptoms and functional impairment of dementia. Brain atrophy is linked to cortical A β level only in the pre-MCI stage but not in MCI and AD stages,⁴⁹ suggesting that cortical A β deposition and neuronal loss start prior to clinical evidence of cognitive decline. In addition, a recent study proposed that the rate of cortical A β deposition slows down over the course of life, whereas the process of neurodegeneration accelerates.⁵⁰ A recent prospective study further reinforced that the process of cortical A β accumulation is extremely slow and protracted, showing approximately 3% of increased deposition per year.⁵¹ Therefore, current depressive symptoms in patients with established MCI or AD are less likely to be associated with the cortical A β level. Findings from a recent study by our group suggest that in patients with MCI, an LMD is linked to an increase in cortical A β deposition in the frontal region.¹⁶ Our previous and current findings strongly suggest that LMD is a stronger predictor of cortical A β accumulation than current depressive state in patients with MCI or AD. Overall, we can speculate that although LMD is strongly

associated with cortical A β accumulation, current depressive symptoms might have an underlying pathology independent of A β neuropathological changes.

Our results are in accordance with a number of previous studies that did not find a relationship between depression and A β deposition. In a neuropathological study of older adults, increased A β accumulation was not associated with current depression.⁵² In a recent investigation, NPI-D score was unrelated to cortical A β deposition in patients with AD (n = 28).⁵³ Similarly, another group concluded that depression was not associated with more severe AD-type pathology in patients with SCI and MCI.¹⁸ Moreover, another study observed no correlation between current Hamilton Depression Scale score and A β 42 level in patients with late-life depression.⁵⁴

The mechanism underlying why depressive symptoms are common in patients with MCI and AD is still elusive. Nevertheless, our current finding reinforces the recent hypothesis that states elevated risk of AD in old patients with depressive symptoms may not be due to abnormalities in A β deposition but rather due to reduced brain reserve secondary to pathological changes in patients.²¹ According to this hypothesis, A β accumulation makes brains vulnerable to other neurotoxic events that may result in emergence of symptoms of dementia. These events include reduced neurotrophic factors,⁵⁵ elevated oxidative stress markers, elevated cortisol, higher white matter intensity volume, and neuroinflammation.²¹ Therefore, our negative result is in agreement with both the A β hypothesis of AD, proposed by Diniz et al, and a finding that suggests that MCI in late-life depression may be caused by non-AD pathology, such as vascular changes in the brain.⁵⁶ Overall, based on previous literature and our current finding, we conclude that the association between depression and cortical A β deposition does not exist, but the relationship is highly influenced by the presence of LMD, heterogeneity of participants, and complex interactions of different pathways underlying both depression and dementia.

There are several limitations to this study. First, there was inconsistency between NPI-D and GDS measures of depression. Based on participants' NPI-D score, more than half of the study participants included in ADNI did not have depressive symptoms, whereas according to GDS score, the majority of patients with MCI and AD had symptoms of depression. This inconsistency may be attributable to methodological differences between the scales. The GDS is a self-report measure, and NPI-D is based on information provided by participants' caregivers or informants. The NPI-D is a more objective measure of participants' depressive symptoms and is less affected by subject bias or cognitive decline. The GDS and NPI-D scores were modestly correlated in MCI and AD groups (n = 455, $r = 0.25$, $P < .01$ and n = 153, $r = 0.19$, $P = .03$, respectively). In order to increase the sensitivity of measuring depressive symptoms, we combined the 2 scales, especially as depression contains both subjective and objective clinical features. Second, few patients had severe depressive symptoms, which is attributable to the ADNI protocol's preferential inclusion of patients with GDS less than 6. The majority of patients had mild to moderate or no symptoms of depression. The inclusion of patients with severe depression could have provided a wider range of symptoms and more conclusive analyses. Third, given that cortical A β deposition reaches a plateau in the early illness phase of AD,⁵¹ our study was limited in that we restricted our cohort to patients who had their PET scan and clinical assessment within a

close temporal proximity. By including more patients, we could have increased the statistical power of our study. Fourth, we did not investigate the relationship between cortical A β accumulation and antidepressant usage. There is one study showing that antidepressants may reduce cerebrospinal fluid (CSF) A β production in healthy individuals and transgenic AD mice.⁵⁷ Future studies need to investigate how antidepressant usage influences cortical A β deposition in patients with MCI and AD. Lastly, the selection bias created by matching participants may influence group differences. To address this, we utilized 3 matched groups to allow comparisons between the 3 groups. Fifth, one of the inclusion criteria of participants in ADNI is their baseline GDS score less than six⁵⁸; excluding patients who are depressed based on their GDS scores may be another limitation, which may reduce the sample sizes of participants with depression and mask the relationship between depressive symptoms and cortical A β levels. However, in our study, we did not restrict our inclusion criteria only to patients at baseline but also included patients with PET-AV-45 scan and clinical assessments at any time point (ie, 2 years after the baseline). This method allowed us to increase the patient samples and statistical power.

Sixth, the causality between the level of cortical A β and depressive symptoms may be bidirectional. There is evidence of infusion of A β peptides inducing depressive-like behaviors in mice.^{59,60} Although these were rodent studies, it is very important to investigate whether there is a bidirectional relationship between depressive symptoms and A β levels in humans. We did not look into the potential role of A β promoting depression, and future studies should investigate this relationship.

Seventh, our finding shows no correlation between current depressive symptoms and cortical A β levels in 4 ROIs that showed increased A β deposition in populations with depression. In addition to ROI analyses, future studies should take a voxel-based approach to confirm whether any other regions show elevated cortical A β levels that may be related to current depressive symptoms. Eighth, MCI has heterogeneous etiologies; thus, patients with MCI have different causes explaining their illness state. In order to eliminate this confounding effect of heterogeneity of MCI, we classified patients with MCI into either “MCI due to AD” (n = 281) or “MCI not due to AD” (n = 91) based on their biomarker criteria, including positive cortical A β and high CSF phosphorylated tau, as suggested by previous studies.^{51,61} In each group, there was no relationship between current depressive symptoms, assessed by GDS and NPI-D score, and cortical A β deposition in frontal, parietal, cingulate and temporal regions (Supplementary Table 5a and b). Thus, current depressive symptoms were not linked to cortical A β , regardless of different etiologies of MCI. Lastly, future prospective studies investigating the changes in A β levels over time in patients with depression versus nondepressed patients should be carried out to verify no difference in the rate of amyloidogenesis between the 2 groups. This finding will further reinforce that cortical A β deposition is not influenced by late-life depressive symptoms.

In conclusion, using a large sample size, we did not find a relationship between current depressive symptoms and cortical A β accumulation in patients with MCI and AD. This finding suggests that the mechanisms associated with current depressive symptoms in AD-MCI may be different from AD pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit organizations, as a \$60 million, 5-year public private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer disease (AD).

Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. The ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and participants have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 participants, but ADNI has been followed by ADNI Grand Opportunity (ADNI-GO) and ADNI-2.

To date, these 3 protocols have recruited over 1500 adults, ages 55 to 90 years, 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. Participants originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

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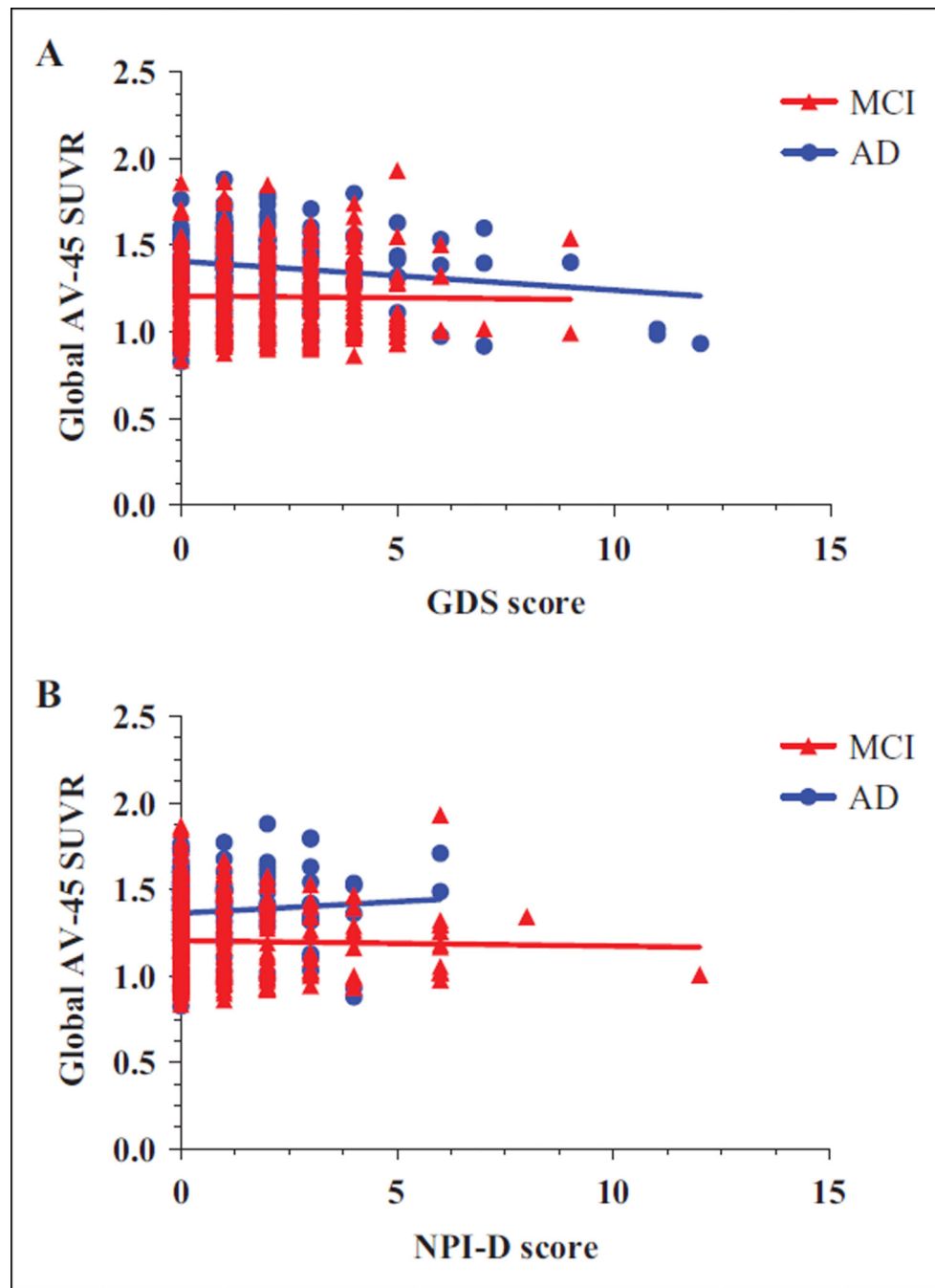


Figure 1. Scatter graphs of global cortical amyloid-β deposition versus GDS (A) and NPI-D (B) score in MCI and AD. AV-45 SUVR indicates florbetpair standardized uptake value ratio; GDS, Geriatric Depression Scale; Global, average SUVR of frontal, cingulate, precuneus, and parietal cortex regions, relative to the cerebellum; MCI, mild cognitive impairment; NPI-D, Neuropsychiatric Inventory score depression/dysphoria domain.

Table 1
 Summary of Analyses Between Cortical Amyloid- β Deposition and Depressive Symptoms.

	n	Region of Interest				Global
		Frontal	Cingulate	Parietal	Temporal	
A. MCI						
GDS						
Tests used						
Partial correlation	455	$r < -0.05$, $P = .34$	$r < -0.03$, $P = .50$	$r < -0.01$, $P = .86$	$r < -0.05$, $P = .61$	$r < -0.05$, $P = .54$
Partial correlation—excluded not depressed	361	$r < -0.05$, $P = .49$	$r = -0.01$, $P = .86$	$r < -0.05$, $P = .97$	$r < -0.05$, $P = .82$	$r < -0.01$, $P = .90$
ANCOVA: low versus high depressed						
	28 each	$F = 3.01$, $P = .09$, $\eta^2 = 0.06$	$F = 2.46$, $P = .12$, $\eta^2 = 0.05$	$F = 1.01$, $P = .32$, $\eta^2 = 0.02$	$F = 1.57$, $P = .22$, $\eta^2 = 0.03$	$F = 1.24$, $P = .27$, $\eta^2 = 0.02$
	28 each	$F = 4.10$, $P = .05$, $\eta^2 = 0.07$	$F = 2.74$, $P = .10$, $\eta^2 = 0.05$	$F = 2.01$, $P = .16$, $\eta^2 = 0.04$	$F = 3.13$, $P = .08$, $\eta^2 = 0.06$	$F = 0.50$, $P = .49$, $\eta^2 = 0.01$
	28 each	$F = 2.50$, $P = .12$, $\eta^2 = 0.05$	$F = 2.31$, $P = .13$, $\eta^2 = 0.04$	$F = 1.14$, $P = .29$, $\eta^2 = 0.02$	$F = 1.75$, $P = .19$, $\eta^2 = 0.03$	$F = 1.00$, $P = .32$, $\eta^2 = 0.02$
NPI-D						
Test used						
Partial correlation	455	$r < -0.10$, $P = .13$	$r < -0.10$, $P = .24$	$r < -0.01$, $P = .25$	$r < -0.10$, $P = .18$	$r < -0.10$, $P = .16$
Partial correlation—excluded not depressed	137	$r < 0.05$, $P = 0.85$	$r < 0.05$, $P = .85$	$r < 0.05$, $P = .83$	$r < 0.05$, $P = .83$	$r < 0.05$, $P = .88$
GDS + NPI-D						
Test used						
ANCOVA: not depressed versus depressed	80 each	$F < 0.01$, $P = 0.98$, $\eta^2 < 0.01$	$F < 0.01$, $P = .99$, $\eta^2 < 0.01$	$F < 0.01$, $P = .94$, $\eta^2 < 0.01$	$F < 0.01$, $P = .96$, $\eta^2 < 0.01$	$F < 0.01$, $P = .97$, $\eta^2 < 0.01$
B. AD						
GDS						
Tests used						
Partial correlation	153	$r < -0.10$, $P = .53$	$r < -0.01$, $P = .92$	$r < -0.05$, $P = .60$	$r < -0.10$, $P = .43$	$r < -0.10$, $P = .36$
Partial correlation—excluded not depressed	124	$r = -0.14$, $P = .08$	$r < -0.10$, $P = .10$	$r = -0.14$, $P = .08$	$r = -0.13$, $P = .10$	$r = -0.17$, $P = .08$

	n	Region of Interest					Global
		Frontal	Cingulate	Parietal	Temporal	Global	
ANCOVA: low versus high depressed	17 each	$P = .17$	$P = .43$	$P = .16$	$P = .18$	$P = .090$	
		$F = 1.43,$ $P = .24,$ $\eta^2 = 0.04$	$F = 0.80,$ $P = .38,$ $\eta^2 = 0.03$	$F = 0.97,$ $P = .33,$ $\eta^2 = 0.03$	$F = 1.97,$ $P = .17,$ $\eta^2 = 0.06$	$F = 0.63,$ $P = .43,$ $\eta^2 = 0.02$	
	17 each	$F = 0.03,$ $P = .96,$ $\eta^2 < 0.01$	$F = 0.11,$ $P = .75,$ $\eta^2 < 0.01$	$F < 0.01,$ $P = .98,$ $\eta^2 < 0.01$	$F = 0.08,$ $P = .71,$ $\eta^2 < 0.01$	$F = 0.16,$ $P = .69,$ $\eta^2 < 0.01$	
	17 each	$F = 0.21,$ $P = .65,$ $\eta^2 < 0.01$	$F = 0.08,$ $P = .78,$ $\eta^2 < 0.01$	$F = 0.42,$ $P = .52,$ $\eta^2 = 0.01$	$F = 0.24,$ $P = .63,$ $\eta^2 < 0.01$	$F = 1.06,$ $P = .31,$ $\eta^2 = 0.03$	
NPI-D							
Test used							
Partial correlation	153	$r < 0.10,$ $P = .40$	$r < 0.10,$ $P = .29$	$r < 0.10,$ $P = .26$	$r = 0.11,$ $P = .21$	$r = 0.10,$ $P = .24$	
Partial correlation—excluded not depressed	57	$r < 0.05,$ $P = .85$	$r < 0.05,$ $P = .90$	$r = 0.13,$ $P = .45$	$r < 0.10,$ $P = .63$	$r = 0.12,$ $P = .49$	
GDS + NPI-D							
Test used							
ANCOVA: not depressed versus depressed	22 each	$F = 0.83,$ $P = .37,$ $\eta^2 = 0.02$	$F = 0.68,$ $P = .42,$ $\eta^2 = 0.02$	$F = 1.07,$ $P = .31,$ $\eta^2 = 0.03$	$F = 1.01,$ $P = .32,$ $\eta^2 = 0.03$	$F = 0.49,$ $P = .49,$ $\eta^2 = 0.01$	

Abbreviations: AD, Alzheimer disease; ANCOVA, analysis of covariance; GDS, Geriatric Depression Scale score; MCI, mild cognitive impairment; NPI-D, Neuropsychiatric Inventory score depression/dysphoria domain; η^2 = partial eta squared (effect size).

Table 2
 Comparison of Cortical Amyloid- β Deposition Between Patients With Low Depression and High Depression Having MCI.

Region of Interests	Low Depressed MCI (n=28)		High Depressed MCI (n=28)		P
	Mean	SD	Mean	SD	
A. First pair					
Frontal	1.38	0.28	1.27	0.25	.09
Cingulate	1.46	0.28	1.36	0.26	.12
Parietal	1.37	0.27	1.32	0.28	.32
Temporal	1.28	0.24	1.21	0.22	.22
Global	1.18	0.20	1.16	0.24	.27
B. Second pair					
Frontal	1.44	0.33	1.27	0.25	.05
Cingulate	1.52	0.33	1.36	0.26	.10
Parietal	1.46	0.37	1.32	0.28	.16
Temporal	1.36	0.33	1.21	0.22	.08
Global	1.19	0.21	1.16	0.24	.49
C. Third pair					
Frontal	1.34	0.31	1.27	0.25	.12
Cingulate	1.44	0.34	1.36	0.26	.13
Parietal	1.36	0.29	1.32	0.28	.29
Temporal	1.27	0.27	1.21	0.22	.19
Global	1.18	0.23	1.16	0.24	.32

Abbreviations: AV-45, ¹⁸F-florbetapir; Global, average AV-45 SUVR of frontal, cingulate, precuneus, and parietal cortex regions, relative to the cerebellum; MCI, mild cognitive impairment; SD, standard deviation; SUVR, standardized uptake value ratio.

Table 3

Comparison of Cortical Amyloid- β Deposition Between Patients With Low Depression and High Depression Having AD.

Region of Interests	Low Depressed AD (n=17)		High Depressed AD (n=17)		P
	Mean	SD	Mean	SD	
A. First pair					
Frontal	1.55	0.22	1.45	0.35	.24
Cingulate	1.61	0.21	1.55	0.35	.38
Parietal	1.53	0.23	1.45	0.35	.33
Temporal	1.46	0.21	1.35	0.31	.17
Global	1.34	0.18	1.28	0.24	.43
B. Second pair					
Frontal	1.46	0.31	1.45	0.35	.96
Cingulate	1.52	0.27	1.55	0.35	.75
Parietal	1.46	0.30	1.45	0.35	.98
Temporal	1.38	0.27	1.35	0.31	.71
Global	1.31	0.26	1.28	0.24	.69
C. Third pair					
Frontal	1.50	0.30	1.45	0.35	.65
Cingulate	1.58	0.30	1.55	0.35	.78
Parietal	1.51	0.25	1.45	0.35	.52
Temporal	1.40	0.29	1.35	0.31	.63
Global	1.35	0.21	1.28	0.24	.31

Abbreviations: AD, Alzheimer disease; AV-45, ^{18}F -florbetapir; Global, average AV-45 SUVR of frontal, cingulate, precuneus, and parietal cortex regions, relative to the cerebellum; SD, standard deviation; SUVR, standardized uptake value ratio.

Table 4

Comparison of Cortical Amyloid- β Deposition Between Patients Without Depression and With Depression Having MCI and AD.

Region of Interests	Not Depressed MCI (n = 80)		Depressed MCI (n = 80)		P
	Mean	SD	Mean	SD	
A. MCI					
Frontal	1.39	0.28	1.35	0.29	.98
Cingulate	1.48	0.29	1.43	0.30	.99
Parietal	1.39	0.28	1.35	0.27	.94
Temporal	1.30	0.26	1.26	0.23	.96
Global	1.19	0.21	1.19	0.22	.97
B. AD					
Not Depressed AD (n= 22) Depressed AD (n= 22)					
Region of Interests	Mean	SD	Mean	SD	P
Frontal	1.51	0.28	1.58	0.33	.37
Cingulate	1.59	0.28	1.64	0.31	.42
Parietal	1.51	0.28	1.57	0.32	.31
Temporal	1.44	0.28	1.50	0.30	.32
Global	1.33	0.22	1.39	0.27	.49

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; SD, standard deviation.