Archival Report

Biological Psychiatry

Late-Life Depression Is Associated With Reduced Cortical Amyloid Burden: Findings From the Alzheimer's Disease Neuroimaging Initiative Depression Project

R. Scott Mackin, Philip S. Insel, Susan Landau, David Bickford, Ruth Morin, Emma Rhodes, Duygu Tosun, Howie J. Rosen, Meryl Butters, Paul Aisen, Rema Raman, Andrew Saykin, Arthur Toga, Clifford Jack Jr., Robert Koeppe, Michael W. Weiner, and Craig Nelson, on behalf of the Alzheimer's Disease Neuroimaging Initiative and the ADNI Depression Project

ABSTRACT

BACKGROUND: We evaluated the role of cortical amyloid deposition as a factor contributing to memory dysfunction and increased risk of dementia associated with late-life depression (LLD).

METHODS: A total of 119 older adult participants with a current diagnosis of major depression (LLD) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) Depression Project study and 119 nondepressed (ND) cognitively unimpaired participants matched on age, sex, and *APOE* genotype were obtained from the ADNI database.

RESULTS: Thirty-three percent of LLD participants met ADNI criteria for mild cognitive impairment. Compared with ND individuals, the LLD group exhibited less global amyloid beta (Aβ) accumulation ($p = .05$). The proportion of amyloid positivity in the LLD group was 19.3% compared with 31.1% for the ND participants ($p = .02$). Among LLD participants, global Aβ was not associated with lifetime number of depressive episodes, lifetime length of depression, length of lifetime selective serotonin reuptake inhibitor use, or lifetime length of untreated depression ($p > .21$ for all). Global Aβ was associated with worse memory performance ($p = .05$). Similar results were found in secondary analyses restricting comparisons to the cognitively unimpaired LLD participants as well as when comparing the LLD group with an ND group that included participants with mild cognitive impairment.

CONCLUSIONS: Contrary to expectation, the LLD group showed less Aβ deposition than the ND group and Aβ deposition was not associated with depression history characteristics. Aβ was associated with memory, but this relationship did not differ between LLD and ND. Our results suggest that memory deficits and accelerated cognitive decline reported in previous studies of LLD are not due to greater cortical Aβ accumulation.

Keywords: Alzheimer's disease, Amyloid, Cognition, Depressive symptoms, Late-life depression, Mild cognitive impairment

https://doi.org/10.1016/j.biopsych.2020.06.017

Subsyndromal symptoms of depression and major depression in older adults are among the most consistently reported risk factors associated with more rapid rates of future cognitive decline (1–8), more rapid conversion to dementia (9,10), and higher rates of incident dementia (11). Specifically, subsyndromal symptoms of depression have been linked to a 2.4-fold increased risk for dementia (12), whereas major depression has been linked to a nearly 4.3-fold increased risk for dementia (13). As a result of these findings, increased amyloid beta (Aβ) deposition in late-life depression (LLD) has been implicated as one potential pathway to increased risk of dementia in this patient population (14).

The accumulation of Aβ plaques in the brain is widely accepted as being one of the primary factors in the degeneration of neurons and cortical atrophy leading to memory and other cognitive dysfunction in Alzheimer's disease (AD) (15–17). Initial support for the possible link between LLD and increased Aβ deposition was found in autopsy studies showing an association between amyloid plaques in dementia patients with a history of major depression (18,19) as well as in studies of plasma $A\beta_{40}$ and cerebrospinal fluid $A\beta_{42}$ levels that indicate altered metabolism of Aβ in LLD (14,20,21). Further support for Aβ as a possible mechanism underlying the connection between LLD and dementia comes from positron emission tomography (PET) studies showing elevated cortical amyloid deposition in LLD relative to control subjects (22,23) and associations between amyloid binding and clinical features of LLD, including increased treatment resistance (24) and apathy severity (25). Studies using PET imaging have also

ISSN: 0006-3223

found positive associations between amyloid burden and subsyndromal depressive symptoms in older adults (26,27), including a higher risk for incident depression (28) and poorer cognitive functioning over time (29). PET imaging has also been used to examine associations between amyloid deposition and depressive symptoms in mild cognitive impairment (MCI) samples, showing increased amyloid deposition and an increased risk for incident dementia (30–33).

Evidence for increased Aβ pathology in LLD has been equivocal, with some studies showing no association of depression history or current depression with increased Aβ (34). In addition, many of the published studies showing elevated Aβ in LLD have been limited by small sample sizes. Only 2 studies (28,33) evaluated *APOE* genotype in group comparisons, which is salient given the known association of *APOE* with AD risk. Furthermore, the majority of previous studies have incomplete depression and treatment histories, which are particularly relevant because of studies that have suggested that selective serotonin reuptake inhibitor (SSRI) treatment may be associated with reductions of Aβ pathology (35). Furthermore, only 2 (29,33) of these previous studies evaluated the relationship of Aβ to memory performance and showed mixed results. Evaluating the association of Aβ to memory functioning in LLD is particularly important because memory dysfunction is central to diagnostic conversion to dementia.

The goal of the present study was to determine if LLD is associated with increased Aβ accumulation and to evaluate the relationship of Aβ deposition to memory performance and depression history characteristics, including SSRI use. Based on previous studies, we predicted that participants with LLD would have higher levels of amyloid deposition than cognitively unimpaired nondepressed (ND) control participants. Furthermore, we expected that greater Aβ accumulation would be associated with poorer memory performance in both LLD and ND participants. Specific to our LLD study sample, we hypothesized that length of lifetime depression history, untreated depression, and number of discrete depressive episodes would be positively associated with Aβ, and that lifetime use of SSRI treatment would be negatively associated with Aβ in the LLD sample.

METHODS AND MATERIALS

Participants

Participants included in the primary analysis to evaluate the relationship between LLD and Aβ PET standardized uptake value ratio (SUVR) included 119 older adults with major depressive disorder (MDD) enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) Depression Project and 119 cognitively unimpaired ND individuals enrolled in the ADNI study. In sensitivity analyses, we also compared LLD and ND individuals restricting the sample to cognitively unimpaired participants in each group. We also compared LLD and ND participants matching the proportion of participants with MCI in each group, as defined by ADNI criteria for determination of MCI. Exclusion of participants with MCI from the ND group in the primary analysis was done to provide the most conservative point of comparison for measures of Aβ PET SUVR between groups because major depression has consistently been associated with memory impairments independent of AD (36,37). All participants provided written informed consent on their enrollment in the study. The study was conducted in accordance with the Declaration of Helsinki for protection of human subjects, with procedures approved by the institutional review boards of each study site.

For participants with LLD, inclusion criteria included current diagnosis of MDD, unipolar type, without psychotic features, with reported symptom severity of ≥15 on the 17-item Hamilton Depression Rating Scale (38), and current episode lasting at least 6 weeks. Diagnoses of MDD were made by a licensed clinical psychologist using the Structured Clinical Interview for DSM (39). Other Axis I disorders and significant current neurological illness, such as epilepsy, Parkinson's disease, traumatic brain injury, or cortical stroke, excluded individuals from participation. Those with diagnoses of dementia or evidence of dementia (<25 on the Mini-Mental State Exam [MMSE]) were also excluded from participation. If inclusion criteria for the study were met, and consent was given, participants underwent a blood draw for DNA and RNA banking (with *APOE* genotyping), magnetic resonance (MR) imaging, and AV-45 (florbetapir) amyloid PET imaging.

For the ND comparison group, data for the present study were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. The ADNI study is conducted in accordance with the Declaration of Helsinki, and procedures were approved by the institutional review boards of all participating sites. All participants provided written informed consent at enrollment. Criteria for cognitively unimpaired participants included an MMSE score of >24, a Global Clinical Dementia Rating of 0.0, and no evidence of memory impairment on neuropsychological assessment based on the revised Wechsler Memory Scale Logical Memory II raw score adjusted for education. MCI criteria included an MMSE score of >24, a Global Clinical Dementia Rating of 0.5, and lower score on the revised Wechsler Memory Scale Logical Memory II relative to an education-corrected cutoff score. Exclusion criteria for the ADNI study at baseline included 1) the presence of MDD or significant symptoms of depression (Geriatric Depression Scale score >6), 2) modified Hachinski ischemia score >5, 3) significant neurological or psychiatric illness, and 4) high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication, and use of narcotic analgesics. ND participants for the primary analysis were selected to match the LLD participants on age, sex, *APOE* ε4 positivity, Aβ PET uptake in the reference region (whole cerebellum), and PET image smoothing parameters (as a proxy for scanner type). ND participants were also restricted to have Geriatric Depression Scale scores <3. In one of two sensitivity analyses, both LLD and ND groups were restricted to cognitively unimpaired participants only and were matched on the same variables as the primary analysis. In a second sensitivity analysis, in which MCI participants were included in both groups, LLD participants were matched to ND participants on diagnosis (proportion of MCI), delayed logical memory, education, and the variables used to match in the primary analysis. The matching procedure was done using propensity scores (40).

Table 1. Demographic and Clinical Characteristics of LLD and ND Groups (*N* = 238)

	ND (*n* = 119)		LLD (*n* = 119)		
Characteristic	Value	Range	Value	Range	*p* Value
Age, Years, Mean ± SD	71.9 ± 5.8	60–89	70.9 ± 5.3	65–91	.15
Education, Years, Mean ± SD	16.5 ± 2.5	12–20	16.3 ± 2.0	12–20	.39
Sex, Female, *n* (%)	72 (61%)		80 (67%)		.35
APOE Status, ε4+, *n* (%)	32 (27%)		32 (27%)		>.99
Cognitive Status, MCI, *n* (%)	0 (0%)		39 (33%)		<.01
MMSE, Mean ± SD	29.1 ± 1.2	24–30	29.1 ± 1.0	26–30	.45
CDR, 0:0.5, *n:n*	118:1		43:75		<.01
GDS Total Score, Mean ± SD	0.6 ± 0.7	0–2	7.3 ± 3.2	1–15	<.01
LM Delayed Recall, Mean ± SD	13.3 ± 3.1	5–23	11.2 ± 4.4	1–20	<.01
Amyloid SUVR, Mean ± SD	1.10 ± 0.16	0.85–1.70	1.06 ± 0.14	0.87–1.61	.02
Amyloid Positivity Rate, Aβ+:Aβ−, *n:n*	37:82		23:96		.05

Group differences were analyzed using Mann-Whitney tests for continuous measures and Fisher's exact test for categorical measures.

CDR, Clinical Dementia Rating Scale; GDS, Geriatric Depression Scale; LLD, late-life depression; LM, Wechsler Adult Intelligence Scale-IIIR Logical Memory Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; ND, nondepressed; SUVR, standardized uptake value ratio.

Procedures

After an initial screening phone interview where inclusion criteria were assessed and demographic data obtained, eligible participants were referred to their corresponding Psychiatry Department site, at either the University of Pittsburgh or the University of California San Francisco, for clinical psychiatric assessment (Structured Clinical Interview for DSM), depression history, and cognitive assessment. Subsequently, participants were evaluated at the ADNI site at the University of Pittsburgh Medical Center or the University of California San Francisco, where they underwent core ADNI study protocols (including cognitive tests, blood draw for DNA and RNA, and MR and PET imaging).

Measures

Memory. Verbal learning and memory were assessed using the revised Wechsler Memory Scale. The Logical Memory test was used to assess learning and memory for stories, with number of story elements recalled as the outcome measure (41).

Depression Severity and History. Severity of depression symptoms at baseline was assessed using the Geriatric Depression Scale (42) and the 17-item Hamilton Depression Rating Scale (38). Depression history was collected with a self-reported retrospective measure that was verified in clinic with research coordinators. Lengths of individual depressive episodes were coded in months. In addition, participants recorded all treatment modalities sought and the duration of each method of treatment, including use of antidepressants. The depression history retrospective measure was developed utilizing the basic structure of the National Institute of Mental Health's life-chart method (43).

Amyloid Burden. Four 5-minute frames were acquired 50–70 minutes after injection and preprocessed as previously described (44). Florbetapir images were coregistered to a contemporaneous structural MR image, which was processed with FreeSurfer v5.3. The cortical summary SUVR was calculated by creating an average of frontal, cingulate, temporal, and parietal regions relative to the whole cerebellum. Aβ-positive status in this cortical summary region was defined as ≥1.11, which is 2 standard deviations above the mean of cognitively normal individuals (45). Individual cortical regions divided by the whole cerebellum also were examined. Finally, for voxelwise analyses, native-space florbetapir images were intensity normalized at the voxelwise level using the mean of the whole cerebellum. The coregistered structural MR image was nonlinearly warped into Montreal Neurological Institute template space, and this transformation was applied to the florbetapir images.

***APOE* Genotype.** DNA was extracted from blood samples using commercial reagents (FlexiGene; Qiagen, Valencia, CA). Two *APOE* single nucleotide polymorphisms, specifically rs7412 and rs429358, were typed using allelic discrimination assays with TaqMan reagents (Applied Biosystems, Foster City, CA). The genotyping results were subsequently incorporated into an algorithm, resulting in designation of ε2, ε3, or ε4 genotypes. For the purpose of this study, genotype was analyzed as a dichotomous variable (presence or absence of 3|4 or 4|4 genotypes, referred to as ε4 allele, commonly associated with increased AD risk).

Statistical Analyses

LLD and ND group differences in demographic characteristics were analyzed using Mann-Whitney tests for continuous measures and Fisher's exact test for categorical measures. Because LLD participants came from 2 PET imaging sites and ND participants came from 33 imaging sites with 9 scanner types/models, we used measures of cerebellum amyloid and PET image smoothing characteristics as covariates in our statistical models to account for observed group differences in cerebellum amyloid and to limit site variability due to scanner type. We compared models summarizing scanner information by their smoothing characteristics and separately by scanner type. Models covarying for smoothing characteristics were selected as the better fitting and more parsimonious models by the Akaike information criterion. Group differences in global and regional Aβ accumulation were tested using robust linear

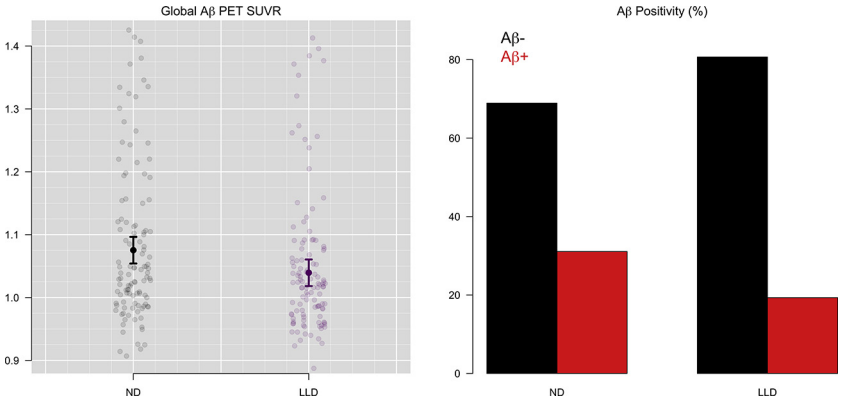

Figure 1. Global amyloid beta (Aβ) positron emission tomography (PET) standardized uptake value ratio (SUVR) and amyloid positivity for the late-life depression (LLD) and nondepressed (ND) groups (*N* = 238).

regression with nonparametric bootstrap permutation tests. Independent variables in the model included age, sex, *APOE* status (at least 1 *APOE* ε4 allele vs. ε4 non-carrier), Aβ uptake in the whole cerebellum, PET image smoothing characteristics, and depression group (LLD vs. ND). Group differences in terms of Aβ positivity were tested using logistic regression. We then evaluated whether memory performance was associated with Aβ deposition. For our LLD-specific analyses, the effect of depression history characteristics (lifetime duration of depression, untreated depression, length of SSRI treatment, and lifetime number of depressive episodes) on global Aβ SUVR was also evaluated with robust linear regression and

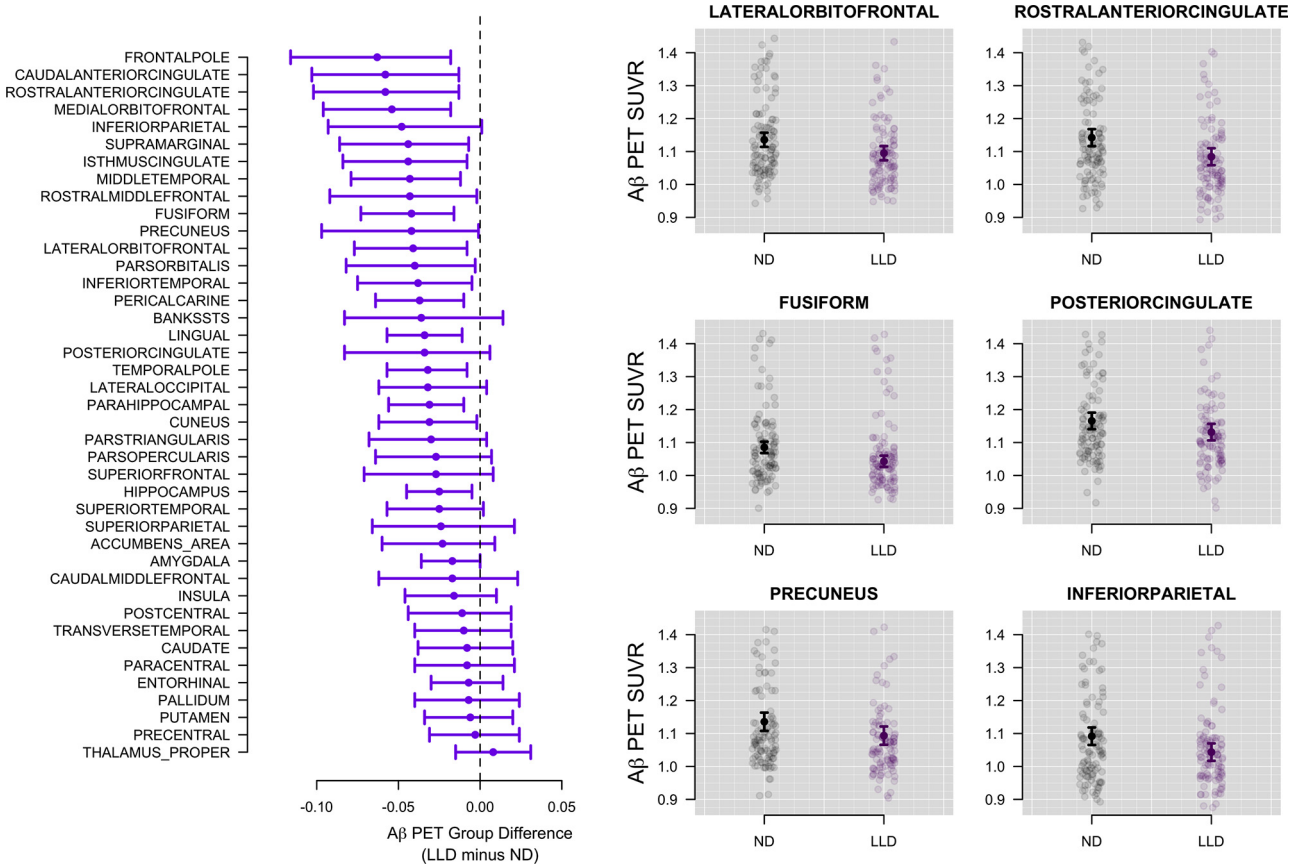

Figure 2. Regional differences in amyloid beta (Aβ) between the late-life depression (LLD) and nondepressed (ND) groups (*N* = 238). Estimated Aβ positron emission tomography (PET) standardized uptake value ratio (SUVR) differences between the LLD and ND groups for all regions are shown on the left. A value of −0.05, for example, indicates that the LLD group had 0.05 lower average SUVR compared with the ND group.

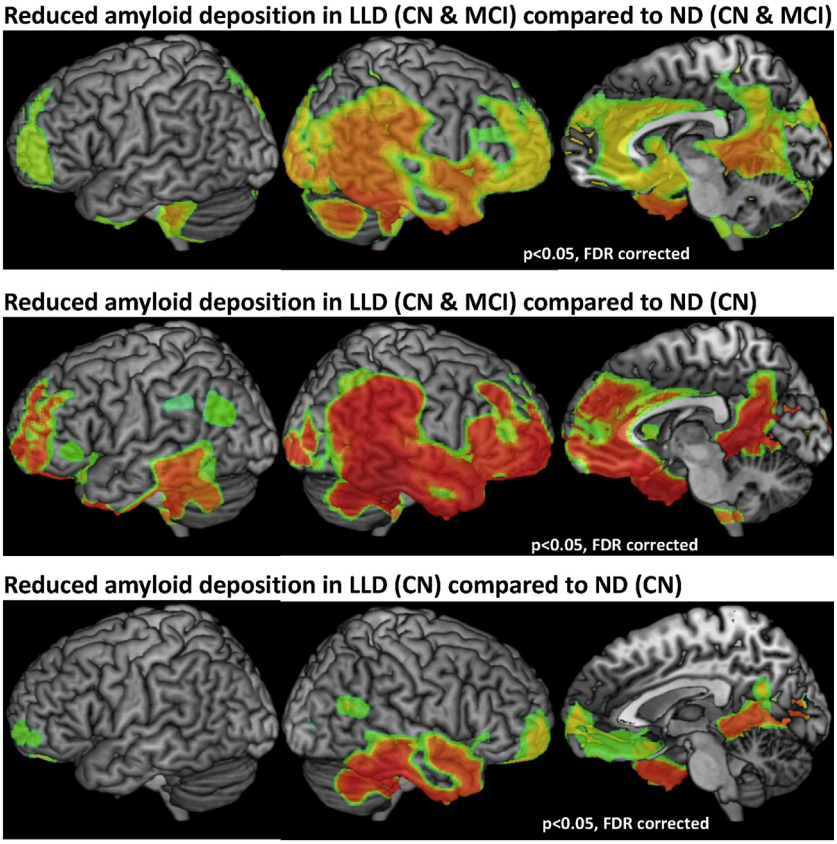

Figure 3. Depression group differences in amyloid beta (Aβ) (*N* = 238). ADNI, nondepressed Disease Neuroimaging Initiative participants; ADNI-D, Alzheimer's Disease Neuroimaging Initiative Depression Project participants; CN, cognitively normal; FDR, false discovery rate; MCI, mild cognitive impairment.

permutation tests. Voxelwise analyses were carried out in SPM12 using the same covariates. The *p* values for group differences in regional Aβ accumulation were adjusted for multiple comparisons using a false discovery rate correction. The *p* values for the effects of depression history characteristics were adjusted using a Holm correction (46). All *p* values were 2 tailed and considered to be significant at the $\alpha = .05$ level. Statistical analyses were conducted with the R Package (v3.6.0, www.r.project.org).

RESULTS

Participants included 119 LLD and 119 cognitively unimpaired ND individuals with a mean age of 71.4 years (SD = 5.6), a mean of 16.4 years of education (SD = 2.2), 63.9% female, and 26.9% *APOE*+. The LLD group and ND group did not differ on these characteristics (Table 1). In the LLD group, 33% met criteria for MCI and the mean Hamilton Depression Rating Scale score was 18.2 (SD = 2.6). By design, the LLD group reported greater symptoms of depression on the Geriatric Depression Scale than the ND group (LLD = 7.3, ND = 0.56; $p < .001$) and they exhibited poorer performance on the logical memory delayed recall test (LLD = 11.2, ND = 13.3; $p < .001$). The two groups did not differ regarding overall measures of mental status (mean MMSE = 29.1 in both groups; $p = .45$). Regarding depression history characteristics, the LLD group had a mean lifetime length of depression of 263.4 months (SD = 223.8), a mean lifetime length of untreated depression of 139.1 months (SD = 190.0), a mean lifetime length of SSRI treatment of 56.8 months (SD = 92.8), and a mean lifetime number of depressive episodes of 2.5 (SD = 1.8).

Aβ Deposition

Compared with the cognitively unimpaired ND group, the LLD group displayed significantly lower global Aβ deposition ($\beta = -0.04$, $p = .05$) and a lower rate of Aβ positivity (19.3% vs. 31.1%; log odds ratio [OR] = −0.97, $p = .02$) (Figure 1). Regional Aβ SUVR and whole-brain differences are shown in Figures 2 and 3. Other significant predictors of Aβ positivity included increasing age (log OR = 0.09, $p < .01$), female sex (log OR = 1.08, $p = .01$), and *APOE* positivity (log OR = 1.47, $p < .01$) (Table 2). Individual regions of interest were compared between groups and adjusted for multiple comparisons (Table S1). Aβ deposition was significantly lower in the LLD group in the frontal pole ($\beta = -0.063$, $p < .001$), lingual gyrus ($\beta = -0.34$, $p < .001$), caudal ($\beta = -0.06$, $p = .02$) and rostral ($\beta = -0.06$, $p = .02$) anterior cingulate, and the fusiform gyrus ($\beta = -0.04$, $p = .02$), medial orbitofrontal cortex ($\beta = -0.05$, $p = .02$), lateral orbitofrontal ($\beta = -0.04$, $p = .05$), supramarginal ($\beta = -0.04$, $p = .02$), middle temporal ($\beta = -0.04$, $p = .04$), parahippocampal ($\beta = -0.03$, $p = .04$), pericalcarine ($\beta = -0.04$,

Table 2. Regression Results of the Relationship Between Late-Life Depression and Amyloid Positivity

Variable	Log Odds Ratio	SE	*z* Value	*p* Value
(Intercept)	−6.36	5.81	−1.10	.27
Whole Cerebellum	7.00	3.04	2.31	.02
Age	0.09	0.03	3.09	<.01
Sex	1.08	0.40	2.72	.01
APOE ε4+	1.47	0.35	4.16	<.01
XY.smoothing	−0.67	0.85	−0.79	.43
Z.smoothing	−1.28	1.05	−1.23	.22
Depression Group	−0.97	0.41	−2.35	.02

p = .0), hippocampus (β = −0.03, p = .04), isthmus cingulate (β = −0.04, p = .04), temporal pole (β = −0.03, p = .04), and inferior parietal (β = −0.05, p = .05) regions. Within the LLD group there was no difference in amyloid positivity or SUVR associated with MCI diagnosis ($p > .23$).

Sensitivity Analyses

Similar results were observed when the ND comparison group was matched for MCI status (Table S2), with the LLD group showing decreased global Aβ SUVR (β = −0.05, p = .02) and reduced amyloid positivity (19.3% vs. 39.5%, log OR = −1.27; p = .002). When only cognitively unimpaired LLD participants were compared with cognitively unimpaired ND participants (Table S3), SUVR between groups was not significantly different (β = −0.03, p = .39), but the rate of amyloid positivity was significantly lower (16.2% vs. 30.0%, log OR = −1.12; p = .03).

Relation Between Memory Performance and Amyloid Deposition

After adjusting for age, sex, education, and depression group, Aβ SUVR was associated with poorer memory performance (β = −3.29, p = .05) (Figure 4), and this relationship did not differ by depression group (p = .25). Depression was significantly associated with poorer memory performance after accounting for age, sex, education, Aβ SUVR, and MCI diagnosis (β = −1.32, p = .01).

Depression Characteristics for the LLD Group

After accounting for age, sex, education, and *APOE* status, and correcting for multiple comparisons, lifetime duration of depression (β = 0.00, $p > .99$), duration of untreated depression (β = 0.00, $p > .99$), lifetime depressive episodes (β = 0.0001, $p > .99$), and length of lifetime SSRI treatment (β = 0.0002, p = .22) were not associated with Aβ PET SUVR (Figure 5).

DISCUSSION

This study evaluated group differences in amyloid deposition in a large well-characterized sample of older adults with and without major depression. Contrary to expectations that the LLD group would exhibit higher rates of amyloid deposition based on literature evidence of accelerated cognitive decline (9) and neurodegeneration in older depressed adults (23), the LLD group had significantly lower total amyloid deposition and

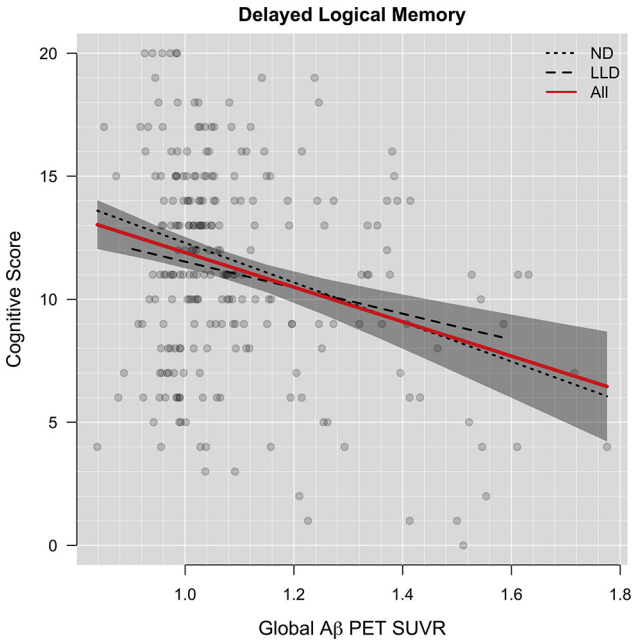

Figure 4. Association of amyloid beta (Aβ) with memory performance (N = 238). Delayed logical memory is plotted against global Aβ positron emission tomography (PET) standardized uptake value ratio (SUVR). Dashed lines show the late-life depression (LLD) and nondepressed (ND) groups separately. The red curve shows both groups combined.

lower rates of amyloid positivity than ND participants. When looking at regional deposition of amyloid, the differences were particularly pronounced in the frontal pole, rostral and anterior cingulate, and medial orbitofrontal and middle temporal cortex. Our results also showed that amyloid burden was associated with memory performance but was not associated with depression history characteristics in this sample. Before discussing our results, it is worth noting that our decision to compare an LLD group of mixed cognitive status (cognitively unimpaired, MCI) with cognitively unimpaired control subjects in primary analyses was to place the most stringent constraints on identifying group differences that might indicate increased amyloid accumulation in the sample, because MDD has been shown to affect memory performance and functional status independent of AD (36,47). Therefore, relying solely on a cognitively matched sample may have likely resulted in a higher incidence of AD pathology in the comparison group. Each of our findings will be discussed below.

In our primary analysis we compared the LLD sample (of whom 33% had MCI) with the ND control subjects without MCI. Our results showed that amyloid burden was reduced in the LLD group. Comparison of the LLD group with an ND control group matched for the proportion with MCI produced similar results. Our finding of reduced amyloid in our depression sample was not expected given prior literature stating that LLD is a risk factor for accelerated cognitive decline and the development of both MCI and dementia (1,9,48), the comorbidity of LLD and AD (49), and cerebrospinal fluid studies of Aβ (19–21). As might be expected, when the comparison subjects matched for cognitive status (MCI) were added into the

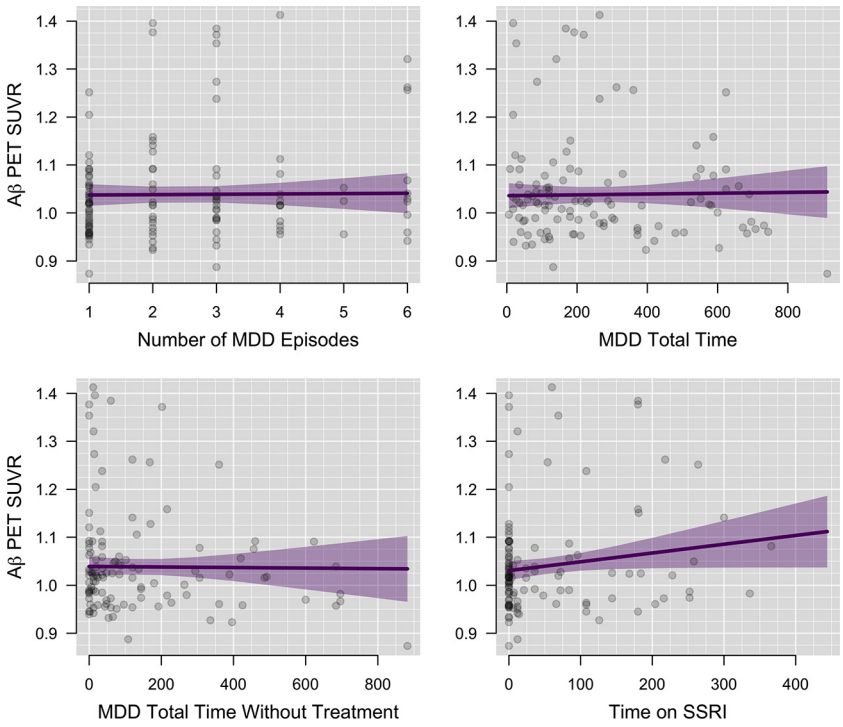

Figure 5. Association of amyloid beta (Aβ) with depression characteristics and treatment history (N = 238). Global Aβ positron emission tomography (PET) standardized uptake value ratio (SUVR) is plotted against depression characteristics. Time variables are depicted in days. MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor.

analysis, these group differences (lower amyloid deposition and positivity in the LLD group) became even more pronounced. However, when restricting the analyses to only cognitively normal LLD and ND participants, SUVR comparisons were no longer significant whereas differences in amyloid positivity persisted. Collectively, these results suggest that other non–amyloid-mediated pathways are likely associated with risk for accelerated cognitive decline and dementia reported in LLD. It is worth noting that most previous work supporting the link between LLD and increased amyloid had not been done with in vivo amyloid PET imaging, nor included a large number of clinically depressed participants with control subjects matched for demographic, genetic, and clinical features for comparison purposes.

It is also possible that there are mechanisms of major depression that reduce amyloid deposition. In particular, reduced cerebral blood flow or hypometabolism may limit amyloid uptake in the regions most affected in depression, specifically, regions such as the cingulate and orbitofrontal cortex. However, in our data we did not see any association of depression history that was significantly associated with amyloid that would have supported this hypothesis. Similarly, we did not see any association of depression treatments, most notably length of SSRI treatments, with decreased amyloid accumulation in the sample. We also note that the majority of LLD participants in this sample were early onset, with long histories of depression, and there is the potential for late onset of depression being more strongly linked to increased amyloid burden.

In the entire sample of LLD and ND subjects, we also reported an association between amyloid burden and decreased memory performance. These results are notable in that the association between cognition and amyloid is often weak in cognitively normal individuals (50) and the majority of our sample were cognitively unimpaired. Furthermore, we reported the expected association between memory performance and depression status, with LLD participants performing worse on memory tests. We did not, however, see an interaction between amyloid positivity and depression status with regard to memory performance. Taken together, we would conclude that the impact of depression on memory function, independent of amyloid, is likely a significant contributor to risk of future cognitive decline. This relationship could be a direct consequence of depressed mood on cognition and functional status, or it could stem from other factors such as cortical atrophy associated with depressive symptoms (51). Furthermore, for individuals with other concurrent neurodegenerative processes, including amyloid deposition, this additional effect of depression could contribute to accelerated rates of cognitive decline and faster conversion to dementia.

Although our results are robust and have several possible explanations to consider in terms of etiology, there are some limitations to state. In particular, the cross-sectional nature of the data presented does not allow for evaluation of longitudinal cognitive function or future amyloid status in either group. That is, it is possible that the LLD group will still experience accelerated cognitive decline relative to ND participants when followed over the course of years, or will convert more rapidly to amyloid positivity when measured over time. Furthermore, our results suggest that there is potential for sampling bias in that individuals with MCI due to AD that also have concurrent LLD

may have 2 distinct contributors to cognitive dysfunction. As a result, these individuals with greater amyloid burden and associated impact on memory performance may be more likely to receive a dementia diagnosis earlier and would have been excluded from this study. In addition, despite protocols designed to limit site-specific effects of PET image acquisition and our approach to minimize these potential effects in our analyses, there is the potential that site-specific imaging acquisition influenced our results, given that our imaging data were obtained from many sites. To our knowledge, this study is the first to investigate in vivo amyloid differences in large samples of clinically depressed and ND older adults that matched participants on *APOE* status. Given known associations between *APOE* and amyloid accumulation, we believe this is a critical factor to consider when evaluating links between amyloid and depression. Our sample also met criteria for current major depression and reported long lifetime histories of depression and various depression treatments, which also represent critical considerations when evaluating group differences in amyloid.

Although we did not evaluate longitudinal outcomes in this study, our results suggest that increased cortical amyloid burden is not a primary causal factor in reported increased risk for dementia associated with major depression in older adults (13). This conclusion is strengthened by a lack of association between depression characteristics and history of treatment with amyloid burden. In contrast, our findings that depression was strongly linked to memory dysfunction, independent of amyloid, suggests that LLD may accelerate progression to dementia by contributing to cognitive and functional burden among individuals with concurrent MCI or incipient neurodegenerative disease.

ACKNOWLEDGMENTS AND DISCLOSURES

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Depression project (ADNI-D) (National Institute of Mental Health Grant No. R01098062 and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant No. U01 AG024904).

We acknowledge the Ray and Dagmar Dolby Family Fund for research support and Avid Radiopharmaceuticals for providing florbetapir for this study.

Data used in preparation of this article were obtained from the ADNI-D and ADNI databases (www.loni.usc.edu). As such, the investigators within the ADNI-D and ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI-D and ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and contributions from the following: Abbott, AstraZeneca, Bayer Schering Pharma, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan Corp., Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson and Johnson, Eli Lilly and Co., Medpace, Merck and Co., Novartis, Pfizer, F. Hoffman–La Roche, Schering-Plough, and Synarc as well as nonprofit partners the Alzheimer's Association and Alzheimer's Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private-sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of California, Los Angeles.

RSM has received research support from the National Institute of Mental Health and Johnson and Johnson. SL has received research support from the National Institute on Aging and has consulted for NeuroVision and Cortexyme. RR has received research support from the National Institute on Aging, Eli Lilly, and Janssen. MWW has served on the scientific advisory boards for Pfizer, BOLT International, Neurotrope Bioscience, Alzheon, the Alzheimer's Therapeutic Research Institute, Eli Lilly, the University of Pennsylvania's Neuroscience of Behavior Initiative, the National Brain Research Centre (India), Dolby Family Ventures, and ADNI. CN has been an advisor or consultant to Assurex, Eiasi, FVS-7, and Janssen. The other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Departments of Psychiatry (RSM, PSI, DB, MWW, CN) and Radiology (DT, MWW), University of California, San Francisco; Memory and Aging Center (HJR), Department of Neurology, University of California, San Francisco; Center for Imaging of Neurodegenerative Diseases (RSM, RM, ER, DT, MWW), Veterans Administration Medical Center, San Francisco; Helen Wills Neuroscience Institute (SL), University of California, Berkeley; Department of Neurology (PA, RR), University of Southern California, San Diego; Alzheimer's Therapeutic Research Institute (PA, RR), San Diego; Laboratory of Neuro Imaging (AT), Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, California; Clinical Memory Research Unit (PSI), Faculty of Medicine, Lund University, Lund, Sweden; Department of Psychiatry (MB), Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Department of Radiology and Imaging Sciences (AS), Indiana University School of Medicine, Indianapolis, Indiana; Mayo Clinic (CJ), Rochester, Minnesota; and Department of Radiology (RK), University of Michigan, Ann Arbor, Michigan.

Address correspondence to R. Scott Mackin, Ph.D., at scott.mackin@ucsf.edu, or Philip Insel, M.S., at philipinsel@gmail.com.

Received Mar 15, 2020; revised May 26, 2020; accepted Jun 9, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2020.06.017.

REFERENCES

1. Yaffe K, Blackwell T, Gore R, Sands L, Reus V, Browner WS (1999): Depressive symptoms and cognitive decline in nondemented elderly women: A prospective study. Arch Gen Psychiatry 56:425–430.
2. Sachs-Ericsson N, Joiner T, Plant EA, Blazer DG (2005): The influence of depression on cognitive decline in community-dwelling elderly persons. Am J Geriatr Psychiatry 13:402–408.
3. Chodosh J, Kado DM, Seeman TE, Karlamangla AS (2007): Depressive symptoms as a predictor of cognitive decline: MacArthur Studies of Successful Aging. Am J Geriatr Psychiatry 15:406–415.
4. Bielak AA, Gerstorf D, Kiely KM, Anstey KJ, Luszcz M: Depressive symptoms predict decline in perceptual speed in older adulthood. Psychol Aging 26:576–583.
5. Comijs HC, Jonker C, Beekman AT, Deeg DJ (2001): The association between depressive symptoms and cognitive decline in community-dwelling elderly persons. Int J Geriatr Psychiatry 16:361–367.
6. Grabovich A, Lu N, Tang W, Tu X, Lyness JM: Outcomes of subsyndromal depression in older primary care patients. Am J Geriatr Psychiatry 18:227–235.
7. Cui X, Lyness JM, Tu X, King DA, Caine ED (2007): Does depression precede or follow executive dysfunction? Outcomes in older primary care patients. Am J Psychiatry 164:1221–1228.
8. Wilson RS, Barnes LL, Mendes de Leon CF, Aggarwal NT, Schneider JS, Bach J, *et al.* (2002): Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology 59:364–370.
9. Gabryelewicz T, Styczynska M, Luczywek E, Barczak A, Pfeffer A, Androsiuk W, *et al.* (2007): The rate of conversion of mild cognitive impairment to dementia: Predictive role of depression. Int J Geriatr Psychiatry 22:563–567.
10. Modrego PJ, Ferrandez J (2004): Depression in patients with mild cognitive impairment increases the risk of developing dementia of

Alzheimer type: A prospective cohort study. Arch Neurol 61:1290–1293.
11. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R (2010): Depressive symptoms and risk of dementia: The Framingham Heart Study. Neurology 75:35–41.
12. Chan W-C, Lam LC-W, Tam CW-C, Lui VW-C, Chan SS-M, Chan W-M, Chiu HF-K (2010): Prevalence of neuropsychiatric symptoms in Chinese older persons with mild cognitive impairment—a population-based study. Am J Geriatr Psychiatry 18:948–954.
13. Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JL, *et al.* (2013): Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol 70:374–382.
14. Kita Y, Baba H, Maeshima H, Nakano Y, Suzuki T, Arai H (2009): Serum amyloid beta protein in young and elderly depression: A pilot study. Psychogeriatrics 9:180–185.
15. Braak H, Braak E (1991): Morphologische Veranderungen der menschlichen Endhirnrinde bei Demenz [Morphological changes in the human cerebral cortex in dementia]. J Hirnforsch 32:277–282.
16. Oh H, Madison C, Villeneuve S, Markley C, Jagust WJ (2014): Association of gray matter atrophy with age, beta-amyloid, and cognition in aging. Cereb Cortex 24:1609–1618.
17. Kawas CH, Greenia DE, Bullain SS, Clark CM, Pontecorvo MJ, Joshi AD, Corrada MM (2013): Amyloid imaging and cognitive decline in nondemented oldest-old: The 90+ Study. Alzheimers Dement 9:199–203.
18. Rapp MA, Schnaider-Beeri M, Grossman HT, Sano M, Perl DP, Purohit DP, *et al.* (2006): Increased hippocampal plaques and tangles in patients with alzheimer disease with a lifetime history of major depression. JAMA Psychiatry 63:161–167.
19. Sweet RA, Hamilton RL, Butters MA, Mulsant BH, Pollock BG, Lewis DA, *et al.* (2004): Neuropathologic correlates of late-onset major depression. Neuropsychopharmacology 29:2242–2250.
20. Pomara N, Doraiswamy PM, Willoughby LM, Roth AE, Mulsant BH, Sidtis JJ, *et al.* (2006): Elevation in plasma Abeta42 in geriatric depression: A pilot study. Neurochem Res 31:341–349.
21. Sun X, Steffens DC, Au R, Folstein M, Summergrad P, Yee J, *et al.* (2008): Amyloid-associated depression: A prodromal depression of Alzheimer disease? JAMA Psychiatry 65:542–550.
22. Kumar A, Kepe V, Barrio JR, Siddarth P, Manoukian V, Elderkin-Thompson V, Small GW (2011): Protein binding in patients with late-life depression. Arch Gen Psychiatry 68:1143–1150.
23. Wu K-Y, Hsiao I-T, Chen C-S, Chen C-H, Hsieh C-J, Wai Y-Y, *et al.* (2014): Increased brain amyloid deposition in patients with a lifetime history of major depression: Evidenced on ^{18}F-florbetapir (AV-45/Amyvid) positron emission tomography. Eur J Nucl Med Mol Imaging 41:714–722.
24. Li P, Hsiao I-T, Liu C-Y, Chen C-H, Huang S-Y, Yen T-C, *et al.* (2017): Beta-amyloid deposition in patients with major depressive disorder with differing levels of treatment resistance: A pilot study. EJNMMI Res 7:24–24.
25. Eyre HA, Siddarth P, van Dyk K, Cyr Ns, Baune BT, Barrio JR, *et al.* (2017): Neural correlates of apathy in late-life depression: A pilot [^{18}F] FDDNP positron emission tomography study. Psychogeriatrics 17:186–193.
26. Krell-Roesch J, Lowe VJ, Neureiter J, Pink A, Roberts RO, Mielke MM, *et al.* (2018): Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: The Mayo Clinic Study of Aging. Int Psychogeriatr 30:245–251.
27. Donovan NJ, Locascio JJ, Marshall GA, Gatchel J, Hanseeuw BJ, Rentz DM, *et al.* (2018): Longitudinal association of amyloid beta and anxious-depressive symptoms in cognitively normal older adults. Am J Psychiatry 175:530–537.
28. Harrington KD, Gould E, Lim YY, Ames D, Pietrzak RH, Rembach A, *et al.* (2017): Amyloid burden and incident depressive symptoms in cognitively normal older adults. Int J Geriatr Psychiatry 32:455–463.
29. Gatchel JR, Rabin JS, Buckley RF, Locascio JJ, Quiroz YT, Yang H-S, *et al.* (2019): Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. JAMA Netw Open 2:e198964.
30. Brendel M, Pogarell O, Xiong G, Delker A, Bartenstein P, Rominger A, Alzheimer's Disease Neuroimaging Initiative (2015): Depressive symptoms accelerate cognitive decline in amyloid-positive MCI patients. Eur J Nucl Med Mol Imaging 42:716–724.
31. Moon B, Kim S, Park YH, Lim J-S, Youn YC, Kim SY, *et al.* (2017): Depressive symptoms are associated with progression to dementia in patients with amyloid-positive mild cognitive impairment. J Alzheimers Dis 58:1255–1264.
32. Chung JK, Plitman E, Nakajima S, Chow TW, Chakravarty MM, Caravaggio F, *et al.* (2016): Lifetime history of depression predicts increased amyloid-beta accumulation in patients with mild cognitive impairment. J Alzheimers Dis 49:1189–1190.
33. Wu K-Y, Liu C-Y, Chen C-S, Chen C-H, Hsiao I-T, Hsieh C-J, *et al.* (2016): 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. Eur J Nucl Med Mol Imaging 43:1067–1076.
34. Madsen K, Hasselbalch BJ, Frederiksen KS, Haahr ME, Gade A, Law I, *et al.* (2012): Lack of association between prior depressive episodes and cerebral [^{11}C]PiB binding. Neurobiol Aging 33:2334–2342.
35. Sheline YI, West T, Yarasheski K, Swarm R, Jasielec MS, Fisher JR, *et al.* (2014): An antidepressant decreases CSF Aβ production in healthy individuals and in transgenic AD mice. Sci Transl Med 6:236re4.
36. Porter RJ, Gallagher P, Thompson JM, Young AH (2003): Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 182:214–220.
37. Butters MA, Whyte EM, Nebes RD, Begley AE, Dew MA, Mulsant BH, *et al.* (2004): The nature and determinants of neuropsychological functioning in late-life depression. Arch Gen Psychiatry 61:587–595.
38. Hamilton M (1960): A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56.
39. American Psychiatric Association (1994): DSM-IV, Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychiatric Association.
40. Ho DE, Imai K, King G, Stuart EA (2007): Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Polit Anal 15:199–236.
41. Wechsler D (1987): Wechsler Memory Scale—Revised: Manual. Psychological Corporation.
42. Yesavage JA (1988): Geriatric Depression Scale. Psychopharmacol Bull 24:709–711.
43. Born C, Amann BL, Grunze H, Post RM, Schärer L (2014): Saving time and money: A validation of the self ratings on the prospective NIMH Life-Chart Method (NIMH-LCM). BMC Psychiatry 14:130.
44. Jagust WJ, Landau SM, Koeppe RA, Reiman EM, Chen K, Mathis CA, *et al.* (2015): The Alzheimer's Disease Neuroimaging Initiative 2 PET Core: 2015. Alzheimer Dement 11:757–771.
45. Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, *et al.* (2012): Amyloid deposition, hypometabolism, and longitudinal cognitive decline. Ann Neurol 72:578–586.
46. Holm S (1979): A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70.
47. Jaeger J, Berns S, Uzelac S, Davis-Conway S (2006): Neurocognitive deficits and disability in major depressive disorder. Psychiatry Res 145:39–48.
48. Byers AL, Yaffe K (2011): Depression and risk of developing dementia. Nat Rev Neurol 7:323–331.
49. Chi S, Wang C, Jiang T, Zhu X-C, Yu J-T, Tan L (2015): The prevalence of depression in Alzheimer's disease: A systematic review and meta-analysis. Curr Alzheimer Res 12:189–198.
50. Hedden T, Oh H, Younger AP, Patel TA (2013): Meta-analysis of amyloid-cognition relations in cognitively normal older adults. Neurology 80:1341–1348.
51. Gonzales MM, Insel PS, Nelson C, Tosun D, Mattsson N, Mueller SG, *et al.* (2017): Cortical atrophy is associated with accelerated cognitive decline in mild cognitive impairment with subsyndromal depression. Am J Geriatr Psychiatry 25:980–991.