Received: 29 June 2020 | Accepted: 1 November 2020

DOI: 10.1002/gps.5459

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Relationship between neuropsychiatric symptoms and Alzheimer's disease pathology: An in vivo positron emission tomography study

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Abstract

Objectives: To investigate the relationship between amyloid-β- and tau-based Alzheimer's disease (AD) pathologies assessed using positron emission tomography imaging and neuropsychiatric symptoms (NPS) in a sample of AD continuum including clinically normal subjects and patients with mild cognitive impairment or AD.

Methods: We analyzed datasets of the Alzheimer's disease Neuroimaging Initiative and included amyloid-positive subjects who underwent an AV-45 scan within 1 year of an AV-1451 scan ($n = 99$). Correlation between standardized uptake value ratio (SUVR) of AV-45 and AV-1451 and the Neuropsychiatric Inventory (NPI) score (and its four domain subscores for hyperactivity, psychosis, affective, and apathy) was evaluated. Stepwise logistic regression analysis was used to examine the influence of SUVRs on the presence of NPS. SUVRs were also tested for their ability to discriminate the group with NPS using receiver operating characteristic (ROC) curve analyses.

Results: Significant positive relationships were found between the total NPI score and affective symptoms and Braak 1&2 (transentorhinal region) AV-1451 SUVR. Stepwise logistic regression analysis identified tau accumulation in the area of Braak 1&2 as a significant covariate discriminating the presence of affective symptoms. The area under the ROC curve analysis showed that subjects with affective symptoms were discriminated by AV-1451 SUVR with an accuracy of 77.7%.

Conclusions: Tau aggregation in the transentorhinal region, where neurodegeneration affected by tau pathology was seen in the early stage of AD, correlated with more severe NPS, especially affective symptoms. Therefore, tau pathology in the transentorhinal cortex might be associated with affective symptoms in the early stage of AD.

Data used in preparation of this article were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (http://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 the analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

KEYWORDS
Alzheimer's disease, amyloid β, neuropsychiatric symptoms, positron emission tomography, tau aggregation

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia. The cerebral aggregation of both amyloid-β (Aβ) plaques and tau-related neurofibrillary tangles (NFTs) are well-known neuropathological changes in AD. The amyloid cascade model supported by in vitro and in vivo data proposes that the accumulation of Aβ is the triggering factor for AD, bringing about the hyper phosphorylation and aggregation of tau, synaptic loss, and cell death.[1,2] With advances in positron emission tomography (PET) using radiotracers that bind to Aβ, it became clear that AD has a long preclinical course, whereby clinically normal (CN) subjects show biomarker abnormalities up to 15 years before the onset of dementia.[3–5]

Although AD is usually considered a cognitive disorder, almost all individuals diagnosed with AD develop neuropsychiatric symptoms (NPS) at some stage during the disease course, and NPS have been associated with a higher likelihood for cognitive decline.[6] A cohort study of older CN adults, those with subjective cognitive concerns, and those with mild cognitive impairment (MCI) indicated that more severe affective symptoms, including depression, irritability, agitation, disinhibition, anxiety, and apathy, were predictive of a more rapid progression of cognitive decline across all groups.[7] In a prospective cohort study estimating the risk of incident MCI in CN subjects with or without NPS at baseline, the prevalence of symptoms, including irritability, agitation, disinhibition, anxiety, and apathy, was shown to increase the risk for later MCI.[8] Furthermore, studies estimating the risk of the onset of AD in subjects with MCI showed that NPS, such as agitation, depression, and apathy, are associated with the progression from MCI to AD.[6]

To date, a few groups have studied the relationship between NPS and amyloid burden, and some have suggested that NPS reflect the underlying amyloid pathology.[9,10] A high cortical amyloid burden or abnormal cerebrospinal fluid Aβ levels have been shown to be associated with apathy, anxiety, depression, and irritability.[11–14] As to the tau pathology, cerebrospinal fluid tau, p-tau181, and t-tau/Aβ42 levels in cognitively normal older adults were shown to predict changes in NPS—higher levels of each of these biomarkers were associated with greater increases in NPS over time.[15] A more significant degree of AD neurodegeneration, characterized by a higher t-tau/Aβ42 ratio, was shown to be correlated with more severe NPS, thus suggesting that more extensive AD neurodegeneration is related to more severe behavioral disturbances in patients with MCI and AD.[16] Recently, the availability of radiotracers that bind to tau has allowed the in vivo PET imaging of tau pathology. Informant-based reports of abnormal night-time behavior were shown to be significantly associated with increased entorhinal tau levels.[17] However, little is known about the relationship between other NPS and regional tau pathology, as assessed using in vivo PET. Herein, we investigated the relationship between Aβ- and tau-based AD pathologies using PET and NPS due to these AD pathologies in a sample of amyloid-positive AD continuum, including CN subjects and patients with MCI or AD, from the AD Neuroimaging Initiative (ADNI).

Key points

- We investigated the relationship between Alzheimer's disease (AD) pathologies and neuropsychiatric symptoms (NPS) to quantify NPS due to AD pathologies.
- We found a significant relationship between the affective symptoms and Braak 1&2 (transentorhinal regions)-AV-1451-SUVR in AD continuum subjects.
- A stepwise logistic regression analysis identified tau accumulation as a significant covariate of the best model discriminating the presence of affective symptoms.
- Our findings may indicate that tau pathology in the transentorhinal cortex might be associated with affective symptoms early in the course of AD.

2 | MATERIALS AND METHODS

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The 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, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org.

2.1 | Participants

Amyloid-positive subjects of AD continuum diagnosed with MCI or AD, as well as CN subjects, were included in this study based on the respective inclusion criteria: CN—subjects without depression, MCI, and dementia and with Mini-Mental State Examination (MMSE) scores between 24 and 30; MCI—subjects with MMSE scores between 24 and 30, objective memory loss measured using the

TABLE 1 Descriptive characteristics of AD continuum subjects (mean ± SD [min-max])

Characteristic/test	All	CN	MCI	AD
Number	99	49	29	21
Gender, M/F	48/51	19/30	18/11	11/10
Age, years	76.5 ± 6.0 (61–85)	76.1 ± 5.2 (63–84)	76.8 ± 7.2 (61–85)	77.1 ± 6.0 (62–85)
Education, years	16.3 ± 2.4 (12–20)	16.8 ± 2.4 (12–20)	15.6 ± 2.6 (12–20)	16.0 ± 2.1 (12–20)
MMSE score	26.9 ± 4.2 (9–30)	29.0 ± 1.1 (26–30)	28.1 ± 1.9 (24–30)	20.3 ± 4.6 (9–26)
ADAS score	19.8 ± 10.8 (5.0–52.0)	12.8 ± 5.0 (5.0–27.0)	20.7 ± 6.5 (6.0–31.67)	20.6 ± 6.4 (18.33–52.0)
Total NPI score	4.9 ± 8.4 (0–44)	2.3 ± 5.8 (0–30)	3.7 ± 3.8 (0–14)	12.4 ± 13.0 (0–44)
Hyperactivity	1.6 ± 3.8 (0–20)	0.6 ± 2.4 (0–14)	1.7 ± 3.3 (0–14)	3.9 ± 5.8 (0–20)
Psychosis	1.2 ± 2.4 (0–14)	0.5 ± 1.1 (0–4)	1.1 ± 2.1 (0–8)	2.7 ± 4.0 (0–14)
Affective	0.6 ± 1.4 (0–7)	0.3 ± 1.1 (0–6)	0.6 ± 1.0 (0–4)	1.4 ± 2.1 (0–7)
Apathy	1.4 ± 3.5 (0–20)	0.8 ± 2.6 (0–12)	0.3 ± 1.0 (0–4)	4.4 ± 5.6 (0–20)
Cortical AV-45 SUVR	1.36 ± 0.19 (1.11–2.23)	1.31 ± 0.16 (1.11–1.71)	1.42 ± 0.22 (1.12–2.23)	1.41 ± 0.18 (1.18–1.71)
Braak 1&2-AV-1451 SUVR (transentorhinal)	1.54 ± 0.37 (0.94–2.68)	1.31 ± 0.17 (0.94–1.68)	1.60 ± 0.30 (1.10–2.39)	2.00 ± 0.35 (1.21–2.68)
Braak 3&4-AV-1451 SUVR (medial temporal and limbic)	1.62 ± 0.40 (1.20–3.68)	1.44 ± 0.17 (1.22–2.02)	1.63 ± 0.30 (1.20–2.37)	2.02 ± 0.59 (1.29–3.68)
Braak -5&6_AV-1451 SUVR (neocortical)	1.63 ± 0.42 (1.22–4.73)	1.49 ± 0.15 (1.22–1.94)	1.63 ± 0.24 (1.24–2.41)	1.96 ± 0.76 (1.36–4.73)

Abbreviations: AD, Alzheimer's disease; ADAS, Alzheimer's disease Assessment Scale-cognitive subscale; CN, clinically normal; F, female; M, male; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation; SUVR, standardized uptake value ratio.

education-adjusted Wechsler Memory Scale Logical Memory II score, a Clinical Dementia Rating of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia; and AD—MMSE scores less than 27, a Clinical Dementia Rating of 0.5 or 1, and meeting the National Institute of Neurological and Communicative Disorders and Stroke & the Alzheimer's disease and Related Disorders Association criteria for probable AD.[18]

We included ADNI-2 and ADNI-3 data, with no duplicate entries, from amyloid-positive subjects aged 60–85 (inclusive) years who had undergone a florbetapir (AV-45) scan within 1 year of undergoing an AV-1451 scan. All participants were selected as amyloid-positive subjects based on preestablished cutoffs (global florbetapir standardized uptake value ratio [SUVR] >1.11).[19] Subjects also underwent neuropsychological assessment within 1 year of both AV-45 and AV-1451 PET imaging (total, $n = 138$; CN, $n = 63$; MCI, $n = 42$; AD, $n = 33$). We excluded subjects who were taking antidepressant and/or other behavioral medications to avoid the effects of these medications on NPS (total; $n = 39$, CN; $n = 14$, MCI; $n = 13$, AD; $n = 12$). Finally, we used the data from 99 subjects for the analysis. The sample consisted of 49 CN individuals and 50 participants diagnosed with either MCI ($n = 29$) or AD dementia ($n = 21$). General data of the participants (age, sex, years of education, MMSE score, and AD Assessment Scale-cognitive subscale-13 [ADAS] score) were extracted from the ADNI databases (Table 1).

2.2 | Standard protocol approvals, registrations, and patient consent

All participants provided written informed consent. The study was approved by the institutional review boards at all participating study sites.

2.3 | NPS assessment

NPS were assessed within 1 year of both AV-45 and AV-1451 scans. Out of 99 subjects, 84 and 89 were assessed before the AV-45 and AV-1451 scans, respectively, while the average number of days counted between the NPS assessment and the scans was 14 ± 97 for the former and 38 ± 57 for the latter. The severity of NPS was evaluated based on the 12-subscore Neuropsychiatric Inventory (NPI) scale (scores range from 0 to 12, where a higher score reflects more severe NPS). Twelve behavioral and psychological symptoms of dementia categories were covered by the questionnaire: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, and problems with eating and sleeping. The NPI items were further classified into four domains according to the factor analysis previously reported by Aalten et al.[20] These four domains and the included items were (i) hyperactivity, including agitation, euphoria, disinhibition, irritability, and aberrant motor behavior (scores range

from 0 to 60); (ii) psychosis, including delusions, hallucinations, and night-time behavior (scores range from 0 to 36); (iii) affective, including depression and anxiety (scores range from 0 to 24); and (iv) apathy, including apathy and eating abnormalities (scores range from 0 to 24).

2.4 | Aβ and tau PET analysis

^{18}F-AV-1451 neuroimaging data obtained from the ADNI-2 and ADNI-3 databases were analyzed. AV-45 scans were collected within 1 year of the AV-1451 scans. The acquisition and image preprocessing protocols used are publicly available on the ADNI database website (http://adni.loni.usc.edu/).

The AV-45 dataset represents mean AV-45 uptake in cortical gray matter-weighted florbetapir of the regions of interest (ROIs) for all participants. The ROIs included the bilateral frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices, as defined by the ADNI group. ROI-based AV-45 SUVRs were calculated with reference to the AV-45 uptake mean of the whole cerebellum. The details of the data processing method are described in 'UC Berkeley- AV-45 Analysis Methods (PDF)' (https://ida.loni.usc.edu/pages/access/studyData.jsp).

For the AV-1451 dataset, tracer retention was quantified in ROIs that anatomically approximated the pathological stages of tangle deposition delineated by Braak and Braak.[21] Weighted mean SUVR was calculated from three composite ROIs that corresponded to the anatomical definitions of Braak stages 1&2 (entorhinal cortex and hippocampus), 3&4 (medial temporal and limbic region), and 5&6 (neocortical region) with reference to the mean AV-1451 uptake of the inferior cerebellum. The details of the data processing method are described in 'UC Berkeley-Flortaucipir (AV-1451) processing methods (PDF)' (https://ida.loni.usc.edu/pages/access/studyData.jsp).

2.5 | Statistics

All demographic characteristics data, NPI scores, and AV-45 and AV-1451 SUVRs from composite ROIs of subjects showed skewed distribution. Spearman's correlation analysis between SUVRs of AV-45 and AV-1451 from composite ROIs and total NPI scores was conducted. We also examined the relationship of any symptomatic cluster of the four NPI domains (hyperactivity, psychosis, affective, and apathy) with SUVRs. When we found a significant relationship between AV-45 and/or AV-1451 SUVR and any symptomatic cluster of the four NPI domains, the Mann–Whitney *U*-test was used to compare SUVR values between the groups with and without the symptom for which a relationship was observed in the above-mentioned correlation analysis.

In addition, stepwise backward deletion multiple logistic regression analysis was used to determine the discriminators of the presence of NPS symptoms whose relationship to AV-45 and/or AV-1451 SUVR were shown in the above-mentioned correlation analysis. The presence of NPS symptoms was defined as a symptoms score >0. The dependent variable was the presence of symptoms, and the independent variables were age, sex, years of education, cognitive function (ADAS score), and the mean AV-45 and/or AV-1451 SUVR. Determined discriminators were tested for their ability to discriminate the groups with NPS symptoms, using receiver operating characteristic (ROC) curves.

All statistical analyses were performed using SPSS for Windows 26.0 (IBM Japan). Statistical tests were two-tailed, and significance was defined as a *p*-value less than 0.05/n using Bonferroni correction (where n refers to the number of multiple comparisons).

3 | RESULTS

3.1 | Spearman's correlation analysis between AV-45- and AV-1451- SUVRs and the total and subscores of NPI

We examined the relationship between the NPI subscores and Braak 1&2-AV-1451 SUVR, we found a significant positive relationship between the affective symptoms score and Braak 1&2-AV-1451 SUVR (Table 2, Figure 1).

3.2 | Comparison of SUVR values between subjects with and without affective symptoms in the amyloid-positive group

We found significantly high tau accumulation in Braak stage 1&2 areas in the subjects with affective symptoms (Table 3). However, we did not observe a difference in cortical amyloid or tau accumulation in Braak stage 3&4 and 5&6 areas (Table 3).

3.3 | Stepwise backward deletion multiple logistic regression analysis discriminating the presence of symptomatic cluster in the amyloid-positive subjects

We identified tau accumulation in Braak stage 1&2 areas as a significant covariate in the best model discriminating the presence of affective symptoms (Table 4). The area under the ROC (AUROC) curve method showed that the optimal cutoff of Braak 1&2-AV-1451 SUVR for the discrimination of the presence of affective symptoms was 1.714 (sensitivity = 60.0%, specificity = 83.8%, AUROC = 0.70, negative predictive value = 86.1%, positive predictive value = 55.6%, accuracy = 77.7%), indicating its value as a potential tool for discriminating the risk of affective symptoms due to AD pathology (Figure 2).

TABLE 2 Spearman's correlation between NPI total and subscores and AV-45 and AV-1451 SUVR in AD continuum subjects

	r (p)				
	Total NPI score	Hyper activity	Psychosis	Affective	Apathy
Cortical AV-45_SUVR	0.22 (0.032)	0.21 (0.036)	0.08 (0.421)	0.09 (0.393)	0.12 (0.235)
Braak 1&2-AV-1451 SUVR (transentorhinal)	0.43 (<0.001*)	0.20 (0.044)	0.25 (0.013)	0.31 (0.002*)	0.16 (0.126)
Braak 3&4-AV-1451 SUVR (medial temporal and limbic)	0.28 (0.006)	0.15 (0.144)	0.15 (0.151)	0.23 (0.021)	0.07 (0.481)
Braak 5&6-AV-1451 SUVR (neocortical)	0.24 (0.015)	0.13 (0.203)	0.09 (0.382)	0.22 (0.029)	0.02 (0.819)

Abbreviations: AD, Alzheimer's disease; NPI, Neuropsychiatric Inventory; SUVR, standardized uptake value ratio.
*$p < 0.0025$ (0.05/20).

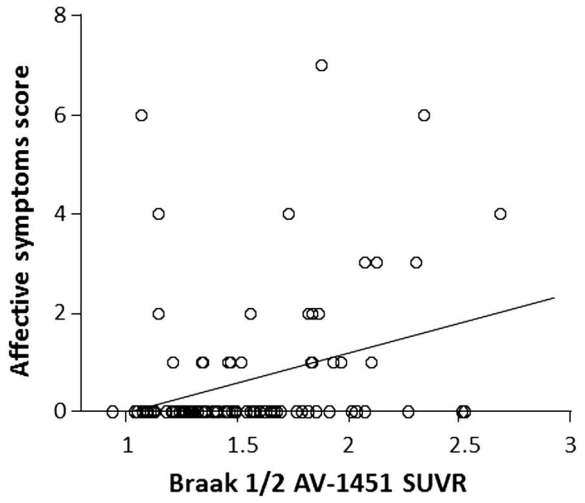

FIGURE 1 Scatter plot of the correlation between tau aggregation in the transentorhinal cortex (Braak 1&2-AV-1451 SUVR) and affective symptoms score in amyloid-positive subjects. There was a significant correlation between Braak 1&2-AV-1451 SUVR and affective symptoms scores. SUVR, standardized uptake value ratio

4 | DISCUSSION

To the best of our knowledge, this is the first in vivo PET imaging study to show a relationship between NPS and tau pathology of the transentorhinal cortex in AD continuum subjects. Tau aggregation in the Braak 1&2 (transentorhinal) regions, where neurodegeneration has been shown to be affected by tau pathology in the early stages of AD, correlated with more severe NPS, especially the affective symptoms such as depression and anxiety.

Emotional dysregulation, characterized by the increased elaboration of negative information, difficulties disengaging from negative material, and deficits in cognitive control when processing negative information due to biased cognitive processing, is one of the central features of affective symptoms.[22] The transentorhinal cortex has extensive connections with the frontal lobes and the limbic system, including the default mode network (DMN), which is associated with emotion regulation[23]; thus, cell death in this region may disrupt pathways involved in emotional and behavioral regulation. Dysfunction of the transentorhinal cortex due to an increase in tau pathology may result in biased cognitive processing and preclude successful modulation of DMN activity during mood regulation; this could then cause affective symptoms in amyloid-positive subjects.

Previous articles have suggested that affective symptoms are major indicators of AD progression.[24] Elderly individuals with affective symptoms who show no overt clinical indications of dementia are nonetheless at a particularly high risk for AD.[25] Additionally, more pronounced neuropathological changes occur in individuals with affective symptoms at the time of AD diagnosis.[26] Furthermore, one study[27] showed that patients with both MCI and affective symptoms have a higher risk of developing AD than those with MCI alone. Together, these findings support our observation of the association between affective symptoms and more severe tau pathology, which are related to a higher risk of the development and progression of AD in amyloid-positive subjects.

The present study investigated the influence of clinico-demographic factors and transentorhinal tau pathology on affective symptoms in subjects of AD continuum. Using stepwise multivariate logistic regression analysis, we established that the vulnerability to affective symptoms can be significantly discriminated by tau accumulation in the transentorhinal cortex in AD continuum subjects. In the ROC curve analysis, we showed that the tau accumulation in the transentorhinal cortex could classify 60.0% of subjects with the presence of affective symptoms and 83.8% of them with an absence of affective symptoms with 77.8% accuracy. ROC curve analysis indicated the value of the tau accumulation in the transentorhinal cortex as a potential screening tool for detecting the vulnerability of affective symptoms due to AD pathology.

Our study has several limitations. First, we searched for ADNI subjects who had both Aβ and tau PET scans acquired at time points close to each other and the NPS assessments. The rigid timing specifications reduced the number of available subjects. Second, as our research focused on the relationship between NPS and AD pathologies, subjects who were on antidepressants and/or on medications for other behavioral issues were excluded from this study. This was done in an effort to avoid the effects of these medications on NPS, even though it may have resulted in a bias towards recruiting individuals with fewer symptoms NPS. Third, given that the NPI is based on responses from an informed caregiver, NPI scores may not accurately reflect the NPS of study participants. Fourth, although previous studies have suggested an association

TABLE 3 Comparison of SUVR values between the groups of affective symptoms (−) and (+) in AD continuum subjects (mean ± SD [min-max])

	SUVR values (mean ± SD [min-max])		Mann–Whitney U	
Region	**Affective symptoms (−) ($n = 74$)**	**Affective symptoms (+) ($n = 25$)**	***Z***	***p***
Cortical AV-45 SUVR	1.35 ± 0.19 (1.11–2.23)	1.39 ± 0.19 (1.12–1.71)	1.176	0.240
Braak 1&2-av-1451 SUVR (transentorhinal)	1.47 ± 0.33 (0.94–2.53)	1.75 ± 0.41 (1.07–2.68)	3.020	0.003*
Braak 3&4-av-1451 SUVR (medial temporal and limbic)	1.58 ± 0.41 (1.20–3.68)	1.73 ± 0.37 (1.26–2.54)	2.384	0.017
Braak 5&6-av-1451 SUVR (neocortical)	1.60 ± 0.45 (1.22-4.73)	1.73 ± 0.33 (1.27–2.45)	2.392	0.017

Abbreviations: AD, Alzheimer's disease; SD, standard deviation; SUVR, standardized uptake value ratio.

*$p < 0.0125$ (0.05/4).

TABLE 4 Results of a stepwise backward deletion multivariate logistic regression analysis discriminating the positiveness of affective symptoms in AD continuum subjects

Step	*β*	OR	95% CI	Wald (df = 1)	*p*
Model 1 ($\chi^2_5 = 13.6$, $p = 0.018$)					
Age	0.04	1.05	0.95–1.15	0.846	0.358
Gender	0.14	1.15	0.37–3.55	0.056	0.814
Education	−0.15	0.86	0.69–1.06	1.964	0.161
ADAS scores	−0.001	1.00	0.93–1.07	0.001	0.970
Braak 1&2-AV-1451 SUVR	2.00	7.41	0.93–59.3	3.561	0.059
Model 2 ($\chi^2_4 = 13.6$, $p = 0.009$)					
Age	0.04	1.05	0.95–1.15	0.857	0.354
Gender	0.14	1.15	0.39–3.39	0.067	0.814
Education	−0.15	0.86	0.70–1.06	2.021	0.155
Braak 1&2-AV-1451 SUVR	1.97	7.18	1.94–26.6	8.681	0.003
Model 3 ($\chi^2_3 = 13.6$, $p = 0.004$)					
Age	0.04	1.04	0.95–1.13	0.806	0.369
Education	−0.16	0.85	0.69–1.05	2.309	0.129
Braak 1&2-AV-1451 SUVR	1.96	7.10	1.92–26.2	8.659	0.003
Model 4 ($\chi^2_2 = 12.7$, $p = 0.002$)					
Education	−0.17	0.85	0.69–1.04	2.537	0.111
Braak 1&2-AV-1451 SUVR	1.97	7.17	1.92–26.2	8.884	0.003
Model 5 ($\chi^2_1 = 10.1$, $p = 0.001$)					
Braak 1&2-AV-1451 SUVR	1.99	7.33	2.02–26.6	9.164	0.002
AUROC of model 5	0.70	-	-	-	-
Youden's index	0.44	-	-	-	-
Cut-off value of Braak 1&2 AV-1451 SUVR	1.714	-	-	-	-
Specificity (%)	60.0	-	-	-	-
Sensitivity (%)	83.8	-	-	-	-
PPV (%)	55.6	-	-	-	-
NPV (%)	86.1	-	-	-	-
Accuracy (%)	77.7	-	-	-	-

Note: The criterion for choosing the operating point along the receiver operating characteristic curve was Youden's index maximum.

Abbreviations: AD, Alzheimer's disease; ADAS, Alzheimer's disease Assessment Scale-cognitive subscale; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; SUVR, standardized uptake value ratio.

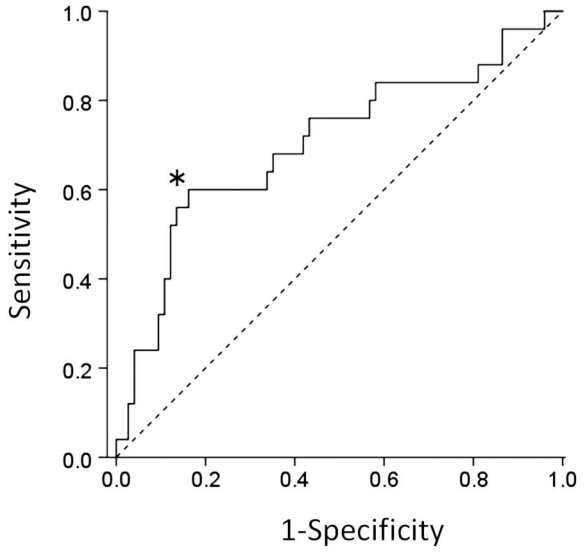

FIGURE 2 AUROC curve models. The AUROC curve analysis evaluated the relevance of tau accumulation in Braak stage 1&2 areas in discriminating the presence of affective symptoms in the model shown in Table 4. With a Braak 1&2-AV-1451 SUVR of 1.714, the Youden index [sensitivity–(1-specificity)] reports a maximum value of 0.438 (sensitivity = 0.600, specificity = 0.838) at the cutpoint indicated by the asterisk. AUROC, area under the receiver operating characteristic

between the ApoE-4 allele and late-onset depression,[28] we could not examine this association, as genotyping of ApoE was not performed for subjects in the entire sample. Fifth, our findings might be, at least in part, attributable to the sampling bias of the ADNI study per se because individuals represented in the ADNI database were those who had access to research institutes or major psychiatric hospitals in the United States and further had some interest in participating in this study. This kind of bias is especially relevant in terms of social status. Last, almost half of the subjects whose SUVR score was higher than 1.714 did not have affective symptoms. We speculated that individual differences in either the cognitive processes or neural networks underlying emotional functions allow some people to cope better than others with tau accumulation-induced brain damage. Further studies are warranted to verify the validity of our speculation.

In our previous study,[14] we found significant associations between cortical Aβ accumulation and depressive symptoms estimated using the Geriatric Depression Scale (GDS) in CN subjects. However, in this study, no relationships were found between the severity of affective symptoms and cortical Aβ deposition. The discrepancies in the findings between these two studies may be due to the differences in the groups compared (only CN vs. CN, MCI, and AD), assessment scales (GDS vs. NPI) and the population background. The effects of the two Aβ- and tau-based AD pathologies on affective symptoms may not be mutually exclusive, as they may cause affective symptoms in a different manner.

In summary, tau aggregation in the transentorhinal region, where the neurodegeneration affected by tau pathology was seen in the early stage of AD, correlated with more severe NPS, especially the affective symptoms (depression and anxiety) in subjects of AD continuum. We established that the vulnerability to affective symptoms can be significantly discriminated by tau accumulation in the transentorhinal cortex in AD continuum subjects. The sample size of this study was modest; with its results await verification by future studies with larger samples. Nonetheless, there is a possibility that tau accumulation in the transentorhinal cortex is a potential biological marker of the vulnerability to affective symptoms in AD continuum subjects.

ACKNOWLEDGMENTS

The authors would like to thank the ADNI participants and study sites for their contributions to the study. The authors report no disclosures. 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 (http://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. This research was supported by the Research Funding for Longevity Sciences (19-11) from the National Center for Geriatrics and Gerontology and Grants-in-Aid for Scientific Research (B) 19H03590, from the Japan Society for the Promotion of Science.

CONFLICT OF INTEREST

The authors have no conflict of interest to report. The sponsor had no role in either the analysis or interpretation of these data or the content of the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Yasuno F, Minami H, Hattori H. Relationship between neuropsychiatric symptoms and Alzheimer's disease pathology: An in vivo positron emission tomography study. *Int J Geriatr Psychiatry*. 2021;36:598–605. https://doi.org/10.1002/gps.5459