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RESEARCH ARTICLE

Longitudinal associations of apathy and regional tau in mild cognitive impairment and dementia: Findings from the Alzheimer's Disease Neuroimaging Initiative

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Abstract

Introduction: It is important to study apathy in Alzheimer's disease (AD) to better understand its underlying neurobiology and develop effective interventions. In the current study, we sought to examine the relationships between longitudinal apathy and regional tau burden in cognitively impaired older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

Methods: Three hundred and nineteen ADNI participants with mild cognitive impairment (MCI) or AD dementia underwent flortaucipir (FTP) tau positron emission tomography (PET) imaging and clinical assessment with the Neuropsychiatric Inventory (NPI) annually. Longitudinal NPI Apathy (NPI-A) scores were examined in relation to baseline tau PET signal in three a priori selected regions implicated in AD and AD-related apathy (supramarginal gyrus, entorhinal cortex [EC] and rostral ante-

rior cingulate cortex [rACC]). Secondary models were adjusted for global cognition (Mini-Mental State Examination score) and cortical amyloid (florbetapir PET).

Results: Higher baseline supramarginal gyrus and EC tau burden were each significantly associated with greater NPI-A over time, while rACC tau was associated with higher NPI-A but did not predict its trajectory over time. These results were retained for supramarginal and EC tau after adjusting models for global cognition and cortical amyloid.

Discussion: Our findings suggest that baseline in vivo tau burden in parietal and temporal brain regions affected in AD, and less so in a medial frontal region involved in motivational control, is associated with increasing apathy over time in older adults with MCI and AD dementia. Future work studying emergent apathy in relation to not only core AD pathology but also circuit level dysfunction may provide additional insight into the neurobiology of apathy in AD and opportunities for intervention.

KEYWORDS

Alzheimer's disease, mild cognitive impairment, neuropsychiatric symptoms, apathy, neuroimaging, tau, positron emission tomography

Highlights

- Tau (Flortaucipir PET) in regions implicated in AD was associated with increasing apathy over time
- Cortical amyloid was also found to be a robust predictor of the trajectory of apathy
- Evidence of synergy between regional tau and amyloid in overall higher levels of apathy

1 | INTRODUCTION

Neuropsychiatric symptoms (NPS) are distressing symptoms that commonly occur across the Alzheimer's disease (AD) spectrum. Apathy is among the most common NPS in individuals diagnosed with mild cognitive impairment (MCI) and AD dementia. This symptom is characterized by diminished interest in the activities and plans of others, and decreased motivation in usual activities. NPS, including apathy, may begin even before the manifestation of overt cognitive symptoms and increase in occurrence as cognition declines.[1,2] Apathy is a commonly reported concern for individuals with AD and their care partners and has a negative impact on quality of life, resulting in decreased cognitive and functional ability and increased care partner burden.[3] Population-based studies have shown that the occurrence of NPS is higher in individuals with MCI and AD dementia compared to cognitively normal (CN) older adults, and is associated with disease progression.[4] While there has been progress in developing drug treatments for apathy in AD including methylphenidate,[5] future progress will be enhanced by better understanding of the neurobiological mechanisms involved in the context of AD progression.

Previous investigations in this area have found significant cross-sectional associations between apathy and several biomarkers of AD pathology.[6,7] Neuroimaging studies in AD across a spectrum of structural, functional, and molecular imaging modalities highlighted associations between apathy and medial frontal regions involved in the neurobiology of motivation or reward, particularly the anterior cingulate cortex (ACC).[8–13] For example, individuals with AD and apathy compared to those without apathy were found to have reduced cortical thickness, or reduced cerebral blood flow or metabolism in the orbitofrontal cortex and ACC,[10,14–16] in addition to gray matter reduction in the ACC.[14] In contrast, other studies have reported associations between apathy and temporal and parietal regions implicated in AD progression.[15,17,18] Among these, separate studies conducted on Alzheimer's Disease Neuroimaging Initiative (ADNI) samples showed associations between apathy and variables of interest (reduced cortical thickness and regional hypometabolism) in the temporal and parietal lobes.[13,17,19] In particular, [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) hypometabolism in a representative parietal region, the supramarginal gyrus, was significantly associated with apathy trajectory over time.[19] To our knowledge, only one exploratory study from the ADNI has examined apathy in relation to in vivo molecular neuroimaging, looking at tau and apathy cross-sectionally in CN participants, along with participants with MCI and AD dementia.[20] This cross-sectional study found that apathy was associated with elevated

tau (flortaucipir [FTP] PET) in the precuneus and entorhinal cortex (EC)—two regions associated with aging and AD—but not with regions traditionally associated with affective symptoms and motivation (ACC, orbitofrontal cortex).

These prior findings underscore the importance of understanding the neurobiology of apathy in the context of AD progression. A key step in advancing this understanding is investigating the relationship between the regional distribution of tau (a biomarker closely linked to cognitive symptoms of AD) and the evolution of apathy over time. Thus far, to our knowledge, no studies have explored changes in apathy over time in relation to regional tau measured through PET imaging in cognitively impaired older adults.

To fill this critical gap, the objective of the current study was to examine relationships between apathy over time and regional tau burden in individuals with MCI and AD dementia. Given previous findings highlighting temporal and parietal regions versus medial frontal regions in AD-associated apathy, we hypothesized that greater tau burden in regions associated with AD (the supramarginal gyrus and EC), and one involved in motivation and reward (the rostral [r]ACC), would predict increasing apathy over time in older adults with MCI or AD. To test this hypothesis, we focused on three representative brain regions in the temporal, parietal, and medial frontal cortices (supramarginal gyrus, EC, and ACC), previously implicated in AD and AD-related apathy.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional sources (eg, PubMed). An examination of the relationships between apathy and AD pathology is needed to better understand neurobiological mechanisms for therapeutic intervention that could delay disease progression. Research has shown that tau may correlate more closely with cognitive and behavioral manifestations in AD than amyloid. These relevant citations are appropriately cited.
2. **Interpretation**: Our findings suggest that tau burden in brain regions associated with AD, and less so with mood regulation, is associated with increasing apathy over time in individuals with MCI and AD dementia.
3. **Future directions**: Further study of emergent apathy in relation to core AD pathology and other neurobiological mechanisms—such as cerebrovascular disease and network connectivity—will provide additional insight into neurobiology and opportunities for interventions that could slow clinical progression and alleviate patient and caregiver burden.

2 | METHODS

2.1 | Participants

The study sample consisted of cognitively impaired older adults with MCI or AD dementia, enrolled in the ADNI-3 study (73.15% MCI, 26.85% AD dementia, age 55 to 95 years, 57.37% male; details of consent, study procedures and inclusion/exclusion criteria of participants can be found on adni.loni.usc.edu). CN participants were not included because they had a low burden of NPS. Participants were non-depressed at study entry (15-item Geriatric Depression Scale [GDS] score of <6), and were excluded if they had a diagnosis of 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 had current use of certain psychotropic medications (antipsychotics and mood stabilizers). Participants who underwent FTP PET neuroimaging within a year of completing the Neuropsychiatric Inventory (NPI) were included in analyses. Diagnoses were determined by the principal investigator or co-investigators at each site utilizing cognitive and functional assessments. The study was approved by the local Institutional Review Board of each participating ADNI site; informed consent was obtained from participants and their study partners before any study procedures were completed.

2.2 | Clinical assessments

The NPI[21,22] is a study partner-based measure developed to assess the frequency and severity of 12 NPS domains: depression, apathy, anxiety, appetite, sleep, hallucinations, delusions, agitation, irritability, euphoria, disinhibition, and aberrant motor behavior. Each item is measured on a scale of 1 to 4 for the frequency of symptom occurrence, and 0 to 3 for severity of the symptom exhibited. The total score for each symptom domain is calculated from the product of the frequency and severity scores, ranging from 0 to 12, with a higher score corresponding to greater symptom severity. The NPI apathy item (NPI-A) asks the study partner: "Do they seem less interested in his or her usual activities and in the plans of others?" The NPI was completed annually. The total score for the NPI-A in the scale (severity × frequency, 0 to 12) was used for analyses.

Global cognition was included as a covariate in secondary analyses, measured by the Mini-Mental State Examination (MMSE),[23] with lower scores indicative of greater impairment.

2.3 | Tau and amyloid PET neuroimaging

Acquisition and processing of FTP and florbetapir (FBP) PET imaging was previously described in detail.[24,25] FBP scans were co-registered to corresponding MRI scans, and segmented and parcellated with FreeSurfer (version 5.3.0) to define the amyloid cortical gray matter, with the whole cerebellum as the reference region yielding an SUVR (UC Berkeley—AV45 Analysis Methods, ADNI). FTP scans were segmented and parcellated with FreeSurfer (version 5.3.0) and co-registered to corresponding MRI scans, in order to calculate the mean FTP uptake within each FreeSurfer-defined region with the cerebellar cortex as the reference region yielding an SUVR (UC Berkeley—AV1451 Analysis Methods, ADNI). Three bilateral subcortical and

cortical regions of interest (ROIs) were chosen, based on prior studies, as regions implicated in AD: the EC, supramarginal gyrus, and one region implicated in the neurobiology of reward and motivation, the rACC. We also considered investigating a fourth ROI, the precuneus, given the recent cross-sectional findings showing an association between FTP uptake in this region and apathy.[20] However, FTP uptake in this region and in the supramarginal gyrus were highly correlated ($r = 0.9$, $p = 0.001$). Thus, we elected to focus on the supramarginal gyrus as our representative parietal region in analyses based on previous work showing an association between FDG metabolism in this region and longitudinal apathy.[19] Weighted volumes were calculated for each region (described as follows) and used in analyses, according to the following formula and as previously described (UC Berkeley—AV45 Analysis Methods, ADNI): Weighted volume = [(LH SUVR * LH VOLUME) + (RH SUVR * RH VOLUME)]/(LH VOLUME + RH VOLUME). This can be described narratively as follows: (1) each SUVR was multiplied by the corresponding volume; (2) these two values were added together; and (3) the result was divided by the total volume.

2.4 | Statistical analysis

Analyses for this study were carried out using R (R Core Team, 2021), MATLAB,[26] and SAS (version 9.4). Linear mixed effects models with backward elimination ($p < 0.05$ for significance) were utilized in primary analyses to examine the association between longitudinal NPI-A scores (dependent variable) and baseline tau in a given brain region as well as its interaction with time (regional tau PET × time). Time was measured as months since baseline where baseline was considered to be the visit in which the NPI was first administered. Each tau ROI (EC, rACC, or supramarginal gyrus) was tested in its own independent model with covariates of age at baseline, sex, and years of education, their interactions with time, as well as a covariate accounting for time at tau acquisition (FTP PET scan), relative to each apathy assessment. All predictor terms were subject-level, time-constant variables, except for the time indicator itself and its interactions. In secondary analyses, the models mentioned above were repeated for NPI-A with the addition of global cognition (MMSE; collected at baseline) × time or cortical amyloid (FBP PET) × time as covariates. Finally, for the tau region with the most significant association with apathy over time, a separate model was carried out with an interaction of regional tau × cortical amyloid × time. Unstandardized partial regression coefficients (β) with 95% confidence intervals (CIs), *t*-values, and significance test results (*p*-values) were calculated.

3 | RESULTS

Participant demographics at baseline are shown in Table 1. The sample was comprised of 319 participants from the ADNI, with a diagnosis of either MCI (73.15% of the sample) or AD dementia (26.85%). The sample was on average just above 75 years of age, highly educated, and predominantly White. Participants had an average duration of observation of 4.79 visits, and were followed for an average of 48.3 months.

TABLE 1 Demographics at baseline of sample participants (73.0% with MCI, 27.0% with dementia).

	Average ± SD	Min–max
Age (years)	75.4 ± 8.26	55.74–94.03
Years of education	16.08 ± 2.66	8–20
Apathy (NPI-A)	0.61 ± 1.62	0.00–8.00
MMSE	27.34 ± 2.62	17.0–30.0
Entorhinal tau	1.28 ± 0.29	0.78–2.59
rACC tau	1.09 ± 0.19	0.70–2.93
Supramarginal gyrus tau	1.16 ± 0.3	0.81–2.89
Sex (% male)	57.37	
Race (% White)	93.59	

Abbreviations: MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI-A, Neuropsychiatric Inventory apathy item; rACC, rostral anterior cingulate cortex.

Detailed descriptions of the follow-up duration are provided in Tables S1 and S2.

3.1 | Primary analyses: Associations between regional tau (FTP PET) and longitudinal apathy

Results from primary analyses are shown in Tables 2–4 and Figures 1 and 2. In the model with supramarginal tau, FTP retention was significantly associated with greater apathy over time (supramarginal gyrus × time: $\beta = 0.0309$, 95% CI = 0.016, 0.044, $t = 4.03$, $p < 0.0001$), as shown in Table 2 and Figure 1. Education was negatively associated with apathy over the course of the study, such that those with higher education had lower apathy over the course of the study ($\beta = -0.069$, 95% CI = −0.127, −0.012, $t = -2.40$, $p = 0.0167$)).

In primary linear models examining the relationship between EC tau (FTP retention) and longitudinal apathy, EC tau was associated with greater apathy over time (EC × time: $\beta = 0.03$, 95% CI = 0.014, 0.039, $t = 4.24$, $p < 0.0001$) as shown in Table 3 and Figure 2. Again, we observed a main effect of education, where higher education was associated with lower apathy over the course of the study ($\beta = -0.067$, 95% CI = −0.122, −0.01, $t = -2.35$, $p = 0.0192$).

Finally, we examined the relationship between longitudinal apathy and tau (FTP retention) in the rACC. We observed a marginal main effect between rACC tau (FTP retention) and greater NPI apathy (rACC: $\beta = 0.7644$, 95% CI = 0.05785, 1.47, $t = 2.12$, $p = 0.034$), as shown in Table 4 (ie, rACC was related to the overall level of NPI apathy across the time span of the study as a whole). However, rACC tau did not predict the trajectory of apathy change over time (ie, the interaction rACC × time was nonsignificant).

3.2 | Secondary models adjusting for amyloid FBP PET and global cognition

To determine whether tau (FTP retention) in the three ROIs was associated with longitudinal apathy when accounting for cortical amyloid,

TABLE 2 Apathy scores over time as predicted by supramarginal gyrus tau. Model: NPI-A ~ Supramarginal tau + Supramarginal tau × time + time of tau PET relative to apathy assessment + (age + sex + education) × time.

Predictor	Partial β	95% CI	*t*-value	*p*
Time at PET	−0.0007	−0.012, −0.003	−3.32	0.0009
Education	−0.069	−0.127, −0.012	−2.40	0.0167
Supramarginal tau	0.202	−0.373, 0.776	0.69	0.491
Time	−0.069	−0.115, −0.022	−2.92	0.0038
Supramarginal tau × time	0.0309	0.016, 0.044	4.03	<0.0001

Note: Results from primary linear mixed effects model with backward elimination. Predictors surviving backward elimination ($p < 0.05$ for significance) are shown. (By convention, nonsignificant terms that are also included within higher order terms that are significant, are not backward eliminated, eg, the nonsignificant main effect for Supramarginal in the table above).
Abbreviations: NPI-A, Neuropsychiatric Inventory apathy item; PET, positron emission tomography.

TABLE 3 Apathy scores over time as predicted by EC tau. Model: NPI-A ~ EC tau + EC tau × time + time of tau PET relative to apathy assessment+ (age + sex + education) × time.

Predictor	Partial β	95% CI	*t*-value	*p*
Time at PET	−0.00741	−0.012,−0.00	−3.54	0.0004
Education	−0.06674	−0.122,−0.01	−2.35	0.0192
Entorhinal tau	0.3215	−0.25,0.89	1.09	0.2741
Time	−0.026	−0.043,−0.010	−3.19	0.0016
Entorhinal tau × time	0.03	0.014, 0.039	4.24	<0.0001

Note: Results from primary linear mixed effects model with backward elimination. Predictors surviving backward elimination ($p < 0.05$ for significance) are shown. (By convention, nonsignificant terms that are also included within higher order terms that are significant, are not backward eliminated, eg, the nonsignificant main effect for Entorhinal tau in the table above).
Abbreviations: EC, entorhinal cortex; NPI-A, Neuropsychiatric Inventory apathy item; PET, positron emission tomography.

TABLE 4 Apathy scores over time as predicted by rACC tau. Model: NPI-A ~ rostral ACC tau + rostral ACC tau × time +time of tau PET relative to apathy assessment+ (age + sex + education) × time.

Predictor	Partial β	95% CI	*t*-value	*p*
rostral ACC tau	0.7644	0.058, 1.47	2.12	0.034
Time at PET	−0.007	−0.012, −0.003	−3.47	0.0006
Education	−0.080	−0.138, −0.023	−2.75	0.0062
Time	0.007	0.0032, 0.012	3.45	0.0007

Note: Results from primary linear mixed effects model with backward elimination. Predictors surviving backward elimination ($p < 0.05$ for significance) are shown.
Abbreviations: ACC, anterior cingulate cortex; NPI-A, Neuropsychiatric Inventory apathy item;PET, positron emission tomography.

we carried out a series of secondary models adjusting for amyloid FBP PET (cortical aggregate).

In a secondary model with supramarginal gyrus tau (FTP PET) and cortical amyloid (FBP PET), both supramarginal gyrus tau and cortical amyloid were significantly associated with increased longitudinal apathy over time (supramarginal tau × time: $\beta = 0.0196$, 95% CI = 0.004,0.0358, $t = 2.40$, $p = 0.017$; amyloid × time of apathy: $\beta = 0.026$, 95% CI = 0.0098, 0.042, $t = 3.15$, $p = 0.0017$; Table S3). In a model with EC tau and cortical amyloid, both predictors of interest were significantly associated with increased longitudinal apathy over time (EC tau × time: $\beta = 0.015$, 95% CI = 0.0004, 0.029, $t = 2.02$, $p = 0.0434$; amyloid × time of apathy: $\beta = 0.0267$, 95% CI = 0.00994, 0.044, $t = 3.12$, $p = 0.0019$, Table S4). In contrast, in a model with rACC tau and cortical amyloid, only cortical amyloid was associated with longitudinal apathy (ie, rACC tau × time was nonsignificant, and for the main effect of rACC: $\beta = 0.6314$, 95% CI = −0.135, 1.397, $t = 1.62$, $p = 0.106$; amyloid × time of apathy: $\beta = 0.03412$, 95% CI = 0.01884, 0.0494, $t = 4.38$, $p < 0.0001$; Table S5).

To explore potential synergy between regional tau and cortical amyloid in predicting longitudinal apathy, we carried out an analysis introducing a cortical amyloid × tau PET × time interaction term as a predictor of interest in a model with dependent variable longitudinal apathy. We focused on tau in the supramarginal gyrus—the tau PET ROI with the most robust observed association with longitudinal apathy. We found a significant effect for the two-way interaction amyloid × tau ($\beta = 3.3615$, 95% CI = 1.421, 5.30, $t = 3.40$, $p = 0.0007$; Table S6),

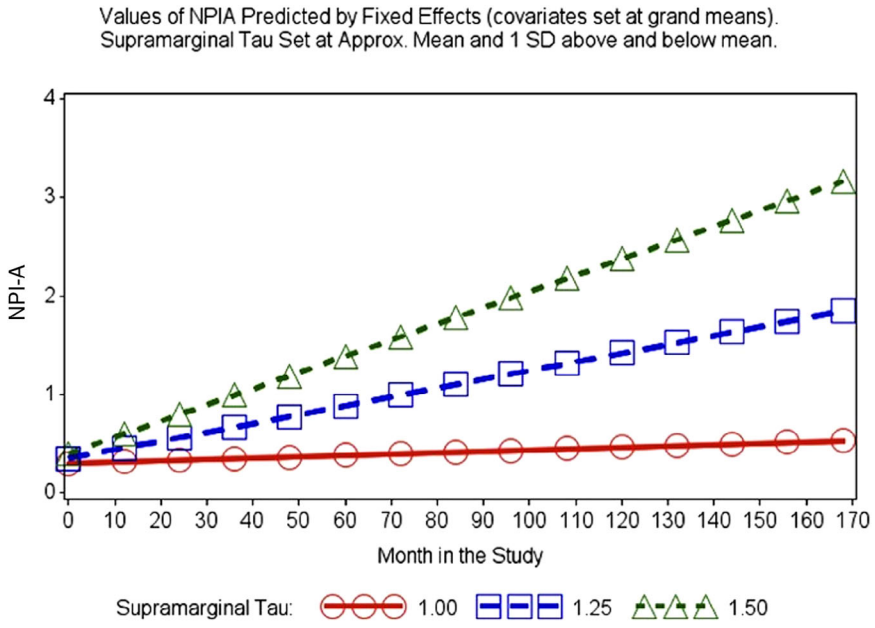

FIGURE 1 Estimated NPI-A scores over time as predicted by supramarginal gyrus tau (FTP PET), showing values of NPI-A predicted by fixed effects (covariates set at grand means). Values of supramarginal tau (FTP PET) are shown at approximate sample mean (blue squares), and at one standard deviation above (green triangles) and below (red circles) the sample mean. NPI-A, Neuropsychiatric Inventory apathy item; FTP, flortaucipir; PET, positron emission tomography.

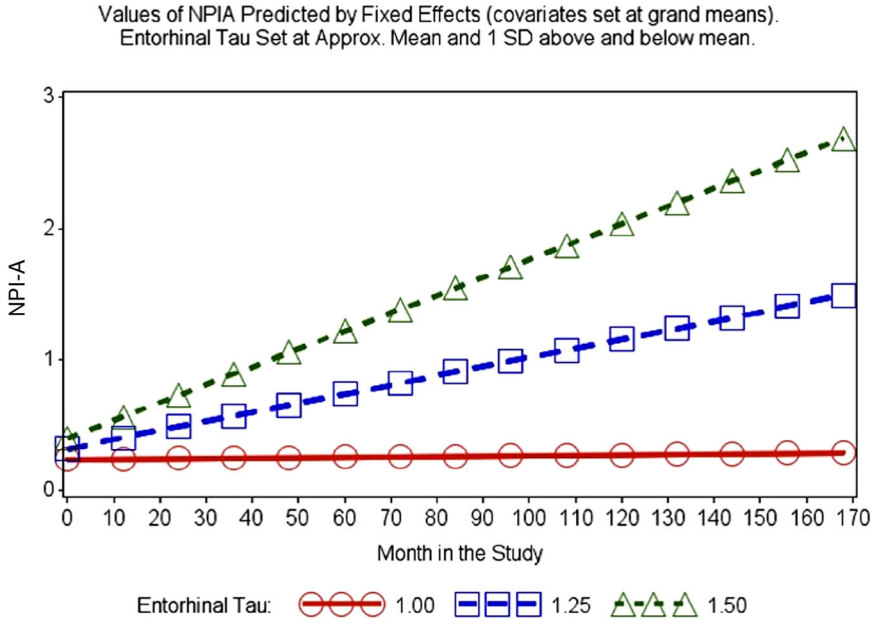

FIGURE 2 Estimated NPI-A scores over time as predicted by entorhinal tau (FTP PET), showing values of NPI-A predicted by fixed effects (covariates set at grand means). Values of entorhinal tau (FTP PET) are shown at approximate sample mean (blue squares), and at one standard deviation above (green triangles) and below (red circles) the sample mean. NPI-A, Neuropsychiatric Inventory (NPI) apathy item; FTP, flortaucipir; PET, positron emission tomography.

but the three-way interaction with time (amyloid × tau × time) was not significant. This result supports a possible positive additive synergy between regional tau and cortical amyloid and their association with greater apathy across the study as a whole.

Additional sensitivity models were run adjusting for global cognition (MMSE) at baseline. We found that supramarginal tau (FTP PET) was positively associated with the trajectory of increase of longitudinal apathy (supramarginal gyrus × time: $\beta = 0.015$, 95% CI = 0.0006, 0.029, $t = 2.04$, $p = 0.041$), whereas MMSE was a negative predictor of apathy trajectory—those with lower MMSE scores had more accelerated apathy over time (MMSE × time: $\beta = -0.0009$, 95% CI = −0.0017, −0.0002, $t = -2.60$, $p = 0.009$), as shown in Table S7. We observed a similar pattern of results for EC tau (EC tau × time: $\beta = 0.0146$, 95% CI = 0.0019, 0.0273, $t = 2.26$, $p = 0.024$; MMSE × time of apathy: $\beta = -0.0009$, 95% CI = −0.0016, −0.0001 $t = -2.25$, $p = 0.025$; Table S8). In contrast, in a secondary analysis with rACC tau (FTP PET), MMSE was a negative predictor of rate of longitudinal change in apathy ($\beta = -0.00115$, 95% CI = −0.00187, −0.0004 $t = -3.11$, $p = 0.0019$), whereas there was no association between rACC tau (FTP PET) and apathy over time, or across the study as a whole ($\beta = 0.4054$, 95% CI = −0.2778, 1.0887, $t = 1.17$, $p = 0.244$; Table S9).

4 | DISCUSSION

Apathy is one of the most common and distressing NPS in AD. Despite its prevalence and clinical significance, the neural correlates of apathy in MCI and AD dementia remain poorly understood. In the current

study, we focused on one of these potential neural correlates—regional tau pathology—and its relationship to the trajectory of apathy over time in older adults on the MCI-dementia continuum from the ADNI study. We examined associations between longitudinal apathy and tau pathology in three representative brain regions in the temporal, parietal, and medial frontal cortices affected in AD (supramarginal gyrus and EC), and implicated in the neurobiology of motivation and reward across clinical syndromes—the rACC. We found that tau in regions implicated in AD were significantly associated with increasing apathy over time. These associations persisted when taking into account global cognition (measured through MMSE scores). Moreover, in additional, secondary analyses, we found that cortical amyloid was a robust predictor of apathy trajectory, and we found evidence of synergy between regional tau and amyloid in overall higher levels of apathy.

Our results support a role for tau in the temporal and parietal regions in the pathophysiology of apathy over time across the AD continuum. Of note, in our analyses, we selected the supramarginal gyrus and entorhinal cortex as representative proxies of the parietal and temporal regions, respectively. We and others obtained similar results when examining FDG metabolism in an earlier cohort of ADNI.[19] Frontal regions (such as the rACC) that regulate motivation and reward are commonly affected in individuals with apathy,[27] as is noted more consistently in later stages of AD.[28] Our findings and related studies suggest that involvement of these regions may occur through mechanisms other than solely the deposition of regional tau pathology or neurodegeneration in earlier stages; that is, tau deposition in the rACC is not a significant predictor of increasing apathy over time in early AD. For example, a study examining another possible neurobiological correlate of apathy, namely cortical thickness, reported a lack of association between lower anterior cingulate cortical thickness and increased apathy in older adults at earlier stages of AD.[18] The authors suggest this may be due to a compensatory inflammatory response in the ACC in earlier stages of disease progression,[18] and that different mechanisms may underlie apathy at early versus late stages of AD. A majority of our sample consisted of older adults with a diagnosis of MCI (73.15%) compared to AD dementia (26.85%), and this skewing towards early disease stages may have thus influenced our findings.

It is also important to note that while the association between tau deposition in the rACC and apathy trajectory was not significant in our study, the role of the rACC in AD-associated apathy may also occur through other mechanisms. For example, another study conducted on MCI and AD participants of the ADNI found that participants with apathy had significantly reduced functional connections in the dorsal ACC.[29] It will be critical in future work to continue to probe mechanisms such as structural and functional connectivity and cerebrovascular injury in relation to apathy during different stages of AD.

Previously reported cross-sectional findings from the ADNI demonstrate a significant relationship between greater tau burden in the entorhinal and precuneus regions and NPS (as measured by NPI total scores); this association was driven by affective symptoms, in particular apathy, in individuals with MCI and AD dementia.[20] Examining longitudinal relationships from this study, we now show that tau burden in temporal and parietal brain regions affected in AD is associated with greater apathy over time in participants with MCI and AD dementia. Furthermore, we also report a significant association between cortical amyloid and increased apathy over time in these regions. This emphasizes the robust relationship between this particular NPS and biomarkers associated with the development of MCI and AD and supports apathy as a core symptom in AD clinical progression. Overall, our findings show an association between both amyloid and tau—in regions of early AD pathology (the temporal and parietal cortices)—and highlight the significance of apathy as an early manifestation of AD. The significance of the longitudinal associations between apathy and AD pathology in participants with MCI and dementia, as seen in this large sample, underscores the importance of examining NPS in these populations.

Strengths of the study lending to the salience of these findings include the ADNI's large sample size, well-characterized participants, and rigorous quality control of data collection in a multisite study. Notwithstanding, this study does have certain limitations. Despite the large sample size, ADNI-3 participants are recruited based on select criteria. Additionally, this sample consists of participants who are highly educated and mostly White, and therefore not representative of or generalizable to larger more diverse populations. Given the observed associations, future studies should explore these symptoms in more diverse populations to increase generalizability of findings across different communities. Future studies should also examine apathy symptom development over longer follow-up durations, as just under 50% of participants had 2 or fewer study visits (Table S2). Furthermore, study participants had relatively low apathy scores at baseline; this raises the question of how best to model fluctuations in apathy over time. These lower scores could be due to several reasons; for example, participants with lower NPS in general may be more readily able to participate in longitudinal, observational multimodal studies. Alternatively, as apathy in particular is being investigated in this study, it could be a question of motivation, such that participants with higher levels of apathy at baseline were less likely to voluntarily enroll in such an observational study. It is important to note, however, that several studies have reported significant findings based on similar NPS ranges at baseline. NPS scores have previously been found to be associated with increased risk of incident dementia despite low symptom severity at baseline[30] and also with more rapid decline in performance on neuropsychological measures.[31]

In conclusion, the results of this study demonstrate the association between tau burden in regions implicated in AD and apathy over time. Moreover, secondary models show that these results persist when taking into account global cognition and cortical amyloid as predictors of higher apathy in this sample. These models demonstrate the importance of apathy as a target for symptom management in developing interventions for patients affected by AD, and their care partners. To build upon these findings, in future studies it will be important to consider additional sensitive measures to detect NPS and capture fluctuations. Moreover, studies should examine individuals with a more

severe range of apathy symptoms or emergent apathy in order to more closely examine this association with AD pathology. Furthermore, taking a more exploratory approach to see if this observed effect applies across all regions associated with AD versus apathy could help inform behavioral modification and treatment options. Finally, exploring the trajectory of these relationships using longitudinal PET imaging and in relation to other neurobiological mechanisms—including structural and functional integrity of neural networks and cerebrovascular disease—captured through neuroimaging and plasma biomarkers, will help researchers better understand the utility and approaches for focusing on apathy as a potential treatment target in AD.

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CONFLICT OF INTEREST STATEMENT

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Author disclosures are available in the supporting information.

CONSENT STATEMENT

Consent was not necessary for data analysis reported in this manuscript, as all data provided by ADNI are deidentified and open source.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: COLLABORATORS

Data used in preparation of this article was 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.