Received: 16 February 2021 | Accepted: 26 February 2021

DOI: 10.1002/gps.5530

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Affective symptoms and regional cerebral tau burden in early-stage Alzheimer's disease

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Funding information
National Institutes of Health; U.S. Department of Defense

Abstract

Objective: Neuropsychiatric symptoms (NPS) are often present in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia. NPS are associated with structural and functional changes in the brain such as atrophy, regional hypometabolism, and hypoperfusion, considered proxies of neurodegeneration. Our objective was to evaluate the association between NPS and regional cerebral tau burden, a more direct representation of neurodegeneration, in cognitively normal (CN), MCI, and AD dementia individuals.

Methods: Cross-sectional NPS were assessed using the Neuropsychiatric Inventory (NPI) in 410 CN, 199 MCI, and 61 AD dementia participants who underwent flortaucipir tau positron emission tomography as part of the AD Neuroimaging Initiative (ADNI). Total NPI score and two factors of NPS (affective and hyperactive) were used in analyses. Linear regression models with backward elimination were employed with NPI as dependent variable and regional tau or tau-amyloid interaction as predictor of interest. Covariates included education, age, sex, Rey Auditory Verbal Learning Test Total Learning, and Trail Making Test B.

Results: There were significant associations ($p < 0.05$) between the NPI variables (total score, Affective factor) and entorhinal and precuneus tau across all participants. These associations were also significant for the tau-amyloid interaction. These effects were significant in cognitively symptomatic participants (MCI and AD dementia), but not in CN participants.

Conclusions: Increased tau burden in the entorhinal and precuneus cortices was modestly associated with greater NPS in MCI and AD dementia. Further evaluation of NPS and their effect on early-stage AD could aid in finding new interventions and slowing disease progression.

KEYWORDS
affective symptoms, Alzheimer's disease, amyloid, mild cognitive impairment, neuropsychiatric symptoms, positron emission tomography, tau

Key Points

- Neuropsychiatric symptoms (NPS) are common manifestations of early-stage Alzheimer's disease (AD)
- In the current study, we found that increased tau burden in the entorhinal and precuneus cortices was modestly associated with greater NPS in MCI and AD dementia
- These associations were noted with affective symptoms in particular
- These associations were seen in participants with greater amyloid burden in particular

1 | INTRODUCTION

Alzheimer's disease (AD) is a major public health concern and has affected approximately 5.8 million Americans in 2018, a number that is expected to double by mid-century as the population ages.[1] Progression of AD is marked by cognitive and functional decline and is accompanied by a variety of neuropsychiatric symptoms (NPS).[2–5] NPS, such as depression and apathy, constitute a major aspect of the health concerns for individuals with AD and have a negative effect on individuals' quality of life, as well as that of their loved ones, increasing caregiver burden.[6,7] In population-based studies, the frequency of NPS is greater in individuals with mild cognitive impairment (MCI) and AD dementia than in cognitively normal (CN) individuals,[4,8] and has been shown to be associated with disease progression,[6,9] indicating a need for further research in this area.

Recent advances in neuroimaging and broader knowledge of the neuropathology of AD has led to better understanding of the relationship between NPS and brain regions affected by disease progression. Previous studies displayed relationships between affective symptoms, such as apathy, depression, and anxiety, occurring early in the disease process, and structural and functional changes in the brain representing a proxy of neurodegeneration: Apathy, characterized by lack of motivation and loss of interest in usual activities, has been associated with the medial frontal (anterior cingulate and orbitofrontal cortex), inferior temporal, insula, posterior cingulate, and lateral parietal atrophy, hypoperfusion, hypometabolism, and decreased connectivity in patients with MCI and AD dementia.[10–20] In addition, there has been post-mortem evidence of increased anterior cingulate tau burden in patients with apathy in later stages of AD.[21] Another common affective NPS in MCI and AD dementia is depression, which has been associated with atrophy of the entorhinal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex.[22,23] Anxiety has been associated with lateral temporal, insula, precuneus, and amygdala atrophy, hypoperfusion, and hypometabolism.[24–26] Hyperactive NPS are also common in individuals with AD, often occurring later in the disease process. Agitation, an example of a hyperactive NPS characterized by oppositional behavior and aggression has been associated with atrophy, hypometabolism, and altered connectivity of the frontal, anterior cingulate, and posterior cingulate cortices, and in the later stages of AD there has been post-mortem evidence of increased tau burden in the medial orbitofrontal and anterior cingulate cortices.[13,27–30]

A recent systematic review focused on affective symptoms and AD biomarkers, reported associations with amyloid and tau biomarkers in addition to the neurodegeneration associations described above.[31] It concludes that there are inconsistent associations with apathy, anxiety, irritability, and agitation, and no consistent associations with depression. However, few studies, not included in the systematic review, have assessed the relationship between NPS and regional tau burden in the brain. One such recent study has shown an association between greater apathy and right anterior cingulate and dorsolateral prefrontal tau burden in MCI and AD dementia, especially in individuals with elevated cortical amyloid.[32] Another study in CN older adults showed an association between depressive symptoms and inferior temporal and entorhinal cortex tau burden.[33]

Tau is one of the hallmarks of AD pathology and has been the focus of many studies in recent years.[34,35] In the third phase of the AD Neuroimaging Initiative (ADNI-3), tau positron emission tomography (PET) scans, utilizing the tracer flortaucipir (FTP) (a.k.a. AV-1451) were introduced to the study allowing for a broader investigation of tau accumulation in the brain.[36–39] In addition to FTP PET scans, ADNI-3 also assesses amyloid burden in the brain using the tracer florbetapir (a.k.a. AV45). These scans have been utilized both in research and clinical practice to assess the burden of cortical amyloid due to MCI and dementia.[40] Increases in amyloid and tau are associated with the progression of cognitive decline and AD dementia.[41,42]

In the current study, we investigated the relationship between regional cerebral tau burden, utilizing FTP PET, and NPS across CN, MCI and AD dementia. To assess NPS in these participants we used the Neuropsychiatric Inventory (NPI),[43,44] an informant-based measure, that evaluates the frequency and severity of 12 NPS. We hypothesized that there would be a significant relationship between the NPI Affective factor score and medial frontal regions such as the anterior cingulate and orbitofrontal cortices as shown with other imaging modalities above, as well as associations with the entorhinal and inferior temporal cortices, which are regions of early tau deposition in AD. We further hypothesized that a tau-amyloid interaction will display similar associations between the aforementioned tau regions interacting with cortical amyloid and the NPI Affective factor. Determining the relationship between NPS and tau burden in AD can further elucidate the pathophysiology of these distressing symptoms and help find targets for treatment.

2 | MATERIALS AND METHODS

2.1 | Participants

Data for the current study were obtained from the ADNI database (adni.loni.usc.edu) on 410 CN, 199 MCI, and 61 AD dementia participants taking part in the ADNI3 study. ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early-stage AD. Participants were excluded if they had a 15-item Geriatric Depression Scale score greater than 5, had major depression or bipolar disorder in the past year, had a history of schizophrenia, had agitation or behavioral issues in the past 3 months that may affect their participation, or current use of certain psychotropic medications (anticholinergic antidepressants, neuroleptics, anxiolytics, or sedative hypnotics). Only participants who underwent FTP tau PET neuroimaging within a year of completing the NPI were included in the sample. The participants were 56–95 years old and 48.1% female. Diagnoses were determined by the principal investigator or co-investigators at each site utilizing cognitive and functional assessments, as previously described.[45,46] The study was approved by the local Institutional Review Board of each participating ADNI site. Participants and study partners reviewed and signed a consent form before any study procedures were completed.

2.2 | Clinical assessments

The NPI[43,44] is an informant-based measure that assesses the frequency and severity of 12 NPSs: depression, anxiety, apathy, sleep, appetite, delusions, hallucinations, agitation, euphoria, disinhibition, irritability, and aberrant motor behavior. Each item is assessed on a scale of one to four for frequency and 0–3 for severity. The total score for each symptom is determined by the product of the frequency and severity scores in a range of 0–12. A greater NPI item score is indicative of higher NPS severity. A Total NPI score, the sum of all 12 item scores (range 0–144), was used in analyses. Moreover, an Affective factor (consisting of the anxiety, apathy, depression, appetite, and sleep items) and a Hyperactivity factor (consisting of the agitation, irritability, aberrant motor behavior, and disinhibition items) were based on a prior factor analysis as previously described.[16] For the purpose of our study we derived the Affective and Hyperactive factor scores by averaging the items they consisted of (range 0–12) rather than running the factor analysis again.

Cognitive assessments were used as covariates in analyses. The Rey Auditory Verbal Learning Test (RAVLT)[47] total learning score assesses performance of episodic memory. In this assessment, participants are presented a list of 15 words over five trials and are asked to repeat them after a distractor list and a delay. The total learning score ranges between 0 and 75 and lower scores indicate poorer performance. The Trail Making Test B (TMT-B) score was used to assess executive function (divided attention and task switching performance).[48] It is recorded by the time it takes an individual to complete the task, where higher scores indicate greater impairment.

2.3 | Amyloid and tau PET data

FTP and Florbetapir PET imaging acquisition and processing was previously described in detail.[49,50] Briefly, FTP scans were co-registered to corresponding MRI scans that were segmented and parcellated with Freesurfer (version 5.3.0) in order to calculate the mean FTP uptake within each Freesurfer-defined region with cerebellar cortex as the reference region yielding a standardized uptake value ratio (SUVR) (UC Berkeley—AV1451 Analysis Methods, ADNI). Eight bilateral subcortical and cortical regions of interest (ROI) were chosen, based on prior studies of NPSs in AD:[11,12,16,17,19,32,33] entorhinal cortex, inferior temporal cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, posterior cingulate cortex, precuneus, and supramarginal gyrus. Florbetapir scans were co-registered to corresponding MRI scans that were segmented and parcellated with Freesurfer (version 5.3.0) to define the amyloid cortical gray matter ROI (frontal, anterior cingulate, posterior cingulate, lateral parietal, and lateral temporal) that make up an aggregate cortical ROI with whole cerebellum as the reference region yielding an SUVR (UC Berkeley—AV45 Analysis Methods, ADNI). An amyloid status cutoff of florbetapir SUVR of 1.10 was employed as previously predefined with amyloid-negative ≤ 1.10 and amyloid-positive > 1.10.

2.4 | Statistical analysis

All analyses for this study were done using SPSS version 26.0 (IBM). Initially, Pearson correlations between the NPI variables (Total NPI score, Affective factor, and Hyperactive factor) and each tau region (dorsolateral prefrontal cortex, entorhinal cortex, inferior temporal cortex, orbitofrontal cortex, posterior cingulate cortex, precuneus cortex, anterior cingulate cortex, and supramarginal cortex) were performed to evaluate the unadjusted associations across all participants and then by the individual diagnoses (CN, MCI, and AD dementia). The tau regions with associations of $p < 0.05$ were then used in the primary analyses.

Linear regression models with backward elimination ($p < 0.10$ for retention, $p < 0.05$ for significance) were used as the primary analyses to examine the association between the three NPI variables in separate analyses (dependent variable) and the significant tau regions identified from the unadjusted correlations. Each tau region was tested in its own model. We adjusted for multiple comparisons utilizing a Bonferroni correction with a p value of <0.00,625 indicating significance (based on the eight different brain regions used in these analyses). We included the following covariates: education, age, sex, RAVLT Total Learning Score, and TMT-B. RAVLT and TMT-B

were included as covariates because memory impairment and executive dysfunction are associated with greater NPS in individuals with MCI and AD dementia.[51–53]

In secondary analyses, the above models were repeated for the NPI factor with significant associations with the addition of an interaction term between regional tau and cortical amyloid. Then, for the NPI factor with significant associations, models were repeated with the individual NPI items comprising the factor (i.e., apathy, depression, anxiety, etc.) for tau regions with significant associations in prior models. Finally, sensitivity analyses were carried out separately in cognitively asymptomatic (CN) and symptomatic (combined MCI and AD dementia) participants. We did not adjust for multiple comparisons in the secondary analyses.

Unstandardized coefficients (β) with 95% confidence intervals (CI), Partial regression correlations (pr), and significance test results (p values) were reported.

3 | RESULTS

Participant demographics and characteristics, including cognitive, tau, and amyloid values by diagnostic group can be found in Table 1. Individual NPI item scores, factor scores, and Total NPI score can be found in Table 2.

Unadjusted correlations across all participants showed significant associations between the total NPI score and all eight tau regions (r = 0.08–0.24, p = 0.04–<0.001) (see Table 3). Significant associations were also seen between the Affective factor and seven of the tau regions (r = 0.10–0.23, p = 0.01–<0.001; see Table 3), and between the Hyperactive factor and six of the tau regions (r = 0.09–0.18, p = 0.02–<0.001; see Table 3). Correlations performed within each diagnostic group did not yield significant results.

3.1 | Primary analyses

Linear regression models with backward elimination using the previously mentioned covariates were analyzed for all tau regions identified in the unadjusted correlations across all participants in the entire cohort utilizing the NPI total score, NPI Affective Factor and NPI Hyperactive Factor. This yielded significant associations with tau regions for the Total NPI score (entorhinal cortex tau: β = 3.52, 95% CI = 1.01, 6.02, pr = 0.11, p = 0.006; precuneus tau: β = 4.58, 95% CI = 1.59, 7.58, pr = 0.12; p = 0.003) and Affective factor (entorhinal cortex tau: β = 0.46, 95% CI = 0.14, 0.78, pr = 0.11; p = 0.005; precuneus tau: β = 0.60, 95% CI = 0.22, 0.98, pr = 0.12, p = 0.002). These results survived Bonferroni correction. The Hyperactive factor did not yield significant associations.

TABLE 1 Participant demographics and characteristics

Diagnosis	All	CN	MCI	AD Dementia
n	670	410	199	61
Age (Years)	74.5 ± 7.8	73.6 ± 7.3	75.4 ± 8.4	77.3 ± 8.4
Sex (% female)	48.1	41.2	58.3	60.7
Education (Years)	16.6 ± 2.5	16.8 ± 2.3	16.3 ± 2.6	15.8 ± 2.7
Race (% white)	90.7	88.8	93.5	95.1
MMSE	28.1 ± 2.6	29.1 ± 1.2	27.8 ± 2.0	22.3 ± 3.5
CDR sum of boxes	0.9 ± 1.9	0.1 ± 0.2	1.5 ± 0.9	5.6 ± 2.5
Trail making test B	91.7 ± 58.4	72.9 ± 33.9	104.2 ± 56.7	192.9 ± 92.9
RAVLT total learning	41.3 ± 12.8	47.1 ± 10.4	34.8 ± 10.0	23.3 ± 7.5
Dorsolateral prefrontal cortex FTP SUVR	1.04 ± 0.18	1.01 ± 0.09	1.04 ± 0.16	1.26 ± 0.38
Entorhinal FTP SUVR	1.17 ± 0.23	1.10 ± 0.13	1.22 ± 0.26	1.49 ± 0.31
Inferior temporal cortex FTP SUVR	1.25 ± 0.28	1.18 ± 0.15	1.27 ± 0.27	1.69 ± 0.49
Orbitofrontal cortex FTP SUVR	1.10 ± 0.15	1.08 ± 0.11	1.11 ± 0.16	1.23 ± 0.25
Posterior cingulate FTP SUVR	1.11 ± 0.18	1.07 ± 0.10	1.12 ± 0.16	1.33 ± 0.37
Precuneus FTP SUVR	1.13 ± 0.22	1.08 ± 0.09	1.13 ± 0.16	1.47 ± 0.51
Anterior cingulate FTP SUVR	1.05 ± 0.14	1.04 ± 0.11	1.06 ± 0.15	1.13 ± 0.23
Supramarginal FTP SUVR	1.09 ± 0.20	1.06 ± 0.10	1.09 ± 0.17	1.37 ± 0.46
Cortical florbetapir (amyloid) SUVR	1.15 ± 0.23	1.10 ± 0.15	1.21 ± 0.28	1.44 ± 0.22
Amyloid status (% amyloid-positive)	40.3	30.0	49.5	89.7

Abbreviations: AD, Alzheimer's disease; CDR, clinical dementia Rating; CN, cognitively normal; FTP, flortaucipir; MCI, mild cognitive impairment; MMSE, mini mental state exam; RAVLT, Rey Auditory Verbal Learning Test; SUVR, standardized uptake value ratio

TABLE 2 Factor, individual, and total neuropsychiatric inventory (NPI) scores

Diagnosis	All	CN	MCI	AD Dementia
Affective factor	0.44 ± 0.91	0.21 ± 0.59	0.59 ± 0.82	1.51 ± 1.77
Depression	0.44 ± 1.25	0.27 ± 1.01	0.65 ± 1.44	0.90 ± 1.72
Anxiety	0.29 ± 1.24	0.08 ± 0.57	0.43 ± 1.49	1.23 ± 2.52
Apathy	0.40 ± 1.44	0.09 ± 0.64	0.52 ± 1.44	2.16 ± 3.09
Sleep	0.70 ± 1.80	0.49 ± 1.51	0.94 ± 1.95	1.33 ± 2.66
Appetite	0.37 ± 1.50	0.13 ± 0.84	0.38 ± 1.46	1.92 ± 3.22
Hyperactive factor	0.28 ± 0.76	0.10 ± 0.43	0.41 ± 0.84	1.02 ± 1.39
Agitation	0.27 ± 1.04	0.10 ± 0.62	0.40 ± 1.18	0.97 ± 2.06
Irritability	0.53 ± 1.61	0.27 ± 1.05	0.78 ± 1.97	1.43 ± 2.69
Disinhibition	0.19 ± 0.90	0.05 ± 0.48	0.35 ± 1.10	0.61 ± 1.74
Aberrant motor behavior	0.14 ± 0.85	0.00 ± 0.05	0.12 ± 0.76	1.08 ± 2.28
Total NPI score	3.41 ± 7.13	1.46 ± 4.25	4.65 ± 6.52	12.5 ± 13.7

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; MCI, mild cognitive impairment.

TABLE 3 Unadjusted Pearson correlations between NPI variables and regional tau across all participants

Brain Region FTP SUVR	NPI Total Score	NPI Affective Factor	NPI Hyperactive Factor
Dorsolateral prefrontal cortex	0.142**	0.139**	0.092*
Entorhinal	0.241**	0.232**	0.171**
Inferior temporal cortex	0.212**	0.198**	0.151**
Orbitofrontal cortex	0.098*	0.097*	0.066
Posterior cingulate	0.167**	0.157**	0.126**
Precuneus	0.225**	0.211**	0.176**
Anterior cingulate	0.078*	0.072	0.056
Supramarginal	0.176**	0.163**	0.135**

Abbreviations: FTP, flortaucipir; NPI, neuropsychiatric inventory; SUVR, standardized uptake value ratio

*$p < 0.05$; **$p < 0.001$

3.2 | Secondary analyses

Subsequent analyses included an interaction between regional tau and amyloid. Significant associations were found for tau × amyloid interactions with the Affective factor (entorhinal cortex tau x amyloid: $\beta = 0.35$, 95% CI = 0.13, 0.57, $pr = 0.17$, $p = 0.002$; precuneus tau x amyloid: $\beta = 0.43$, 95% CI = 0.19, 0.68, $pr = 0.18$, $p = 0.001$; see Figure 1).

The NPI items within the Affective factor were further analyzed, examining regional tau associations (not including an interaction with amyloid): Entorhinal cortex tau displayed significant associations for the NPI Depression item ($\beta = 0.50$, 95% CI = 0.06, 0.94, $pr = 0.09$, $p = 0.03$), NPI Anxiety item ($\beta = 0.79$, 95% CI = 0.33, 1.24, $pr = 0.13$, $p = 0.001$), and NPI Apathy item ($\beta = 0.57$, 95% CI = 0.08, 1.07, $pr = 0.09$, $p = 0.02$). Precuneus tau yielded significant associations with NPI Anxiety item ($\beta = 0.65$, 95% CI = 0.11, 1.18, $pr = 0.09$, $p = 0.02$), NPI Apathy item ($\beta = 1.03$, 95% CI = 0.45, 1.62, $pr = 0.14$, $p = 0.001$), and NPI Appetite item ($\beta = 1.49$, 95% CI = 0.85, 2.14, $pr = 0.18$, $p < 0.001$).

Analyzing the NPI items within the Affective factor including an interaction between regional tau and amyloid showed significant associations between entorhinal cortex tau x amyloid and NPI Apathy item ($\beta = 3.34$, 95% CI = 1.13, 5.54, $pr = 0.16$, $p = 0.003$; see Figure 2), precuneus tau x amyloid and NPI Apathy item ($\beta = 0.51$, 95% CI = 0.13, 0.88, $pr = 0.14$, $p = 0.008$), and NPI Appetite item ($\beta = 3.76$, 95% CI = 0.36, 7.17, $pr = 0.12$, $p = 0.03$).

When including only cognitively asymptomatic (CN) participants, there were no significant associations between the Affective factor and regional tau. When including only cognitively symptomatic (combined MCI and AD dementia) participants, there were significant associations between Affective factor and entorhinal cortex tau ($\beta = 0.58$, 95% CI = 0.08, 1.08, $pr = 0.14$, $p = 0.02$) and precuneus tau ($\beta = 0.73$, 95% CI = 0.16, 1.29, $pr = 0.16$, $p = 0.01$), as well as

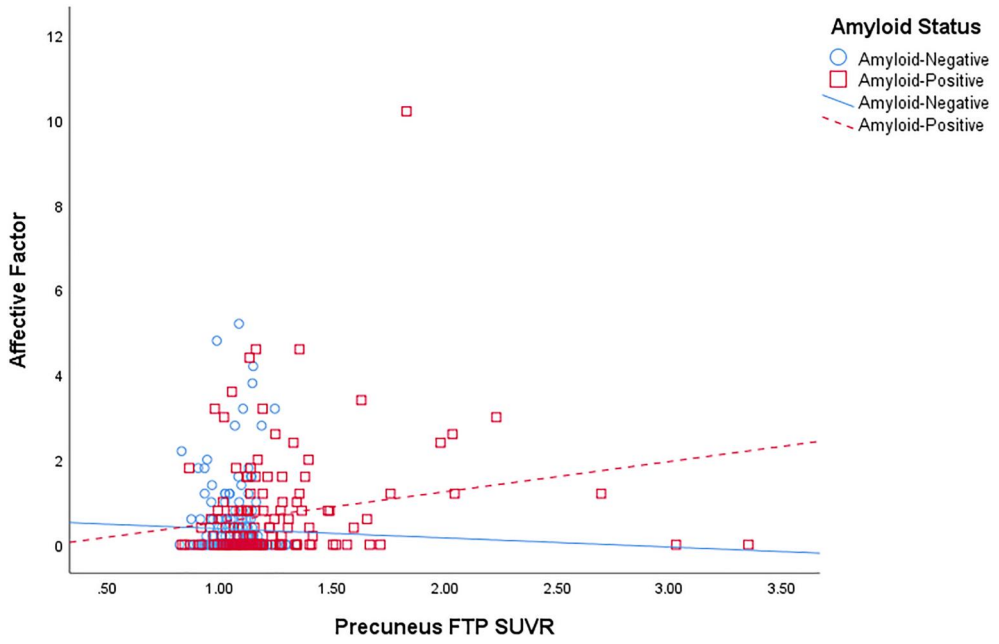

FIGURE 1 Scatter plot of precuneus FTP (tau) SUVR versus Affective factor in all participants, stratified by Amyloid Status (amyloid-positive = florbetapir SUVR > 1.10; amyloid-negative = florbetapir SUVR ≤ 1.10). The above results remain significant after removing the single outlier for Affective Factor (score >10). Abbreviations: FTP, flortaucipir; SUVR, standardized uptake value ratio

entorhinal cortex tau x amyloid (β = 0.44, 95% CI = 0.11, 0.77, pr = 0.23, p = 0.01).

4 | DISCUSSION

In these exploratory analyses, tau accumulation in the entorhinal cortex and precuneus cortex were modestly associated with greater overall NPS and affective symptoms in particular across CN, MCI, and AD dementia participants. The same associations were noted when looking at symptomatic participants (MCI and AD dementia combined), but not when looking at CN participants only, suggesting that these associations were driven by the symptomatic participants. When analyses were run again, including an interaction term between regional tau and cortical amyloid, affective symptoms were associated with greater entorhinal cortex and precuneus tau in individuals with greater amyloid burden. There were no significant associations with the hyperactivity factor.

In our study, we also examined the association between the individual NPI Affective factor symptoms (anxiety, apathy, depression, and appetite) with tau accumulation in the precuneus and entorhinal regions. We found associations between tau burden in the entorhinal cortex and symptoms of depression, anxiety, and apathy. There was also a relationship between tau burden in the precuneus cortex and anxiety, apathy, and appetite. Previous research has shown that depressive symptoms are associated with the entorhinal cortex,[22,23] which is supported by our findings. Many previous studies have shown an association between medial frontal regions and apathy,[12,14,15,20] which we did not replicate here. This could be due to an association between biomarkers of early AD pathology (entorhinal and precuneus cortices tau deposition) and early AD symptoms (affective symptoms) rather than a direct localization of the affective symptoms. However, a prior study showed an association between medial and lateral parietal hypometabolism and apathy across the AD spectrum,[17] which is supported by our findings with precuneus tau. Moreover, we did show that in individuals with elevated cortical amyloid, entorhinal cortex and precuneus tau related to apathy. This is consistent with a recently reported association between apathy and the interaction between cortical amyloid and frontal tau in MCI and AD dementia.[32] Furthermore, prior studies focused on cognition in AD, have similarly shown an association between the interaction of amyloid and tau and cognitive decline, supporting a two-hit hypothesis of pathology in AD.[42]

Additional findings in our study are the association between precuneus tau-cortical amyloid interaction and appetite, and the association between precuneus tau and anxiety, which is supported by prior studies showing relationships between parietal and temporal pathology and anxiety.[24–26] Therefore, the results of our study are in agreement with previous studies primarily employing neuroimaging measures that are proxies of neurodegeneration in relation to NPS. Our findings extend this evidence to suggest that an in vivo measure of tau deposition is associated with NPS. While neurodegenerative changes correlate with tau pathology in AD, they are not necessarily equivalent, leading to recent further refining of the research criteria for AD to include biomarkers of amyloid, tau, and neurodegeneration.[54] The current study has added to the knowledge of changes in the brain of individuals with MCI and AD dementia and how they relate to comorbid affective symptoms.

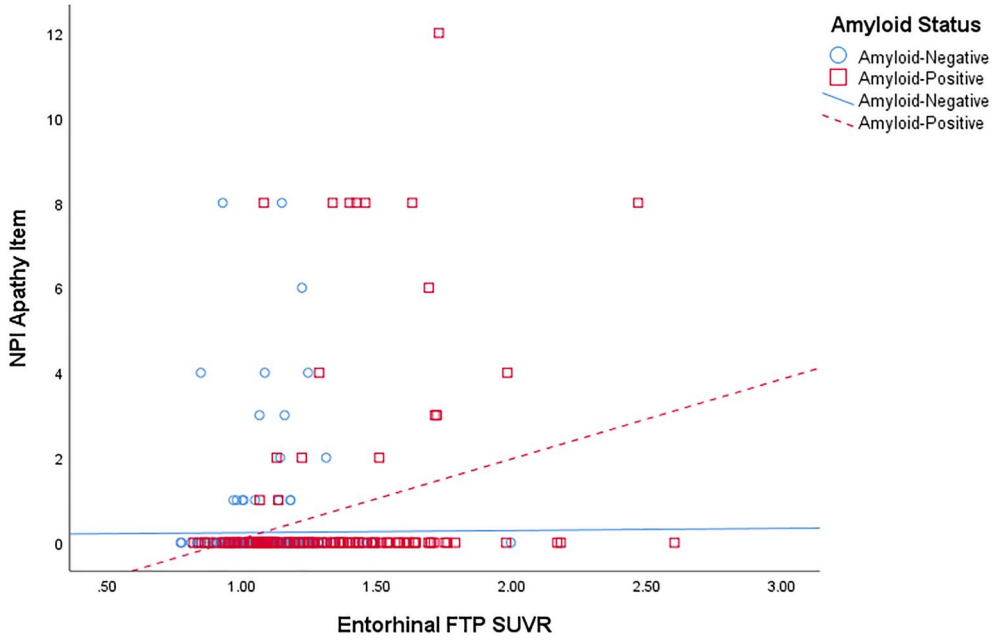

FIGURE 2 Scatter plot of entorhinal cortex FTP (tau) SUVR versus NPI Apathy item in all participants, stratified by Amyloid Status. Abbreviations: FTP, flortaucipir; NPI, neuropsychiatric inventory; SUVR, standardized uptake value ratio

A strength of our research was utilizing data from the ADNI-3 study, which is a multi-center study with a multitude of NPS assessments, cognitive testing, and multi-modal imaging data. As longitudinal tau and clinical data are collected in ADNI-3, we plan to extend this novel approach towards the analysis of cerebral tau accumulation and NPS. Those efforts will help understand the directionality of clinical-imaging associations, opening the door to new treatment targets for NPS in early-stage AD.

There were several limitations to our research. First, the participants recruited into the ADNI study are selected only if they meet specific criteria. Therefore, the sample is not representative of the general population and is more comparable to samples that take part in other MCI and AD dementia observational studies and clinical trials as they have similar inclusion and exclusion criteria. Furthermore, there is a lack of diversity amongst the ADNI-3 participants with most participants identified as white, which also contributes to the sample being less generalizable to the older adult population. Second, the sample size for the AD dementia group was relatively small, and for that reason we combined that group with the MCI group in our secondary analyses focused on cognitively symptomatic versus asymptomatic participants. A larger sample size for MCI and AD dementia groups may have yielded significant results when assessing the individual groups on their own. Moreover, the MCI group could be further split into early and late MCI in determining the associations between NPS and regional tau burden. Third, we noted very few NPS in the CN group, which is likely the reason there were no associations with regional tau and NPS in that group alone despite its large sample size. Fourth, participants did not endorse as many hyperactive symptoms when compared to affective symptoms, likely because hyperactive symptoms occur more frequently in cohorts with more advanced AD than that of the ADNI-3 sample. Therefore, future studies with more impaired participants are necessary to better assess the relationship between hyperactive symptoms and regional tau burden. Fifth, this was an exploratory cross-sectional study including only one FTP PET and NPS assessment. Perhaps a longitudinal study assessing the changes in NPS and tau accumulation in the brain as disease progression occurs will reveal more robust associations between NPS and regional tau burden. Another possibility for future research would be to analyze the differences between the associations of Tau and NPS and the associations between atrophy representing neurodegeneration and NPS.

In conclusion, the current study displayed a modest association between affective NPS and increased regional cerebral tau accumulation, specifically in the entorhinal cortex and precuneus across CN, MCI, and AD dementia participants, driven by the cognitively symptomatic participants. These associations were independent of age, education, sex, executive function, and memory. Further exploration in longitudinal studies of the association between cerebral tau burden and NPS will provide a better understanding of the association between these clinical and pathological features of early-stage AD, paving the road to more effective targeted treatments.

ACKNOWLEDGMENTS

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH–12–2–0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical

Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST

Nicole S. Tommasi, Christopher Gonzalez, Danielle Briggs, and Michael J. Properzi have nothing to disclose. Jennifer R. Gatchel has received research support from Merck. Gad A. Marshall has received research salary support from Eisai Inc., Eli Lilly and Company, Janssen Alzheimer Immunotherapy, Novartis, and Genentech, and consulting fees from Grifols Shared Services North America, Inc., Eisai Inc., and Pfizer.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Tommasi NS, Gonzalez C, Briggs D, Properzi MJ, Gatchel JR, Marshall GA. Affective symptoms and regional cerebral tau burden in early-stage Alzheimer's disease. *Int J Geriatr Psychiatry*. 2021;1–9. https://doi.org/10.1002/gps.5530