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Depressive symptoms and tau accumulation in the inferior temporal lobe and entorhinal cortex in cognitively normal older adults: a pilot study

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Abstract

Background—Depressive symptoms are common in older adults and associated with increased morbidity and cognitive decline. These symptoms occur during preclinical and prodromal stages of Alzheimer's disease (AD), but their relationship to tau, one of the main AD proteinopathies, is poorly understood.

Objective—The objective of this study was to investigate the cross-sectional association between depressive symptoms and cerebral tau (¹⁸F T807 (a.k.a. ¹⁸F-AV-1451) tau positron emission tomography (PET) imaging) in cognitively normal (CN) older adults.

Methods—We measured depressive symptoms using the Geriatric Depression Scale (GDS), and *in vivo* cerebral tau using T807 PET in 111 CN older adults. We employed general linear

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regression models to evaluate the relationship of GDS score regressed on entorhinal cortex (EC) or inferior temporal (IT) tau in separate backward elimination models. Other predictors included age, sex, and in secondary analyses, amyloid (Pittsburgh Compound B (PiB) PET).

Results—Higher GDS was significantly associated with greater IT tau (partial $r=0.188$, $p=0.050$) and marginally associated with greater EC tau (partial $r=0.183$, $p=0.055$). In additional analyses including both linear and quadratic age terms, we found a significant u-shaped relation of GDS to age ($p=0.001$).

Conclusions—Results suggest that IT and EC tau are modestly associated with depressive symptoms in CN older adults. Findings suggest a link between depressive symptoms and tau mediated neurodegeneration in a region vulnerable in AD. Future longitudinal studies examining the association of more severe depressive symptoms and cerebral tau accumulation are needed to substantiate this finding and to guide prevention and treatment in AD.

Keywords

tau; Positron emission tomography (PET) amyloid; depression; depressive symptoms; Alzheimer's disease; cognitively normal

Introduction

Geriatric depression and Alzheimer's disease (AD) are leading causes of morbidity and mortality worldwide and confer tremendous personal and public health burden [1, 2]. Depressive symptoms, both major depression and subclinical depressive symptoms, are common in older adults, in whom they are disabling and can be associated with functional impairment, decreased quality of life, and cognitive impairment [1, 3]. The neurobiology of subclinical depressive symptoms in late life is incompletely understood, and treatment and preventative measures are likewise limited in their efficacy [3, 4].

While a number of neurobiological mechanisms underlying late life depression have been proposed [4], increasing evidence suggests that these symptoms in a subset of older adults may be a prodrome and/or risk factor for cognitive impairment progressing to amnesic mild cognitive impairment (MCI) and AD dementia, representing among the earliest clinical changes in this pathway [5]. Accordingly, depressive symptoms may represent early clinical markers of neurodegeneration and AD pathogenesis in preclinical AD (a stage of AD biomarker positivity preceding objective cognitive decline), and prodromal AD (a pre-dementia stage of objective cognitive decline and AD biomarker positivity)[6, 7]. Alternatively, but not mutually exclusively, depressive symptoms may confer increased risk for progressive cognitive impairment leading to AD dementia, by directly or indirectly interacting with AD pathogenic pathways.

Two of the hallmarks of AD pathogenesis are accumulation of amyloid-beta ($A\beta$) plaques and neurofibrillary tangles containing hyperphosphorylated tau protein [8]. These proteins accumulate in the context of aging, but the significance of such accumulation on cognition and depressive symptoms remains unclear [9]. Neurodegeneration evidenced by neurofibrillary tangles progresses by a sequential, hierarchical pattern according to six stages, first in the transentorhinal and entorhinal cortex and hippocampus in the context of

aging, progressing to the inferior temporal cortex, then the lateral temporal cortex and limbic regions, and followed by more widespread neocortical involvement in the presence of high A β , correlating with AD dementia at this final stage [8, 10, 11].

Previous work investigating the relationship between depressive symptoms and tau and A β accumulation has been carried out predominantly through cerebrospinal fluid (CSF) and postmortem examinations in study populations of varying levels of depressive and cognitive symptom severity. Pomara and colleagues found lower CSF A β 42 in 28 cognitively normal (CN) older adults with major depression relative to 19 healthy controls [12], but no changes in total or phosphorylated tau, whereas Gudmundsson and colleagues reported higher CSF A β 42 in 14 older women with depression of varying severity compared to 70 healthy control women [13]. Findings from clinical-pathological studies have similarly included varied subject populations and follow up and yielded mixed results [14]. Wilson and colleagues, in a post-mortem cohort of 582 older adults found that depression was associated with rate of cognitive decline but that this was independent of markers of dementia-related pathology, including A β plaque and tau tangle density [15]. While subjects in the study cohort had a range of cognitive impairment, in two separate post-mortem studies of AD dementia subjects, comorbid depression was associated with higher burden of tau neurofibrillary tangles [16] and lifetime history of depression with both higher neurofibrillary tangles and A β plaques [17]. Together, these contrasting results provide evidence both for and against an association between depressive symptoms and AD proteinopathies, and suggest that amyloid and tau accumulation may be differentially related to depressive symptoms in older adults. These findings also underscore that the association between depression and AD proteinopathies may vary in part based on depression severity and degree of cognitive impairment.

Additional evidence for an association between depressive symptoms and AD proteinopathies has come from positron emission tomography (PET) neuroimaging studies in subjects with a range of depression and cognitive symptom severity. However, studies have thus far been limited to amyloid PET [6, 7, 18]. Amyloid was not cross-sectionally associated with subclinical depressive symptoms in a cohort of cognitively normal elderly [6], and was not elevated in older adults with major depressive disorder relative to healthy controls [18]. In contrast, studies by Lavretsky, Kumar and colleagues have shown associations between depressive symptoms in CN, MCI, and late life depression subjects and retention of a PET ligand thought to bind both amyloid and tau [19, 20]. However, these studies were limited by the ligand binding non-specifically to both amyloid and tau rather than distinguishing between the proteinopathies [19, 20].

Despite evidence that tau neurofibrillary tangle accumulation correlates more closely with AD clinical symptoms than A β [21, 22], thus far, to our knowledge, the association between subclinical depressive symptoms and *in vivo* cerebral tau has never before been investigated. Gaining a better understanding of this association in the context of aging holds importance for the development of more effective prevention and treatment measures targeting both depressive symptoms and progressive cognitive decline, and for identifying the earliest preclinical changes that might provide a window of opportunity for intervention. The advent of tau PET imaging using ¹⁸F T807 (a.k.a. ¹⁸F-AV-1451) [11] puts us in a unique position to

fill this gap in the literature and to examine the association of depressive symptoms and regional tau burden concomitant with amyloid in CN older adults. The objective of the current study was to examine the cross-sectional relationship of depressive symptoms and *in vivo* cerebral tau burden in a large cohort of CN older adults. We chose to focus on CN older adults without major psychiatric, medical or neurological illness in this study given the prevalence of mild depressive symptoms in this population, and in order to investigate how subclinical depressive symptoms correlate with tau in the absence of MCI, dementia and variable psychiatric and neurological disease severity and illness history. Specifically, we were interested in focusing on depressive symptoms integral to the neurodegenerative process in preclinical AD without the contribution of symptoms secondary to life-long recurrent depressive illness. We hypothesized that tau accumulation in the entorhinal cortex (EC) and inferior temporal lobe (IT), two early sites of accumulation, would be associated with increased depressive symptoms. Further, based on previous findings in CN older adults [6, 18], we hypothesized that depressive symptoms would be more robustly associated with tau relative to amyloid.

Materials and Methods

Subjects

The sample of 111 subjects was drawn from the Harvard Aging Brain Study (HABS), an ongoing prospective longitudinal observational cohort study of cognitive aging. The details of this study are described elsewhere [23]. Briefly, HABS subjects undergo clinical assessments annually and multi-modal imaging at baseline and three years later; ^{18}F T807 tau PET imaging was conducted as part of the third annual assessment. All study subjects also undergo APOE genotyping to determine APOE e4 carrier status[24]. HABS subjects are English-speaking community dwelling elders; none of the subjects had the following: history of neurological disease or cortical stroke, head trauma, history of severe and persistent mental illness (schizophrenia, schizoaffective disorder, bipolar disorder), moderate to severe major depressive disorder, and substance use in the two years prior to study entry. A history of mild depression or anxiety treated with serotonin or dual serotonin and norepinephrine reuptake inhibitors, bupropion, or nortriptyline was allowed at HABS study entry. In addition, subjects with scores of 11 or greater on the 30-item Geriatric Depression Scale (GDS) (corresponding to clinically significant mild depression) [25] were excluded at HABS study entry, but not on subsequent annual follow up. The HABS protocol was approved by the Partners Healthcare IRB. Informed consent was obtained from all study subjects prior to the initiation of any study procedures.

For the analyses presented here, we selected all HABS subjects who met the following criteria at the time of analyses: completion of both ^{18}F T807 tau PET imaging at the third annual assessment and PiB amyloid PET imaging; remained in the CN diagnostic group (Clinical Dementia Rating Scale (CDR) global score 0; education adjusted Mini-Mental State Examination (MMSE) score 26–30, performance on Logical Memory (LM) Delayed Recall within 1.5 standard deviations adjusted for education)[26–28]; and completion of T807 tau PET imaging within one year of neuropsychiatric symptoms assessment (on

average, time between neuroimaging assessments and clinical assessment was 86.25 +/- 50.34 days, see Table 1).

Clinical Measures

A detailed series of cognitive and neuropsychological tests were administered to subjects at the baseline of HABS and at subsequent follow up [29, 30]. Depressive symptoms were assessed using the self-report 30-item GDS [25]. The GDS is a continuous scale in which higher scores indicate greater depression [25]. Educational attainment (years of education) and antidepressant medication use (selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs) or other antidepressant medications) was obtained by self-report. For analyses presented here, we utilized GDS data that were collected in closest temporal proximity to PET imaging, as above.

¹⁸F T807 tau PET image acquisition and processing

Tau PET imaging using ¹⁸F T807 (a.k.a. AV1451) was carried out at the Massachusetts General Hospital PET facility. ¹⁸F T807 was acquired 60–100 minutes following a 9.0 to 11.0 mCi bolus injection in 4 × 5 minute frames. Image processing, ROI generation, and registration of PET data sets to ROIs (bilateral inferior temporal and entorhinal cortex) were carried out as described previously [11, 31, 32]. ¹⁸F T807 binding in ROIs was expressed as the standardized uptake volume ratio (SUVR) to cerebellum using the FreeSurfer cerebellar grey ROI as reference [11]. PiB PET data: Fibrillar cortical amyloid burden was measured using PiB PET at the Massachusetts General Hospital PET facility, with image acquisition carried out as described previously [29, 33–35]. Data were expressed as a PiB distribution volume ratio (DVR) with cerebellar gray as reference. ¹¹C PiB retention was calculated in a large aggregate region of interest (ROI) comprised of frontal, lateral temporal and parietal, and retrosplenial cortices previously found to have elevated PiB retention in AD dementia [23, 30, 36].

Statistical Analysis

Analyses were carried out using SPSS Version 23 (IBM, Armonk, NY) statistical software. Multiple linear regression models with backward elimination ($p < 0.1$ cut-off) were carried out in which total GDS score was the dependent variable, with the predictor of primary interest being ¹⁸F T807 retention in either the inferior temporal lobe or the entorhinal cortex (in separate regression models). Other predictor terms in the initial full model included age (either linear age, or both linear and quadratic age terms) and sex. Partial regression coefficient estimates (β) and 95% confidence intervals (CI) as well as significance test results (p values) thereof, and percent variance accounted for by the model as a whole, were reported for the final reduced models. Residuals from final models were examined to ensure that their distributions reasonably satisfied significance test assumptions of normality and homoscedasticity. Secondary analyses (separate linear regression models with backward elimination) were carried out with predictors age (either linear age, or both linear and quadratic age terms), sex, and the following: 1) amyloid (PiB retention) and tau (IT or EC); 2) amyloid, tau (IT or EC), and an amyloid X tau (IT or EC) interaction term; 3) and then amyloid alone (without tau).

A series of exploratory analyses were carried out, each introducing one of the following covariates in the initial pool of predictors in separate backward elimination models: education, MMSE score, APOE e4 allele carrier status, or antidepressant medication use (SSRI/SNRI use or other antidepressant use).

Results

Subject demographic, clinical, and PiB PET and T807 PET imaging values (DVR and SUVR) are reported in Table 1. The study cohort was on average 75.91 years old and comprised of 43% males and 57% females. The cohort had an average MMSE of 29.20 $\pm$ 0.99 and had a high level of educational attainment (average: 15.83 $\pm$ 3.00 years). 27% of the study cohort were APOE e4 allele carriers. The average GDS score was 3.93 $\pm$ 3.98 with a range of 0–21; 4.5% of the study cohort had a GDS score above 11 (which would be considered in the range of clinical depression; see Supplementary Figure 1). A minority of subjects (9%) was taking a SSRI or SNRI medication, and fewer subjects (2.7%) were taking other classes of antidepressant medication. T807 retention in the inferior temporal lobe and entorhinal cortex was similar in magnitude across the cohort (1.20 $\pm$ 0.088 and 1.12 $\pm$ 0.115, respectively), as would be expected based on previous observations in CN elders [11], and were significantly correlated (Pearson correlation = 0.702, $p < 0.001$). PiB retention was on average 1.21 $\pm$ 0.231 across all subjects (1.20 being the threshold considered to be amyloid positive; 27.0% of the cohort met criteria for amyloid positivity).

Cross-sectional analyses

In the cross-sectional model examining the association between depressive symptoms and inferior temporal lobe tau (represented by T807 retention), the final reduced model indicated that greater depressive symptoms were significantly associated with greater inferior temporal lobe tau (partial $r = 0.188$, $p = 0.050$). Sex was the only other retained predictor, with the model as a whole being significant ($R^2 = 0.054$, $p = 0.050$; Table 2 and Figure 1a). There was a non-significant trend for higher GDS scores in males ($p = 0.073$). In the model testing the association between depressive symptoms and entorhinal cortex tau, a similar result of marginal significance was obtained, indicating a positive association of depressive symptoms and entorhinal cortex tau (partial $r = 0.183$, $p = 0.055$; Model: $R^2 = 0.053$; $p = 0.054$; Table 3 and Figure 1b), as well as a trend for higher GDS scores in males ($p = 0.072$) (Table 3).

In secondary analyses for dependent variable GDS, when amyloid (represented by PiB retention) was added to the initial pool of predictors including tau (either IT or EC), the same results were obtained, and amyloid was not retained in either model. In a subsequent step, when amyloid, tau, and the interaction term between tau (IT or EC) X amyloid was added to each model, neither a main effect of tau nor amyloid was retained, and the tau X amyloid interaction term was not significant (data not shown). Finally, in a model in which initial predictors subject to backward elimination included amyloid, age, and sex (but not tau), amyloid was not retained in the model, and the model was not significant (data not shown).

In exploratory analyses, we examined the effects of statistically adjusting for education, global cognition (MMSE score), APOE e4 allele carrier status, or antidepressant medication use (SSRI/SNRI or other antidepressant) on the relationship between GDS and tau. When education, APOE e4 allele carrier status or MMSE were each individually added to the initial pool of predictors subject to backward elimination, we obtained either identical results or the same overall pattern and magnitude of results (see Supplementary Table 1). When controlling for the effect of antidepressant use (either SSRI/SNRI or other antidepressant use) in the initial pool of predictors in each backward elimination model, these predictors dropped out of the models and identical results were obtained (data not shown).

Given the frequent co-occurrence of depression and anxiety in older adults and the inclusion of anxiety-related symptoms in the GDS construct, we carried out exploratory analyses replacing the total GDS score with the sub-score corresponding to the GDS anxiety-concentration cluster, derived from a previous GDS factor analysis in the HABS cohort[6]. We did not find a significant association between the GDS anxiety-concentration cluster score and inferior temporal or entorhinal cortex tau (Supplementary Tables 2 & 3).

Though we had no substantive reasons to consider any subject an outlier, we performed a formal outlier analysis, which yielded one outlier in GDS scores (the highest score). We then repeated the primary analyses omitting the subject with that GDS score. In these analyses, we found a marginal association between GDS score and inferior temporal tau (partial $r=0.16$, $p=0.10$) but no association with entorhinal tau in the primary models (data not shown). This suggests, as commonly occurs in cohorts of cognitively normal subjects with a low range of symptoms, that results may be driven by a few of the most symptomatic subjects, in this case, those with the highest GDS scores.

Analyses exploring curvilinear effects of age

We observed a bivariate quadratic relation between age and depressive symptoms in our study cohort ($p=0.001$), with youngest and oldest subjects in the cohort having higher GDS scores according to this predicted fit (Supplementary Figure 2). When we simultaneously included both an age as well as an age squared predictor in our initial full model for GDS versus inferior temporal lobe tau, (which effectively tests for a curvilinear, quadratic effect of age) the quadratic effect of age was significant (partial $r=0.337$ $p<0.001$ for the quadratic age term) and the model as a whole was significant ($R^2=0.169$, $p=0.001$). Inferior temporal tau and sex were also retained in the model though were only marginally significant: there was a trend for a positive association of depressive symptoms and inferior temporal tau (partial $r=0.174$, $p=0.072$) and with male sex (partial $r=0.182$, $p=0.059$) (Supplementary Table 4). Similarly, in a parallel analysis for GDS versus entorhinal cortex tau, the model as a whole was significant ($R^2=0.165$, $p=0.001$), and only the quadratic effect of age was retained as significant (partial $r=0.329$, $p<0.001$) (Supplementary Table 5). Entorhinal cortex tau and sex were also retained in the model though again were only marginally significant: there was a trend for a positive association of depressive symptoms and entorhinal cortex tau (partial $r=0.160$, $p=0.097$) and for depressive symptoms and male sex (partial $r=0.180$, $p=0.062$) (Supplementary Table 5).

In secondary analyses, when amyloid was added to the predictor pool in each model above containing tau (either IT or EC tau), similar results were obtained, and amyloid was not retained. In a subsequent step, when the interaction term between tau (IT or EC) X amyloid was added to each model, neither a main effect of tau nor amyloid was retained, and the tau X amyloid interaction term was not significant (data not shown). Finally, in a model in which initial predictors included amyloid, linear age, quadratic age, and sex (but not tau), the quadratic effect of age was significant (partial $r=0.344$, $p<0.001$ for the quadratic age term) and the model as a whole was significant ($R^2=0.168$, $p=0.001$). Amyloid and sex were also retained in the model, though marginally: there was a trend for a positive association of depressive symptoms and amyloid (partial $r=0.173$, $p=0.074$) and with male sex (partial $r=0.171$, $p=0.077$).

Discussion

Depression in older adults is associated with increased disability and functional and cognitive impairment [1, 3]. Despite the relevance of depressive and other neuropsychiatric symptoms in AD progression, the neurobiology of subclinical depressive symptoms in CN older adults in relation to *in vivo* regional tau burden and amyloid is not well understood. Investigating this association is of clinical relevance, as it could allow earlier detection of older adults most likely to benefit from introduction of therapy to prevent onset of AD dementia and/or of more severe depression.

To our knowledge, this is the first study investigating the neurobiology of depressive symptoms in relationship to *in vivo* cerebral tau with the PET ligand T807 in CN elderly without moderate or severe psychiatric illness. We found that greater depressive symptoms were modestly associated with greater tau (T807 retention) in the inferior temporal lobe, and to a lesser extent, in the entorhinal cortex, when adjusting for sex and linear age (linear age was non-significant and was removed from our backwards elimination models). Further, adjusting individually for education, global cognition, APOE e4 carrier status or antidepressant use did not alter the overall pattern of our findings. We also found a quadratic relationship of age and GDS in our cohort, with both the youngest and oldest subjects having more depressive symptoms. When adjusting for quadratic age in our models, the strength of the effects for inferior temporal tau and entorhinal cortex tau were attenuated, but remained marginally significant and in the same direction as before.

Our findings of a modest association between depressive symptoms and tau in the inferior temporal lobe and, to a lesser extent, in the entorhinal cortex, if substantiated, may support a role for regional tau accumulation as one potential etiological mechanism linking neurodegeneration and depressive symptoms among older adults. While the inferior temporal lobe and entorhinal cortex are not commonly associated with affect regulation, these brain regions have intimate connections to the hippocampus and other limbic system regions that are involved in modulation of affect [37–39], thus providing one potential mechanism by which medial and inferior temporal lobe tau could be related to the pathogenesis of subclinical depressive symptoms. The hippocampus in particular has been implicated in depression in older adults[40]; however, we did not investigate the association

between hippocampal tau and depressive symptoms given concern for relatively low and off-target retention of the tau PET ligand T807 in this brain region [41].

We found similar relationships with depressive symptoms for inferior temporal lobe and entorhinal cortex tau in our models. Given that the entorhinal cortex within the medial temporal lobe is the initial site of vulnerability to tau accumulation with aging, followed by spreading to the inferior temporal lobe, a region more closely associated with tau accumulation during pre-clinical and clinical AD [8, 10, 11], our findings suggest that depressive symptoms may be associated not only with age-related pathology, but also early AD pathology. A related interpretation is that subclinical depressive symptoms are age-related symptoms associated with tau mediated neurodegenerative changes in regions affected early in AD.

A secondary hypothesis of our study was that depressive symptoms would be differentially associated with tau compared to amyloid. Consistent with this, we did not find a significant main effect of amyloid in any of our models, either in those containing amyloid alone, or both amyloid and tau (IT or EC tau). Further, when we introduced a tau X amyloid interaction term into our models, we did not observe a main effect of tau or amyloid and the interaction was non-significant.

Our findings build upon work from our group and others supporting a relationship between depressive symptoms and neurodegeneration in the temporal lobe in older adults that may be a part of or contribute to AD vulnerability and disease progression. Indeed, Donovan et al., investigating depressive symptoms in relation to fibrillar cortical amyloid and hippocampal volume and metabolism in an overlapping cohort from the Harvard Aging Brain Study, found an association between depressive symptoms and reduced hippocampal volume and metabolism, but no association with amyloid [6]. A recent cross-sectional study of late life depression by De Winter et al. also found a reduction in hippocampal volume but no increase in cortical amyloid burden in the depressed vs. control subjects [18]. In contrast, Babulal and colleagues found in a cohort of cognitively normal older adults that mood disturbances (assessed through a combination of scales including the GDS, the Neuropsychiatric Inventory Questionnaire (NPI-Q) and the Profile of Mood States—Short Form (POMS-SF)) were significantly associated with CSF proteinopathies (AB42, total tau, and phospho-tau) and with PiB-PET at one-year follow up but not at baseline [42]. Thus, current evidence argues against a robust cross-sectional association between depressive symptoms and amyloid in older adults at the stage of normal cognition. However, given the trend for greater depressive symptoms being associated with amyloid accumulation in our secondary analysis model containing quadratic age and amyloid as predictors, our findings cannot rule out a role for amyloid in combination with tau and/or other age related and neurodegenerative changes in the pathophysiology of late life depressive symptoms. Future studies with larger sample sizes, longitudinal follow up, and with subjects with more severe depressive and cognitive symptom severity are needed to distinguish between these alternatives.

In analyses exploring the curvilinear effects of age in our study cohort, we found evidence of a quadratic relationship between age and GDS score. While the quadratic relationship

between age and depressive symptoms suggests that the youngest and oldest members of our cohort have the highest depressive symptoms, larger epidemiological studies have not consistently reported a quadratic relationship between age and depression across the lifespan [43–45]. The relationship between age and GDS score we observed may reflect in part the staggered enrollment in our cohort observational study, such that subjects of high and low age ranges were recruited at distinct recruitment periods with subtle differences in recruitment targets and strategies. As such, there may be differences between the youngest and oldest in our cohort in psychosocial, physical health or other variables which underlie the observed relationship between age and GDS score. More detailed and larger scale studies in our cohort and other cohorts are needed to further differentiate between these alternatives.

The relation between age and GDS we observed adds interest but also complexity to our data and the conclusions that we can draw, and may have somewhat obscured the effects of tau that were of primary interest. When introducing a quadratic age term into our models, the quadratic effect was retained as the most significant. Consistent across all models, however, was the relationship between inferior temporal and entorhinal cortex tau accumulation and greater depressive symptoms, either as a significant association or trend.

Another consistent finding was a trend for males having greater depressive symptoms than females. This is in contrast to prevailing evidence for a greater likelihood of depression in females vs. males across the lifespan in the general population [44, 46], though this difference between sexes may diminish in late life [47]. Further, previous epidemiological evidence has focused predominantly on depressive syndromes across the lifespan, rather than subclinical depressive symptoms in older adults, as measured in our study. Our finding may also be driven by factors related to sample selection. Given that our sample is comprised of highly educated individuals who volunteered for the study, the males in the sample may be more likely to endorse depressive symptoms than males in the general population (who may be more prone to underreporting depressive symptoms relative to females). Future work is needed to distinguish between these alternatives in our cohort.

Our study has a number of strengths and limitations. Our study cohort was free of moderate to severe psychiatric illness. Thus, the confounding factor of primary psychiatric illness burden was minimized in our analyses. As such, our sample is relatively controlled from the repetitive stress-induced brain changes and vulnerability hypothesized to occur in the context of chronic psychiatric illness, and instead focuses on subclinical depressive symptoms that may be inherently related to a neurodegenerative process. The absence of moderate to severe depressive illness in our study population at the same time presents a limitation, given the low range of GDS scores in our cohort, with the average score well below the cut-off of what would be considered clinical depression. Thus, the analyses we report are of depressive symptoms rather than depression or a diagnosis of depression. Nonetheless, subclinical depressive symptoms may be a clinically relevant construct among community dwelling elders, given increasing evidence that even subtle changes across a number of neuropsychiatric and behavioral domains, as in mild behavioral impairment, may be among the earliest manifestations in AD progression [48, 49]. It is possible that other neuropsychiatric symptoms, closely-related to depression, such as anxiety, may be influencing our findings. However, we did not find a significant association between tau

burden and the GDS-derived anxiety-concentration cluster. Discerning the relationships between biomarkers and different affective endophenotypes is an important area of ongoing investigation in our cohort. Several prior CSF, clinical-pathological, and neuroimaging studies have revealed more robust associations between depressive symptoms and AD proteinopathies [7, 12, 16, 17, 20]. These studies have done so in subject cohorts with late life major depression and/or varying degrees of cognitive impairment. This suggests that subclinical depressive symptoms may lie on a spectrum of pathogenic change, with increasing severity of both depressive and cognitive symptoms more robustly associated with AD proteinopathies.

There are additional areas of potential limitation of our study and avenues for future investigation. We employed backward elimination regression models, which are sometimes considered to have a liberal bias. However, this is only a problem for large models; our initial model included only a small number of predictors, and only one or two of these were removed. We limited the scope of our analyses to AD-related proteinopathies, though other processes such as neuroinflammation, cerebrovascular disease, microinfarcts, and hippocampal volume loss and sclerosis have been implicated in the pathophysiology of depressive symptoms in older adults [4, 50]. Future work will involve investigation of the relationships among depressive symptoms, AD proteinopathies, and medical and cerebrovascular illness burden, as well as those between depression and cognitive function. Furthermore, given the role of disruption of network structure and function in depressive illness and AD [51–55], future work investigating tau and amyloid accumulation in the context of both neuronal network structure and functional connectivity may provide a more thorough understanding of the pathophysiology of these symptoms in the context of other age-related brain changes.

In conclusion, we found that depressive symptoms were modestly associated with greater tau burden (T807 retention) in the inferior temporal lobe and to a lesser extent, with tau burden in the entorhinal cortex. In contrast, we did not find a significant association with amyloid. While findings from the current pilot study must be interpreted judiciously given the relatively modest associations between tau burden and depressive symptoms and the limitations of our study cohort, these findings warrant further longitudinal investigation in more symptomatic subjects. Preliminarily, they suggest that CN older adults with even mild depressive symptoms deserve close follow up, as these individuals may harbor tau mediated neurodegenerative change in regions affected early in AD pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Scatterplots showing the unadjusted relationships between Geriatric Depression Scale (GDS) score and inferior temporal (panel a) and entorhinal cortex (panel b) tau (^{18}F T807 retention) for all subjects in the cohort.

Table 1

Demographic, Clinical, and Neuroimaging Data

	N	Mean	Range	Standard deviation
Age (years)	111	75.91	(62.25–90.00)	6.65
Sex (% male)	111	43.2		0.50
APOE e4 allele carrier (%)	110	27		
MMSE	110	29.20	(26.0–30.0)	0.99
Education(years)	111	15.83	(9–20)	3.00
GDS	111	3.93	(0–21.0)	3.98
Antidepressant medication use (%)	111			
SSRI/SNRI		9		
Other class		2.7		
Amyloid (PiB aggregate DVR)	111	1.21	(0.95–1.89)	0.23
Tau (inferior temporal lobe T807 SUVR)	111	1.20	(1.02–1.55)	0.088
Tau (entorhinal cortex T807 SUVR)	111	1.12	(0.96–1.50)	0.115
Interval (days)	111	86.25	(0–267)	50.34

Abbreviations: MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale-30 item; SSRI = selective serotonin reuptake inhibitor; SNRI = selective norepinephrine reuptake inhibitor; PiB = Pittsburgh Compound B; DVR = distribution volume ratio; SUVR = standardized uptake volume ratio. Interval represents the time in days between ¹⁸F T807 PET imaging acquisition and GDS data collection.

Final cross-sectional model of GDS score in relation to ¹⁸F T807 retention in the inferior temporal lobe in CN older adults

Table 2

Predictor	Estimate (β)	95% Confidence Interval for β	partial r	Standard error	p value
Tau, Inferior temporal lobe	8.51	(0.016, 17.0)	0.188	4.28	0.050
Male Sex	1.37	(-0.13, 2.88)	0.171	0.759	0.073

Model: F=3.089; df=2,108, p=0.050; R²=0.054

A general linear regression model with backward elimination (p<0.1 cut-off) was carried out for the dependent variable GDS total score. Predictors entered into the model included sex, linear age, and inferior temporal Tau (T807 retention). Predictors retained in the final model following backward elimination with a p<0.1 cut-off are shown along with β estimates, 95% confidence interval, and p value. Tau, Inferior temporal T807 retention in the inferior temporal lobe. CN=cognitively normal; GDS=Geriatric depression scale.

Final cross-sectional model of GDS score in relation to ¹⁸F T807 retention in the entorhinal cortex in CN older adults

Table 3

Predictor	Estimate (β)	95% Confidence Interval for β	partial r	Standard error	p value
Tau, entorhinal cortex	6.36	(−0.143, 12.86)	0.183	3.28	0.055
Male Sex	1.38	(−0.128, 2.89)	0.172	0.761	0.072

Model F=2.99; df=2,108; p=0.054; R²=0.053

A general linear regression model with backward elimination (p<0.1 cut-off) was carried out for the dependent variable GDS total score. Predictors entered into the model included sex, linear age, entorhinal cortex tau (T807 retention). Predictors retained in the final model following backward elimination (p<0.1 cut-off) are shown along with β estimates, 95% confidence interval, and p value. Tau, entorhinal cortex: ¹⁸F T807 retention in the entorhinal cortex. CN=cognitively normal; GDS= Geriatric depression scale.