Title

Association of Midlife Depressive Symptoms with Regional Amyloid-β and Tau in the Framingham Heart Study.

Journal

Journal of Alzheimer's Disease, 82(1)

ISSN

1387-2877

Authors

Gonzales, Mitzi M
Samra, Jasmeet
O'Donnell, Adrienne
et al.

Publication Date

2021

DOI

10.3233/jad-210232

Peer reviewed

HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2022 March 07.

Published in final edited form as:

J Alzheimers Dis. 2021 ; 82(1): 249–260. doi:10.3233/JAD-210232.

Association of Midlife Depressive Symptoms with Regional Amyloid-β and Tau in the Framingham Heart Study

Mitzi M. Gonzales[a,b,*], **Jasmeet Samra**[c,d], **Adrienne O'Donnell**[c,d], **R. Scott Mackin**[e,f], **Joel Salinas**[g], **Mini Jacob**[a,c,h,i], **Claudia L. Satizabal**[a,c,h,i], **Hugo J. Aparicio**[c,i], **Emma G. Thibault**[j], **Justin S. Sanchez**[j], **Rebecca Finney**[c], **Zoe B. Rubinstein**[j], **Danielle V. Mayblyum**[j], **Ron J. Killiany**[i,k], **Charlie S. Decarli**[l,m], **Keith A. Johnson**[j,n,o], **Alexa S. Beiser**[c,d,i], **Sudha Seshadri**[a,b,c,i]

[a]Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Science Center, San Antonio, TX, USA

[b]Department of Neurology, University of Texas Health Science Center, San Antonio, TX, USA

[c]The Framingham Heart Study, Framingham, MA, USA

[d]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

[e]Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

[f]Center for Imaging of Neurodegenerative Disease, Veteran Affairs Administration, San Francisco, CA, USA

[g]Department of Neurology, New York University Grossman School of Medicine, New York, NY, USA

[h]Department of Population Health Sciences, University of Texas Health Science Center, San Antonio, TX, USA

[i]Department of Neurology, Boston University School of Medicine, Boston, MA, USA

[j]Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[k]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA, USA

[l]Department of Neurology, University of California Davis, Davis, CA, USA

[m]Center for Neuroscience, University of California Davis, Davis, CA, USA

[n]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[*]Correspondence to: Mitzi M. Gonzales, PhD, Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, Department of Neurology, University of Texas Health San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA. Tel.: +1 210 450 9047; GonzalesM20@uthscsa.edu.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-0232r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-210232.

[o]Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Abstract

Background: Depressive symptoms predict increased risk for dementia decades before the emergence of cognitive symptoms. Studies in older adults provide preliminary evidence for an association between depressive symptoms and amyloid-β (Aβ) and tau accumulation. It is unknown if similar alterations are observed in midlife when preventive strategies may be most effective.

Objective: The study aim was to evaluate the association between depressive symptoms and cerebral Aβ and tau in a predominately middle-aged cohort with examination of the apolipoprotein (*APOE*) *ε*4 allele as a moderator.

Methods: Participants included 201 adults (mean age 53±8 years) who underwent ^{11}C-Pittsburgh Compound B amyloid and ^{18}F-Flortaucipir tau positron emission tomography (PET) imaging. Depressive symptoms were evaluated with the Center for Epidemiological Studies Depression Scale (CES-D) at the time of PET imaging, as well as eight years prior. Associations between depressive symptoms at both timepoints, as well as depression (CES-D≥ 16), with regional Aβ and tau PET retention were evaluated with linear regression adjusting for age and sex. Interactions with the *APOE ε*4 allele were explored.

Results: Depressive symptoms and depression were not associated with PET outcomes in the overall sample. However, among *APOE ε*4 allele carriers, there was a significant cross-sectional association between depressive symptoms and increased tau PET uptake in the entorhinal cortex (β = 0.446, SE = 0.155, p = 0.006) and amygdala (β = 0.350, SE = 0.133, p = 0.012).

Conclusion: Although longitudinal studies are necessary, the results suggest that *APOE ε*4 carriers with depressive symptoms may present with higher susceptibility to early tau accumulation in regions integral to affective regulation and memory consolidation.

Keywords

Amygdala; amyloid-β; APOE; depression; depressive symptoms; entorhinal; PET imaging; tau

INTRODUCTION

Late-life depression, a prevalent and potentially treatable psychiatric condition that manifests after age 60, has been associated with a four-fold higher risk of incident Alzheimer's disease and related dementias (ADRDs) [1]. Late life depressive symptoms, even below the threshold for a clinical diagnosis, have been associated with cognitive decline and accelerated cerebral atrophy [2, 3]. Depression that develops earlier in the lifespan has also been associated with increased dementia risk [4]. Notably, depressive symptoms have been found to predict incident ADRD up to 25 years before overt cognitive symptoms emerge [5], suggesting that neuropsychiatric symptoms may be an etiological risk factor or an early manifestation of neurodegenerative disease. Enhanced understanding of the neurobiological mechanisms linking depressive symptoms with ADRDs in the prodromal stage may advance the development of novel prevention strategies [6].

Elevations in amyloid-β (Aβ), which can emerge decades prior to dementia diagnosis, are a harbinger for progressive cognitive decline and incident AD [7]. Support for a potential pathogenic link between Aβ deposition and depression is derived from postmortem studies of AD reporting a higher burden of hippocampal Aβ plaques and neurofibrillary tangles in individuals with a lifetime history of depression [8]. Major depression and depressive symptoms in late-life have also been associated with Aβ levels assessed in plasma, cerebrospinal fluid (CSF), and positron emission tomography (PET) imaging [9, 10]. Moreover, multiple cohort studies of older adults have reported that higher cerebral Aβ levels predict increased depressive symptomatology over time [11–13]. Nonetheless, not all studies have reported an association between depression and Aβ levels [9, 14]. A recent investigation from the ADNI Depression study reported that older adults with late-life depression had poorer memory performance, yet lower cerebral Aβ levels than age-matched non-depressed controls [15]. The findings suggest that the association between depression and cognitive decline may be governed, at least in part, by mechanisms outside of the Aβ pathway [14].

As compared to Aβ, tau deposition more strongly correlates with phenotypic ADRD features such as cerebral hypometabolism and cognitive decline [16–19]. As such, tau may also be more closely coupled with neuropsychiatric symptoms. Contrary to this hypothesis, a meta-analytic study failed to detect an association between depression diagnosis and CSF levels of total and phosphorylated tau [20]. To date, only a few studies have examined the association between depression and tau with PET imaging. In the Harvard Aging Brain Study, increased depressive symptoms were related to higher tau PET deposition in the inferior temporal lobe and entorhinal cortex within cognitively unimpaired older adults [21]. A recent study by Babulal et al. reported that cognitively intact older adults with elevated tau PET retention in a composite region comprised of the amygdala, inferior temporal lobe, entorhinal cortex, and the lateral occipital lobe were two times more likely to meet diagnostic criteria for depression [14].

While support exists for a mechanistic link between depression and Aβ and tau accumulation, the findings have been inconsistent across studies. Thus, further research is needed, particularly leveraging PET imaging to better characterize spatial patterns of deposition. The primary aim of the current study was to examine the association of depressive symptoms, as well as the presence of more significant symptoms meeting criteria for depression, with regional Aβ and tau PET retention. While prior literature has focused on older adults [11, 14, 21], the present study examined a predominately middle-aged sample. As ADRDs have a protracted pre-symptomatic period that extends across decades [7], examinations conducted at midlife may shed insight on the initial pathophysiological changes and facilitate preventive efforts. In addition to examining cross-sectional relationships, we also evaluated the association between change in depressive symptomatology over time with PET imaging outcomes. Furthermore, as apolipoprotein (*APOE*) ε4 carriage has been linked with neuropathological protein accumulation [12, 22, 23] and increased risk of depression in some cohorts, we examined interactions with *APOE* ε4 carrier status. Based on previous studies conducted in older adult samples [11, 14, 21], we hypothesized that regional Aβ and tau PET retention levels would be associated with depressive symptoms at baseline and change over time. We further

hypothesized a moderating effect of *APOE* with stronger associations in $\varepsilon 4$ carriers relative to non-carriers. Finally, we conducted sensitivity analyses to examine if our findings remain consistent with adjustment for antidepressant usage. In animal models, selective serotonin reuptake inhibitors (SSRIs) have been associated with lower amyloid beta burden with some converging evidence in human studies [24, 25]. However, population-based research has produced conflicting results with antidepressant use being linked to both increased and decreased risk of incident dementia [26–28]. Therefore, additional research exploring the potentially modifying role of antidepressant usage on PET imaging ing outcomes is necessary.

MATERIALS AND METHODS

Participants

The Framingham Heart Study (FHS) was initiated in 1948 with enrollment of the Original Cohort, followed by the enrollment of the Offspring cohort (children of the Original Cohort and their spouses) in 1971 and enrollment of the Third Generation cohort (grandchildren of the Original Cohort and children of the Offspring Cohort) in 2002 [29]. The Third Generation cohort completed their first examination between 2003–2005, which was followed by their second examination between 2008 to 2011, and their third examination between 2016 to 2019. At the third examination, a subset of the Third Generation cohort completed their first amyloid and tau PET scans for the study. These individuals were included in the current analyses.

Eligibility for the PET imaging sub-study, as well as for inclusion in the current analyses, included age 32 to 75 years at the time of the third examination, prior completion of FHS examination two, and absence of significant neurological conditions including clinical stroke, dementia, and multiple sclerosis. As previously described, FHS participants undergo routine cognitive screening and comprehensive monitoring for continual surveillance of dementia [30], which was exclusionary for participation in the PET imaging sub-study. Depressive symptoms were assessed at examinations 2 and 3. All participants provided written informed consent at the time of enrollment. The study was approved by the Institutional Review Board at Boston University Medical Center and the Massachusetts General Hospital.

Assessment of depressive symptoms

Depressive symptoms were evaluated using the Center for Epidemiological Studies Depression Scale (CES-D) at the second and third examinations [31]. The CES-D is a 20-item self-report questionnaire with response options ranging from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). The total score range is between 0 to 60 points with higher scores indicating greater depressive symptomatology. In accordance with previous studies, a CES-D score of 16 or greater was utilized as the cut-off for depression [32], which has been shown to have strong convergent validity (100% sensitivity, 88% specificity) with diagnostic interviews [33].

Antidepressant use

The use of antidepressant medication (yes or no) was determined by self-report at examination three using the Anatomical Therapeutic Chemical (ATC) classification N06A.

APOE genotype

Leukocyte DNA was acquired from 5–10 ml of whole blood and *APOE* genotype was performed with PCR as previously described [34]. Participants were classified as *APOE* ε4 carriers if they had at least one copy of the ε4 allele.

^{11}C-Pittsburgh Compound B (PiB) Aβ and ^{18}F-Flortaucipir (FTP) tau PET imaging

PiB Aβ and FTP tau PET imaging were conducted on a Siemens ECAT HR + scanner (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; and 2.4 mm slice interval), following previously published methodology [21]. Briefly, PiB PET images were acquired with a 10 to 15 mCi bolus injection followed by a 60 min dynamic acquisition. FTP PET images were obtained across 80 to 100 min using 4 × 5 min frames after a single 9 to 11 mCI bolus injection. PiB and FTP images were co-registered to a structural T1-weighted brain MRI using SPM8. FreeSurfer v6.0 was used to derive regions of interest (ROIs) [35]. PiB retention was expressed as the distribution volume ratio (DVR) using the cerebellar cortex as a reference region [36]. FTP retention was expressed as the standardized uptake value ratio (SUVr) using the cerebellar cortex as a reference. PET data were evaluated without partial volume correction given the relatively young age of the sample with minimal atrophy. A PiB summary measure, frontal, lateral, and retrosplenial (FLR), was derived from the mean of superior frontal, inferior frontal, rostral middle frontal, rostral anterior cingulate, medial orbitofrontal, inferior and middle temporal, inferior parietal, and precuneus regions [36]. Regional precuneus PiB was also examined given the region's susceptibility to early Aβ accumulation [37]. FTP retention was evaluated in regions with vulnerability to early tau deposition including the entorhinal cortex, inferior temporal lobe, amygdala, precuneus, parahippocampus, and hippocampus [38]. An FTP summary measure was derived from the mean of fusiform gyrus, entorhinal cortex, and inferior and middle temporal regions [39]. In addition, PiB and FTP PET retention were also examined in two regions widely implicated in depression, the anterior cingulate and the middle frontal gyms [2, 40]. Across ROIs, values from the left and right hemisphere were averaged.

Statistical analysis

Data normality was visually ascertained. CES-D scores at examinations 2 and 3 and Aβ PET retention in the FLR and precuneus were skewed and were natural log transformed to normalize their distributions. All PET variables were standardized prior to analyses. We calculated annualized change in depressive symptoms as change in raw CES-D score from examination 2 to 3 divided by the time between exams. *APOE* ε4 carrier and non-carrier group diferences in demographic and clinical characteristics were assessed with independent samples *t*-tests or Mann-Whitney U tests for continuous variables and the chi-squared statistic for categorical variables. Associations between depressive symptoms, annualized change in depressive symptoms, and depression at examination 3 with regional

Aβ and tau PET retention were evaluated with linear regression models adjusting for age and sex. Interactions between *APOE ε*4 status with depressive symptoms and annualized change in depressive symptoms for the PET imaging outcomes were evaluated with linear regression with covariates for age and sex. For outcomes with a significant *APOE ε*4 interaction, stratified analyses by *APOE ε*4 carrier status were performed using linear regression adjusted for age and sex. Due to the negligible number of *APOE ε*4 carriers meeting criteria for depression (N = 2), interactions with *APOE ε*4 were not examined with depression at examination 3. Given the possible confound of antidepressant medication usage, sensitivity analyses were performed for all regression models examining main effects and interactions with *APOE ε*4 for PET imaging outcomes with inclusion of an additional covariate for antidepressant use (yes or no). Statistical tests were 2-sided and the criterion for significance was set at p-value of < 0.05. Regression analyses examining main and interactive effects were FDR-corrected for multiple comparisons and the adjusted *p*-values are reported. Analyses were performed using SAS version 9.4.

RESULTS

Participant characteristics

The study sample included 201 participants, mean age 53 ± 8 years, of which 47% were female (Table 1). Seven individuals were missing data on *APOE* genotype and were not included in the stratified analyses. Depressive symptoms were assessed with the CES-D at examinations two and three, which occurred a mean of 7.8 years apart. At examination 3, the median CES-D score was 5 (interquartile range 1, 8). Twelve percent (N = 25) of the sample met criteria for depression and 18% (N = 37) of the total sample was on at least one antidepressant medication. Approximately a quarter of the sample were *APOE ε*4 carriers. There were no significant differences in demographic and clinical characteristics between the *APOE ε*4 carrier and non-carrier groups.

Cross-sectional associations between depressive symptoms, depression, and regional Aβ and tau PET retention

Depressive symptoms, evaluated at examination 3 using the CES-D, were not associated with regional Aβ or tau PET (Table 2). However, there was a significant interaction between depressive symptoms and the *APOE ε*4 allele in their effect on tau PET retention in the entorhinal cortex (interaction effect size = 0.522), amygdala (interaction effect size = 0.507), and hippocampus (interaction effect size = 0.453). Stratified analyses indicated significant associations between depressive symptoms and higher regional tau PET retention in the entorhinal cortex and amygdala in the *APOE ε*4 carrier group (Table 3). In contrast, the *APOE ε*4 non-carrier group evidenced a significant association between depressive symptoms and lower hippocampal tau PET retention

Depression, as defined by CES-D ≥ 16, was not associated with regional Aβ or tau PET retention (Table 4).

Association of annualized change in depressive symptoms with regional Aβ and tau PET retention

Annualized change in depressive symptoms across examinations 2 and 3 was not associated with regional Aβ or tau PET retention (Table 5). There were no significant interactions with *APOE ε*4 carrier status.

Sensitivity analysis

With additional adjustment for antidepressant use, the main effects of the associations between depressive symptoms, annualized change in depressive symptoms, and depression with regional Aβ and tau PET retention remain unchanged (Supplementary Tables 1, 2, and 3). Additionally, the interactions between *APOE ε*4 with both depressive symptoms and annualized change in depressive symptoms remain consistent. For stratified analyses by *APOE ε*4 groups (Supplementary Table 4), the associations between depressive symptoms with regional entorhinal and amygdala tau PET retention in *APOE ε*4 carriers persist. However, the association between depressive symptoms and hippocampal tau PET retention in *APOE ε*4 non-carriers was no longer significant.

DISCUSSION

The current study examined associations between depressive symptoms and regional Aβ and tau PET retention in a predominately middle-aged cohort. In cross-sectional analyses, depressive symptoms and depression were not associated with PET imaging outcomes. Additionally, annualized change in depressive symptoms across a mean of 8 years prior to PET imaging was not associated with Aβ or tau PET retention. However, there was a significant interaction between depressive symptoms and *APOE ε*4 carriage in their effect on regional tau PET deposition in the entorhinal cortex, amygdala, and hippocampus. Within the hippocampus, depressive symptoms were associated with lower tau PET retention in *APOE ε*4 non-carriers. However, the association was no longer significant with adjustment for antidepressant use. Within the entorhinal cortex and the amygdala, depressive symptoms were associated with higher tau PET retention only within *APOE ε*4 carriers. The results suggest that individuals with depressive symptoms and higher genetic risk for AD due to the *APOE ε*4 allele may represent a subgroup at increased vulnerability for neuropathological accumulation in regions susceptible to early ADRD pathogenesis [38]. Longitudinal studies will be necessary to evaluate if higher entorhinal cortex and amygdala tau PET retention confers risk for accelerated cognitive decline and incident dementia in individuals with depressive symptoms.

In our study, depressive symptoms were only associated with higher entorhinal and amygdala tau PET retention in individuals with at least one copy of the *APOE ε*4 allele. The *APOE ε*4 allele is the most robust known genetic risk factor for sporadic AD with a single copy of the allele increasing the relative risk of AD by 2–4 fold [41]. The *APOE ε*4 allele contributes to increased production and reduced clearance of the Aβ protein [42], resulting in higher rates of Aβ PET positivity at earlier ages of onset compared to the *ε*2 and *ε*3 alleles [23]. The *APOE ε*4 allele also propagates tau hyperphosphorylation and *APOE ε*4 carriage is associated with increased tau PET retention independent of Aβ [22,

42, 43]. Therefore, in our predominately middle-aged sample, higher tau PET retention may have only been detectable in *APOE ε*4 carriers, who typically display elevations in Aβ and tau at earlier timepoints [42]. Interestingly, some prior studies of older adults have reported that *APOE ε*4 carriage is associated with increased likelihood of depression particularly in the presence of Aβ PET positivity [12]. Additionally, within individuals with late-life depression, the *APOE ε*4 allele has been associated with hippocampal, frontal, and occipital lobe atrophy [44]. A longitudinal study by Qiu et al. reported that older adults with depression and elevated plasma Aβ 40/42 ratios were at increased risk for incident AD with a modifying effect of *APOE* ε4 [45]. Specifically, *APOE ε*4 carriers with depression and elevated plasma Aβ levels had a 40% increased risk of AD as compared to only 4% in non-carriers. Overall, the results suggest that depressive symptoms, in the context of the *APOE ε*4 allele, may confer risk for incident dementia. As compared to prior research demonstrating associations with Aβ [12, 45], our study identified an interaction between depressive symptoms and *APOE ε*4 carriage for tau PET retention. Additional studies will be necessary to determine if this finding replicates in other cohorts.

Within our study, *APOE ε*4 carriers with higher depressive symptoms displayed increased tau PET retention in the entorhinal cortex and the amygdala. Neuropathological and more recently, PET imaging studies have indicated that the entorhinal cortex and amygdala are early sites of tau accumulation in both normal aging and AD [16, 38, 43]. The medial temporal lobe has a fundamental role in memory consolidation [46]. In older adults without dementia, subtle elevations in entorhinal tau PET retention have been associated with poorer memory performance independent of A [47, 48]. The *APOE ε*4 allele has been found tomoderate this associationwith stronger effects observed in *ε*4 carriers relative to non-carriers [49]. The entorhinal cortex has reciprocal connections with the amygdala [50], a region governing affective modulation. As the amygdala has diffuse connections with brainstem, allocortical, and neocortical regions, it is hypothesized to play a pivotal role in the dispersion of neuropathological proteins, potentially harbingering a progressive downward cognitive trajectory [51]. The entorhinal cortex and amygdala also comprise an affective network and their dysregulation is implicated in the pathogenesis of depressive symptoms [52]. Prior neuroimaging studies of depression have reported accelerated atrophy and altered functional connectivity in the entorhinal cortex and the amygdala [53, 54]. In older adults without dementia, depressive symptoms and repetitive negative thoughts have been associated with elevated entorhinal tau PET retention [55]. A recent study reported that higher neuroticism, a personality trait that increases vulnerability to depression [56], was associated with increased entorhinal cortex, amygdala, and inferior temporal lobe tau PET retention in older adults [57]. The current study advances the literature by indicating that depressive symptoms in the presence of the *APOE ε*4 allelemay be associated with increased regional temporal and limbic tau PET retention as early as midlife.

The mechanisms that may link depressive symptoms with higher entorhinal cortex and amygdala tau PET retention in *APOE ε*4 carriers are not fully understood. Tau accumulation in regions critical to affective regulation may precipitate depressive symptoms [21]. However, it is important to note that annualized change in depressive symptoms did not have significant main or interactive effects with Aβ or tau PET retention. Depressive symptoms may propagate tau accumulation through dysregulation of the hypothalamic-

pituitary-adrenal (HPA) axis [6]. Depression has been linked with impaired negative feedback of the HPA axis and elevated glucocorticoid levels [58]. In animal models, glucocorticoids have been found to accelerate tau pathology [59]. Depressive symptoms have also been associated with higher inflammatory cytokine levels in plasma and CSF [60, 61]. A proteomic study reported that inflammatory processes may be a causal pathway underlying cognitive decline in late-life depression [62]. Inflammatory processes have also been found to accelerate tau phosphorylation [63]. Thus, inflammation may be a mechanism linking depressive symptoms and tau accumulation in individuals with higher genetic susceptibility to AD due to the *APOE ε*4 allele.

In addition to our findings of higher entorhinal cortex and amygdala tau PET retention in association with depressive symptoms in *APOE ε*4 carriers, we also report an association between depressive symptoms and lower hippocampal tau PET retention in *APOE ε*4 non-carriers. However, the finding was attenuated in sensitivity analyses adjusting for antidepressant use. Observational studies have produced conflicting findings with evidence of both increased [26] and lowered incident dementia risk [27, 28] associated with antidepressant use. A meta-analytical study reported that antidepressant use was associated with more than a two-fold increase in risk for incident cognitive impairment or dementia with stronger effects for those who initiated antidepressant use before the age of 65 [64]. In a sample of cognitively unimpaired older adults, individuals taking antidepressant medication were more likely to present with elevated tau on PET imaging relative to individuals not taking antidepressant medication [14]. Moreover, there was an interaction between elevated tau PET retention and antidepressant use for increased likelihood of depression. Longitudinal studies will be necessary to evaluate if antidepressant usage is associated with higher tau accumulation over and above the effects of depressive symptoms alone.

In our study, neither depressive symptoms nor depression were associated with Aβ PET retention. Depressive symptoms have been inconsistently linked with Aβ levels in plasma, CSF, and PET imaging [9, 12, 15]. Population-based studies have provided stronger converging evidence of a longitudinal association of Aβ PET positivity and increased depressive symptomatology over time [11–13]. Similar to our findings, two cross-sectional studies conducted in cognitively unimpaired older adults detected significant associations between depressive symptoms and tau PET retention without concomitant changes in Aβ [14, 21]. The evidence suggests that depressive symptoms may be more tightly coupled with tau than Aβ deposition even in individuals without overt cognitive symptoms.

Our study had several strengths including longitudinal assessments of depression, inclusion of Aβ and tau PET imaging, and a predominately middle-aged sample. Nonetheless, the results must also be considered in the context of the study limitations. While our largely middle-aged cohort provided a unique opportunity to examine early changes in neuropathological protein accumulation associated with depressive symptoms, Aβ and tau deposition at midlife is typically more restricted than within older age groups [65]. Attenuated ranges and regional distributions of Aβ and tau within our sample may have diminished power for detecting significant effects and regions included, such as the hippocampus, may be vulnerable to off-target binding effects [66]. Furthermore, the

clinical significance of continuous ranges of Aβ and tau PET retention in middle-aged adults is unknown. However, elevated cerebral Aβ and tau have been found to predict accelerated cognitive decline even in late midlife [67]. Future longitudinal studies within our cohort will be essential for evaluating the clinical relevance of our findings. Our study examined depressive symptoms and depression in a population-based cohort. A meta-analysis examining depression prevalence using the CES-D within similar settings reported a median prevalence of 8.8% with a range of 3.8 to 12.6% [68], which is highly consistent with the rates observed in our study. While our population-based cohort enabled assessment of subsyndromal depressive symptoms that are widely prevalent, we had more limited power for evaluating associations with annualized change in depressive symptomatology and major depression, which may have contributed to the null findings. In addition, our study does not include formal assessment of depression diagnosis and is unable to disentangle the effects of different subtypes of depression, such as seasonal affective disorder and bipolar disorder. In addition, our study lacks data on anxiety symptomatology. which is frequently comorbid with depression and has been previously associated with Aβ PET imaging outcomes in older adults [39]. Finally, the association between depressive symptoms and PET imaging outcomes may be mediated or moderated by several medical and lifestyle factors such as physical activity engagement, sleep quality, and cardiovascular disease burden [69]. While outside of the scope of the current study, future research with larger sample sizes and longer follow-up periods will be critical for elucidating the causal pathways linking depressive symptoms with tau accumulation.

In summary, our study did not detect associations between depressive symptoms and regional Aβ and tau PET retention within a predominately middle-aged sample. However, depressive symptoms were significantly associated with higher entorhinal cortex and amygdala tau PET retention among *APOE ε*4 carriers. While future longitudinal studies are necessary, the results suggest that *APOE ε*4 carriers with depressive symptoms may present with higher susceptibility to early tau accumulation in regions integral to affective regulation and memory consolidation [47, 48, 51, 53]. As such, the results highlight the importance of ongoing monitoring of depressive symptoms within tertiary care settings. Finally, with further validation, the findings may have relevance for improving detection of individuals at elevated risk for tau accumulation in midlife, who may benefit from preventive trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the FHS participants, the study team, and the investigators and staff of the neurology team. This work was made possible by grants from the National Institutes of Health (N01-HC-25195, HHSN2682015000011, 75N92019D00031) and the National Institute on Aging (AG059421, AG054076, AG054076, AG049607, AG033090, AG066524, NS017950). Dr. Aparicio is supported by an American Academy of Neurology Career Development Award.

REFERENCES

[1]. Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JJ, Mayeux R, Devanand D, Luchsinger JA (2013) Late-life depression, mild cognitive impairment, and dementia. JAMA Neurol 70, 383–389.

[2]. Gonzales MM, Insel PS, Nelson C, Tosun D, Mattsson N, Mueller SG, Sacuiu S, Bickford D, Weiner MW, Mackin RS, Alzheimer's Disease Neuroimaging Initiative (2017) Cortical atrophy is associated with accelerated cognitive decline in mild cognitive impairment with subsyndromal depression. Am J Geriatr Psychiatry 25, 980–991. [PubMed: 28629965]

[3]. Qiu WQ, Himali JJ, Wolf PA, DeCarli DC, Beiser A, Au R (2017) Effects of white matter integrity and brain volumes on late life depression in the Framingham Heart Study. Int J Geriatr Psychiatry 32, 214–221. [PubMed: 27059548]

[4]. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA (2012) Midlife vs late-life depressive symptoms and risk of dementia: Differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry 69, 493–498. [PubMed: 22566581]

[5]. Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D, Duara R, Kukull WA, Chui H, Edeki T, Griffith PA, Friedland RP, Bachman D, Farrer L (2003) Depression as a risk factor for Alzheimer disease: The MIRAGE Study. Arch Neurol 60, 753–759. [PubMed: 12756140]

[6]. Dafsari FS, Jessen F (2020) Depression—an underrecognized target for prevention of dementia in Alzheimer's disease. Transl Psychiatry 10, 1–13. [PubMed: 32066695]

[7]. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R, Elliott C, Masliah E, Ryan L, Silverberg N (2018) NIA-AA research framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 14, 535–562. [PubMed: 29653606]

[8]. Rapp MA, Schnaider-Beeri M, Grossman HT, Sano M, Perl DP, Purohit DP, Gorman JM, Haroutunian V (2006) Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry 63, 161–167. [PubMed: 16461859]

[9]. Harrington KD, Lim YY, Gould E, Maruff P (2015) Amyloid-beta and depression in healthy older adults: A systematic review. Aust N Z J Psychiatry 49, 36–46. [PubMed: 25414381]

[10]. do Nascimento KKF, Silva KP, Malloy-Diniz LF, Butters MA, Diniz BS (2015) Plasma and cerebrospinal fluid amyloid-β levels in late-life depression: A systematic review and meta-analysis. J Psychiatr Res 69, 35–41. [PubMed: 26343592]

[11]. Donovan NJ, Locascio JJ, Marshall GA, Gatchel J, Hanseeuw BJ, Rentz DM, Johnson KA, Sperling RA, Harvard Aging Brain Study (2018) Longitudinal association of amyloid beta and anxious-depressive symptoms in cognitively normal older adults. Am J Psychiatry 175, 530–537. [PubMed: 29325447]

[12]. Harrington KD, Gould E, Lim YY, Ames D, Pietrzak RH, Rembach A, Rainey-Smith S, Martins RN, Salvado O, Villemagne VL, Rowe CC, Masters CL, Maruff P, AIBL Research Group (2017) Amyloid burden and incident depressive symptoms in cognitively normal older adults. Int J Geriatr Psychiatry 32, 455–463. [PubMed: 27114112]

[13]. Babulal GM, Ghoshal N, Head D, Vernon EK, Holtzman DM, Benzinger TL, Fagan AM, Morris JC, Roe CM (2016) Mood changes in cognitively normal older adults are linked to Alzheimer disease biomarker levels. Am J Geriatr Psychiatry 24, 1095–1104. [PubMed: 27426238]

[14]. Babulal GM, Roe CM, Stout SH, Rajasekar G, Wisch JK, Benzinger TL, Morris JC, Ances BM (2020) Depression is associated with tau and not amyloid positron emission tomography in cognitively normal adults. J Alzheimers Dis 74, 1045–1055. [PubMed: 32144985]

[15]. Mackin RS, Insel PS, Landau S, Bickford D, Morin R, Rhodes E, Tosun D, Rosen HJ, Butters M, Aisen P, Raman R, Saykin A, Toga A, Jack C, Koeppe R, Weiner MW, Nelson C, Alzheimer's Disease Neuroimaging Initiative and the ADNI Depression Project (2020) Late-life depression is associated with reduced cortical amyloid burden: Findings from the Alzheimer's Disease Neuroimaging Initiative Depression Project. Biol Psychiatry 89, 757–765. [PubMed: 32980132]

[16]. Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, O'Neil JP, Janabi M, Lazaris A, Cantwell A, Vogel J, Santos M, Miller ZA, Bettcher BM, Vossel KA, Kramer JH, Gorno-Tempini ML, Miller BL, Jagust WJ, Rabinovici GD (2016) Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139, 1551–1567. [PubMed: 26962052]

[17]. Scott MR, Hampton OL, Buckley RF, Chhatwal JP, Hanseeuw BJ, Jacobs HIL, Properzi MJ, Sanchez JS, Johnson KA, Sperling RA, Schultz AP (2020) Inferior temporal tau is associated with accelerated prospective cortical thinning in clinically normal older adults. Neuroimage 220, 116991. [PubMed: 32512123]

[18]. Gordon BA, McCullough A, Mishra S, Blazey TM, Su Y, Christensen J, Dincer A, Jackson K, Hornbeck RC, Morris JC, Ances BM, Benzinger TLS (2018) Cross-sectional and longitudinal atrophy is preferentially associated with tau rather than amyloid β positron emission tomography pathology. Alzheimers Dement (Amst) 10, 245–252. [PubMed: 29780869]

[19]. La Joie R, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, Chaudhary K, Edwards L, Iaccarino L, Janabi M, Lesman-Segev OH, Miller ZA, Perry DC, O'Neil JP, Pham J, Rojas JC, Rosen HJ, Seeley WW, Tsai RM, Miller BL, Jagust WJ, Rabinovici GD (2020) Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. Sci Transl Med 12, eaau5732. [PubMed: 31894103]

[20]. Brown EE, Iwata Y, Chung JK, Gerretsen P, Graff-Guerrero A (2016) Tau in late-life depression: A systematic review and meta-analysis. J Alzheimers Dis 54, 615–633. [PubMed: 27497481]

[21]. Gatchel JR, Donovan NJ, Locascio JJ, Schultz AP, Becker JA, Chhatwal J, Papp KV, Amariglio RE, Rentz DM, Blacker D, Sperling RA, Johnson KA, Marshall GA (2017) Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: A pilot study. J Alzheimers Disease 59, 975–985. [PubMed: 28697559]

[22]. Therriault J, Benedet AL, Pascoal TA, Mathotaarachchi S, Chamoun M, Savard M, Thomas E, Kang MS, Lussier F, Tissot C, Parsons M, Qureshi MNI, Vitali P, Massarweh G, Soucy JP, Rej S, Saha-Chaudhuri P, Gauthier S, Rosa-Neto P (2020) Association of apolipoprotein E ε4 with medial temporal tau independent of amyloid-β. JAMA Neurol 77, 470–479. [PubMed: 31860000]

[23]. Gottesman RF, Schneider AL, Zhou Y, Chen X, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR (2016) The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. Neurology 87, 473–480. [PubMed: 27371485]

[24]. Cirrito JR, Disabato BM, Restivo JL, Verges DK, Goebel WD, Sathyan A, Hayreh D, Angelo G, Benzinger T, Yoon H, Kim J, Morris JC, Mintun MA, Sheline YI (2011) Serotonin signaling is associated with lower amyloid-β levels and plaques in transgenic mice and humans. Proc Natl Acad Sci U S A 108, 14968–14973 [PubMed: 21873225]

[25]. Sheline YI, West T, Yarasheski K, Swarm R, Jasielec MS, Fisher JR, Ficker WD, Yan P, Xiong C, Frederiksen C, Grzelak MV, Chott R, Bateman RJ, Morris JC, Mintun MA, Lee J-M, Cirrito JR (2014) An antidepressant decreases CSF Aβ production in healthy individuals and in transgenic AD mice. Sci Transl Med 6, 236re234.

[26]. Kodesh A, Sandin S, Reichenberg A, Rotstein A, Pedersen NL, Ericsson M, Karlsson IK, Davidson M, Levine SZ (2019) Exposure to antidepressant medication and the risk of incident dementia. Am J Geriatr Psychiatry 27, 1177–1188. [PubMed: 31235427]

[27]. Burke SL, Maramaldi P, Cadet T, Kukull W (2018) Decreasing hazards of Alzheimer's disease with the use of antidepressants: Mitigating the risk of depression and apolipoprotein E. Int J Geriatr Psychiatry 33, 200–211. [PubMed: 28560728]

[28]. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A, Alzheimer's Disease Neuroimaging Imitative (2018) Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. Am J Psychiatry 175, 232–241. [PubMed: 29179578]

[29]. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, O'Donnell CJ, Vasan RS, Wolf PA, Levy D (2007) The third generation cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: Design, recruitment, and initial examination. Am J Epidemioll 165, 1328–1335.

[30]. Satizabal CL, Beiser AS, Chouraki v, chêne g, dufouil c, seshadri s (2016) incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med 374, 523–532. [PubMed: 26863354]

[31]. Radloff LS (1977) The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1, 385–401.

[32]. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ (1977) Assessing depressive symptoms in five psychiatric populations: A validation study. Am J Epidemiol 106, 203–214. [PubMed: 900119]

[33]. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W (1997) Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): Results from a community-based sample of older subjects in The Netherlands. Psychol Med 27, 231–235. [PubMed: 9122304]

[34]. Elosua R, Ordovas JM, Cupples LA, Fox CS, Polak JF, Wolf PA, D'Agostino RA, O'Donnell CJ (2004) Association of APOE genotype with carotid atherosclerosis in men and women the Framingham Heart Study. J Lipid Res 45, 1868–1875. [PubMed: 15258198]

[35]. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980. [PubMed: 16530430]

[36]. Hanseeuw BJ, Betensky RA, Mormino EC, Schultz AP, Sepulcre J, Becker JA, Jacobs HI, Buckley RF, LaPoint MR, Vannini P, Donovan NJ, Chhatwal JP, Marshall GA, Papp KV, Amariglio RE, Rentz DM, Sperling RA (2018) PET staging of amyloidosis using striatum. Alzheimers Dement 14, 1281–1292. [PubMed: 29792874]

[37]. Vlassenko AG, Benzinger TL, Morris JC (2012) PET amyloid-beta imaging in preclinical Alzheimer's disease. Biochim Biophys Acta 1822, 370–379. [PubMed: 22108203]

[38]. Johnson KA, Schultz A, Betensky RA, Becker JA, Sepulcre J, Rentz D, Mormino E, Chhatwal J, Amariglio R, Papp K, Marshall G, Albers M, Mauro S, Pepin L, Alverio J, Judge K, Philiossaint M, Shoup T, Yokell D, Dickerson B, Gomez-Isla T, Hyman B, Vasdev N, Sperling R (2016) Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann Neurol 79, 110–119. [PubMed: 26505746]

[39]. Hanseeuw BJ, Betensky RA, Jacobs HI, Schultz AP, Sepulcre J, Becker JA, Cosio DMO, Farrell M, Quiroz YT, Mormino EC, Buckley RF, Papp KV, Amariglio RA, Dewachter I, Ivanoiu A, Huijbers W, Hedden T, Marshall GA, Chhatwal JP, Rentz DM, Sperling RA, Johnson KA (2019) Association of amyloid and tau with cognition in preclinical Alzheimer disease: A longitudinal study. JAMA Neurol 76, 915–924. [PubMed: 31157827]

[40]. Koolschijn PCM, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS (2009) Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. Hum Brain Mapp 30, 3719–3735. [PubMed: 19441021]

[41]. Qian J, Wolters FJ, Beiser A, Haan M, Ikram MA, Karlawish J, Langbaum JB, Neuhaus JM, Reiman EM, Roberts JS, Seshadri S, Tariot PN, Woods BM, Betensky RA, Blacker D (2017) APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts. PLoS Med 14, e1002254. [PubMed: 28323826]

[42]. Yu JT, Tan L, Hardy J (2014) Apolipoprotein E in Alzheimer's disease: An update. Ann Rev Neurosci 37, 79–100. [PubMed: 24821312]

[43]. Sanchez JS, Becker JA, Jacobs HIL, Hanseeuw BJ, Jiang S, Schultz AP, Properzi MJ, Katz SR, Beiser A, Satizabal CL, O'Donnell A, DeCarli C, Killiany R, El Fakhri G, Normandin MD, Gómez-Isla T, Quiroz YT, Rentz DM, Sperling RA, Seshadri S, Augustinack J, Price JC, Johnson KA (2021) The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. Sci Transl Med 13, eabc0655. [PubMed: 33472953]

[44]. Yuan Y, Zhang Z, Bai F, You J, Yu H, Shi Y, Liu W (2010) Genetic variation in apolipoprotein E alters regional gray matter volumes in remitted late-onset depression. J Affective Disord 121, 273–277.

[45]. Qiu WQ, Zhu H, Dean M, Liu Z, Vu L, Fan G, Li H, Mwamburi M, Steffens DC, Au R (2016) Amyloid-associated depression and ApoE4 allele: Longitudinal follow-up for the development of Alzheimer's disease. Int J Geriatr Psychiatry 31, 316–322. [PubMed: 26250797]

[46]. Suzuki WA, Amaral DG (2004) Functional neuroanatomy of the medial temporal lobe memory system. Cortex 40, 220–222. [PubMed: 15070014]

[47]. Knopman DS, Lundt ES, Therneau TM, Vemuri P, Lowe VJ, Kantarci K, Gunter JL, Senjem ML, Mielke MM, Machulda MM, Boeve BF, Jones DT, Graff-Radford J, Albertson SM, Schwarz CG, Petersen RC, Jack CR (2019) Entorhinal cortex tau, amyloid-β, cortical thickness and memory performance in non-demented subjects. Brain 142, 1148–1160. [PubMed: 30759182]

[48]. Maass A, Lockhart SN, Harrison TM, Bell RK, Mellinger T, Swinnerton K, Baker SL, Rabinovici GD, Jagust WJ (2018) Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. J Neurosci 38, 530–543. [PubMed: 29192126]

[49]. Weigand AJ, Thomas KR, Bangen KJ, Eglit GML, Delano-Wood L, Gilbert PE, Brickman AM, Bondi MW, Alzheimer's Disease Neuroimaging Initiative (2020) APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia. Alzheimers Dement 17, 61–69. [PubMed: 32886451]

[50]. Wahlstrom KL, Alvarez-Dieppa AC, McIntyre CK, LaLumiere RT (2021) The medial entorhinal cortex mediates basolateral amygdala effects on spatial memory and downstream activity-regulated cytoskeletal-associated protein expression. Neuropsychopharmacology 46, 1172–1182. [PubMed: 33007779]

[51]. Nelson PT, Abner EL, Patel E, Anderson S, Wilcock DM, Kryscio RJ, Van Eldik LJ, Jicha GA, Gal Z, Nelson RS, Nelson BG, Gal J, Azam MT, Fardo DW, Cykowski MD (2018) The amygdala as a locus of pathologic misfolding in neurodegenerative diseases. J Neuropathol Exp Neurol 77, 2–20. [PubMed: 29186501]

[52]. Ramasubbu R, Konduru N, Cortese F, Bray S, Gaxiola-Valdez I, Goodyear B (2014) Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. Front Psychiatry 5, 17. [PubMed: 24600410]

[53]. Nolan M, Roman E, Nasa A, Levins KJ, O'Hanlon E, O'Keane V, Willian Roddy D (2020) Hippocampal and amygdalar volume changes in major depressive disorder: A targeted review and focus on stress. Chronic Stress 4, 2470547020944553. [PubMed: 33015518]

[54]. Damborská A, Honzírková E, Barteček R, Hořínková J, Fedorová S, Ondruš Š, Michel CM, Rubega M (2020) Altered directed functional connectivity of the right amygdala in depression: High-density EEG study. Sci Rep 10, 4398. [PubMed: 32157152]

[55]. Marchant NL, Lovland LR, Jones R, Pichet Binette A, Gonneaud J, Arenaza-Urquijo EM, Chételat G, Villeneuve S, Prevent AD Research Group (2020) Repetitive negative thinking is associated with amyloid, tau, and cognitive decline. Alzheimers Dement 16, 1054–1064. [PubMed: 32508019]

[56]. Duggan C, Sham P, Lee A, Minne C, Murray R (1995) Neuroticism: A vulnerability marker for depression evidence from a family study. J Affect Disord 35, 139–143. [PubMed: 8749842]

[57]. Schultz SA, Gordon BA, Mishra S, Su Y, Morris JC, Ances BM, Duchek JM, Balota DA, Benzinger TLS (2020) Association between personality and tau-PET binding in cognitively normal older adults. Brain Imaging Behav 14, 2122–2131. [PubMed: 31486975]

[58]. Anacker C, Zunszain PA, Carvalho LA, Pariante CM (2011) The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? Psychoneuroendocrinology 36, 415–425. [PubMed: 20399565]

[59]. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM (2006) Glucocorticoids increase amyloid-β and tau pathology in a mouse model of Alzheimer's disease. J Neurosci 26, 9047–9056. [PubMed: 16943563]

[60]. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM, Pariante CM, Howes OD (2020) Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun 87, 901–909. [PubMed: 32113908]

[61]. Enache D, Pariante CM, Mondelli V (2019) Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid,

positron emission tomography and postmortem brain tissue. Brain Behav Immun 81, 24–40. [PubMed: 31195092]

[62]. Diniz BS, Sibille E, Ding Y, Tseng G, Aizenstein HJ, Lotrich F, Becker JT, Lopez OL, Lotze MT, Klunk WE, Reynolds CF, Butters MA (2015) Plasma biosignature and brain pathology related to persistent cognitive impairment in late-life depression. Mol Psychiatry 20, 594–601. [PubMed: 25092249]

[63]. Lee DC, Rizer J, Selenica M-LB, Reid P, Kraft C, Johnson A, Blair L, Gordon MN, Dickey CA, Morgan D (2010) LPS-induced inflammation exacerbates phospho-tau pathology in rTg4510 mice. J Neuroinflammation 7, 56–56. [PubMed: 20846376]

[64]. Moraros J, Nwankwo C, Patten SB, Mousseau DD (2017) The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: A systematic review and meta-analysis. Depress Anxiety 34, 217–226. [PubMed: 28029715]

[65]. Jack CR Jr., Wiste HJ, Weigand SD, Therneau TM, Knopman DS, Lowe V, Vemuri P, Mielke MM, Roberts RO, Machulda MM, Senjem ML, Gunter JL, Rocca WA, Petersen RC (2017) Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50–95 years: A cross-sectional study. Lancet Neurol 16, 435–444. [PubMed: 28456479]

[66]. Lee CM, Jacobs HIL, Marquié M, Becker JA, Andrea NV, Jin DS, Schultz AP, Frosch MP, Gómez-Isla T, Sperling RA, Johnson KA (2018) 18F-flortaucipir binding in choroid plexus: Related to race and hippocampus signal. J Alzheimers Dis 62, 1691–1702. [PubMed: 29614677]

[67]. Betthauser TJ, Koscik RL, Jonaitis EM, Allison SL, Cody KA, Erickson CM, Rowley HA, Stone CK, Mueller KD, Clark LR, Carlsson CM, Chin NA, Asthana S, Christian BT, Johnson SC (2020) Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age. Brain 143, 320–335. [PubMed: 31886494]

[68]. Vilagut G, Forero CG, Barbaglia G, Alonso J (2016) Screening for depression in the general population with the Center for Epidemiologic Studies Depression (CES-D): A systematic review with meta-analysis. PloS One 11, e0155431. [PubMed: 27182821]

[69]. Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, DeKosky ST, Becker JT (2008) Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci 10, 345–357. [PubMed: 18979948]

Table 1

Demographics and clinical characteristics of the sample by apolipoprotein E (*APOE*) ε4 carrier status

	Total Sample (N = 201)	*APOE* ε4 Non-carriers (N = 147)	*APOE* ε4 Carriers (N = 47)	*p*
Age, y	53.4 ± 8.0	53.5 ± 7.8	53.3 ± 8.8	0.887[a]
Female, N (%)	94 (47%)	73 (50%)	19 (40%)	0.270[c]
Education, N (%)				
High School Degree	22 (11%)	18 (12%)	4 (9%)	0.699[c]
Some College	57 (29%)	44 (30%)	13 (28%)	
College Degree	115 (59%)	85 (58%)	30 (64%)	
Depressive symptoms (CES-D) at Examination 2, Median (Q1-Q3)	3 (1–8)	3 (1–9)	3 (1–7)	0.445[b]
Depression (CES-D ≥ 16) at Examination 2, N (%)	7 (4%)	6 (5%)	0	-
Depressive Symptoms (CES-D) at Examination 3, Median (Q1-Q3)	5 (2–9)	5 (2–10)	5 (1–9)	0.320[b]
Depression (CES-D ≥ 16) at Examination 3, N (%)	25 (12%)	22 (15%)	2 (4%)	-
Time Between Examinations 2 and 3, y	7.8 ± 0.4	7.8 ± 0.4	7.8 ± 0.4	0.778[a]
Annualized Change in CES-D Between Examinations 2 and 3, Median (Q1-Q3)	0.1 (−0.1–0.5)	0.1 (−0.1–0.5)	0.0 (−0.1–0.5)	0.492[b]
Antidepressant Use at Exam 3	37 (18%)	27 (18%)	8 (17%)	0.763[c]
Aβ PET Composite (FLR)[†]	1.40 ± 0.02	1.40 ± 0.02	1.40 ± 0.02	0.135[a]
Tau PET Composite (Temporal Lobe)	1.09 ± 0.06	1.09 ± 0.06	1.11 ± 0.06	0.072[a]

Group differences were assessed with independent *t*-tests [a] or Mann-Whitney U tests[b] for continuous variables and the chi-squared statistic[c] for categorical variables.

[†]Natural log transformed.

Values represent mean ± standard deviationunless otherwise noted. *APOE*, apolipoprotein E; CES-D, Center for Epidemiological Studies Depression Scale; Aβ, amyloid-β; FLR, frontal, lateral and retrosplenial.

Table 2

Associations of depressive symptoms with standardized regional amyloid-β and tau positron emission tomography (PET) retention

	Depressive Symptoms (CES-D†)[a]		Interaction Between Depressive Symptoms (CES-D†) and *APOE ε4*[b]
	β (SE)	*p*	*p*
FLR Aβ †	−0.031 ± 0.068	0.836	0.223
Precuneus Aβ †	−0.017 ± 0.071	0.885	0.118
Anterior Cingulate Aβ	−0.033 ± 0.071	0.836	0.320
Middle Frontal Gyrus Aβ	−0.082 ± 0.068	0.683	0.394
Entorhinal Tau	0.032 ± 0.074	0.836	0.025*
Inferior Temporal Tau	0.039 ± 0.072	0.836	0.230
Amygdala Tau	−0.046 ± 0.073	0.836	0.025*
Precuneus Tau	−0.127 ± 0.074	0.683	0.637
Parahippocampus Tau	−0.029 ± 0.075	0.836	0.215
Hippocampus Tau	−0.067 ± 0.056	0.683	0.046*
Anterior Cingulate Tau	−0.101 ± 0.074	0.683	0.223
Middle Frontal Gyrus Tau	0.003 ± 0.070	0.968	0.478

† Natural log transformed.

[a] *β* ± SE and FDR-corrected *p*-values derived from linear regression models examining the associations between depressive symptoms (natural log transformed Center for Epidemiological Studies Depression Scale score) with regional Aβ and tau PET retention, adjusting for age and sex.

[b] FDR-corrected *p*-values derived from linear regression models examining the interaction between depressive symptoms (natural log transformed Center for Epidemiological Studies Depression Scale) and *APOE ε4* for regional Aβ and tau PET retention with adjustment for age, sex, and *APOE ε4*.

CES-D, Center for Epidemiological Studies Depression Scale; *APOE*, apolipoprotein E; FLR, frontal, lateral and retrosplenial; Aβ, amyloid-β.

Table 3

Associations of depressive symptoms with standardized regional tau positron emission tomography (PET) retention stratified by *APOE ε*4 carrier status

	Depressive Symptoms (CES-D†)[a]	
	β±SE	***p***
Tau entorhinal		
*APOE ε*4 positive	0.446 ± 0.155	0.006*
*APOE ε*4 negative	−0.076 ± 0.083	0.364
Amygdala Tau		
*APOE ε*4 positive	0.350 ± 0.133	0.012*
*APOE ε*4 negative	−0.157 ± 0.088	0.078
Tau hippocampus		
*APOE ε*4 positive	0.244 ± 0.131	0.070
*APOE ε*4 negative	−0.209 ± 0.090	0.022*

[a] *β*±SE and FDR-corrected *p*-values derived from linear regression models stratified by *APOE ε*4 carrier status examining the associations between depressive symptoms (natural log transformed Center for Epidemiological Studies Depression Scale score) with regional tau PET retention, adjusting for age and sex.

CES-D, Center for Epidemiological Studies Depression Scale; *APOE*, apolipoprotein E.

Table 4

Associations of depression with standardized regional amyloid-β and tau positron emission tomography (PET) retention

	Depression (CES-D score ≥16)[a]	
	β ± SE	***p***
FLR Aβ[†]	0.183 ± 0.197	0.664
Precuneus Aβ[†]	0.241 ± 0.205	0.664
Anterior Cingulate Aβ	0.042 ± 0.207	0.839
Middle Frontal Gyrus Aβ	0.075 ± 0.197	0.839
Entorhinal Tau	−0.133 ± 0.213	0.721
Inferior Temporal Tau	0.128 ± 0.209	0.721
Amygdala Tau	−0.219 ± 0.211	0.664
Precuneus Tau	−0.249 ± 0.215	0.664
Parahippocampus Tau	−0.187 ± 0.216	0.664
Hippocampus Tau	−0.052 ± 0.164	0.664
Anterior Cingulate Tau	−0.238 ± 0.214	0.664
Middle Frontal Gyrus Tau	0.059 ± 0.201	0.839

[†]Natural log transformed for normality.

[a]β ± SE and FDR-corrected *p*-values derived from linear regression models examining the association between depression, as defined by Center for Epidemiological Studies Depression Scale score >16, with regional Aβ and tau PET retention, adjusting for age and sex.

CES-D, Center for Epidemiological Studies Depression Scale; FLR, frontal, lateral and retrosplenial; Aβ, amyloid-β.

Table 5

Associations of annualized change in depressive symptoms and regional amyloid-β and tau positron emission tomography (PET) retention derived from linear regression

	Annualized Change in Depressive Symptoms (CES-D†)[a]		Interaction of Annualized Change in Depressive Symptoms (CES-D) × *APOE ε4*[b]
	β **± SE**	***p***	***p***
FLR Aβ†	0.051 ± 0.070	0.947	0.903
Precuneus Aβ†	0.066 ± 0.073	0.947	0.903
Anterior Cingulate Aβ	0.081 ± 0.073	0.947	0.903
Middle Frontal Gyrus Aβ	0.050 ± 0.070	0.947	0.903
Entorhinal Tau	−0.011 ± 0.076	0.979	0.217
Inferior Temporal Tau	0.023 ± 0.074	0.979	0.896
Amygdala Tau	0.006 ± 0.075	0.979	0.270
Precuneus Tau	−0.071 ± 0.076	0.947	0.903
Parahippocampus Tau	−0.006 ± 0.077	0.979	0.516
Hippocampus Tau	−0.051 ± 0.058	0.947	0.217
Anterior Cingulate Tau	−0.002 ± 0.076	0.979	0.743
Middle Frontal Gyrus Tau	0.027 ± 0.071	0.979	0.711

†Natural log transformed for normality.

[a] β ± SE and FDR-corrected *p*-values derived from linear regression models examining the associations between annualized change in depressive symptoms (derived from Center for Epidemiological Studies Depression Scale raw scores) with regional Aβ and tau PET retention, adjusting for age and sex.

[b] FDR-corrected *p*-values derived from linear regression models examining the interaction between annualized change in depressive symptoms (derived from Center for Epidemiological Studies Depression Scale raw scores) and *APOE ε4* for regional Aβ and tau PET retention with adjustment for age, sex, and *APOE ε4*.

CES-D, Center for Epidemiological Studies Depression Scale; *APOE*, apolipoprotein E; FLR, frontal, lateral and retrosplenial; Aβ, amyloid-β.