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RESEARCH ARTICLE

APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia

Alexandra J. Weigand[1] | **Kelsey R. Thomas**[2,3] | **Katherine J. Bangen**[2,3] | **Graham M.L. Eglit**[2] | **Lisa Delano-Wood**[2,3] | **Paul E. Gilbert**[4] | **Adam M. Brickman**[5] | **Mark W. Bondi**[2,3] | **for the Alzheimer's Disease Neuroimaging Initiative**[1]

[1] San Diego State University/University of California, San Diego Joint Doctoral Program, San Diego

[2] Veterans Affairs San Diego Healthcare System, San Diego, California, USA

[3] Department of Psychiatry, University of California, San Diego, California, USA

[4] Department of Psychology, San Diego State University, California, USA

[5] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA

Correspondence
Mark W. Bondi, VA San Diego Healthcare System (116B), 3350 La Jolla Village Drive, San Diego, CA 92161, USA.
Email: mbondi@ucsd.edu

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Abstract

Introduction: Apolipoprotein E (APOE) interacts with Alzheimer's disease pathology to promote disease progression. We investigated the moderating effect of APOE on independent associations of amyloid and tau positron emission tomography (PET) with cognition.

Methods: For 297 nondemented older adults from the Alzheimer's Disease Neuroimaging Initiative, regression equations modeled associations between cognition and (1) cortical amyloid beta (Aβ) PET levels adjusting for tau and (2) medial temporal lobe (MTL) tau PET levels adjusting for Aβ, including interactions with APOE ε4-carrier status.

Results: Adjusting for tau PET, Aβ was not associated with cognition and did not interact with APOE. In contrast, adjusting for Aβ PET, MTL tau was associated with all cognitive domains. Further, there was a stronger moderating effect of APOE on MTL tau and memory associations in ε4-carriers, even among Aβ-negative individuals.

Discussion: Findings suggest that APOE may interact with tau independently of Aβ and that elevated MTL tau confers negative cognitive consequences in Aβ-negative ε4 carriers.

KEYWORDS
amyloid, apolipoprotein E, cognition, memory, positron emission tomography, tau

1 | INTRODUCTION

The apolipoprotein E (APOE) ε4 allele has been consistently identified as the strongest genetic susceptibility marker for increased risk and accelerated onset of sporadic Alzheimer's disease (AD).[1,2] Most research on mechanisms underlying APOE ε4 allelic effects has focused on the role of pathologic amyloid beta 1-42 (Aβ), demonstrating that APOE isoforms are involved in the oligomerization, aggregation, degradation, and clearance of Aβ,[3,4] and that ε4-carriers have increased incidence of Aβ positron emission tomography (PET) positivity as well as accelerated Aβ PET accumulation.[5,6]

Recent findings, however, point to the influence of APOE on pathologic tau accumulation and consequent neurodegeneration, even in the context of normal Aβ. Specifically, Shi et al. demonstrated that, in a transgenic mouse model of tauopathy, mice with a knock-in APOE ε4 genotype had accelerated phosphorylation of tau and associated neurodegeneration despite the absence of pathologic Aβ.[7] A subsequent study by this group revealed that this APOE-tau association was primarily mediated by increased microglial activation.[8] Further, a recent PET study found that ε4-carriers had increased tau PET uptake in the entorhinal cortex and hippocampus independently of Aβ and other demographic factors.[9] These findings suggest an Aβ-independent

pathway by which APOE genotype acts upon tau pathology to promote neuronal and cognitive dysfunction. Although inflammatory mechanisms appear to have a primary role in this APOE–tau association, possibly by increasing cytokine-induced phosphorylation of healthy tau monomers,[10] other mechanisms including cerebrovascular alterations and gliotransmitter dysfunction may also be at play.[11,12]

Although animal studies implicate APOE ε4 genotype in the pathologic role of tau independently of Aβ,[7,13] there is a paucity of analogous research investigating APOE-related effects on human biomarkers of tau independently of one's Aβ level. Specifically, studies investigating APOE, tau PET, and their interactive effects on cognition in Aβ negative (A–) individuals are notably lacking. Given this gap in the literature, we independently assessed associations between cognitive performance and (1) cortical Aβ PET controlling for medial temporal lobe (MTL) tau PET, and (2) MTL tau PET controlling for cortical Aβ PET, including interactions with APOE ε4 status. For any observed interaction between PET and ε4 status, we also ran stratified follow-up analyses assessing these interactions separately among individuals with negativity and positivity for the other pathology (eg, tau by APOE interaction on cognition separately in Aβ positive [A+] and A– individuals). Both linear and quadratic effects of Aβ and tau were examined a priori given the possible threshold effect of these pathologies, as demonstrated by previous non-linear associations of Aβ, tau, and APOE biomarkers with brain metabolism[14] and cognition,[15,16] as well as the non-linear dynamic trajectories of these pathologic and cognitive markers.[17] We hypothesized that presence of an APOE ε4 allele would have a deleterious moderating effect on the association between tau and cognition independent of Aβ PET level and regardless of Aβ positivity status.

HIGHLIGHTS

- Tau positron emission tomography (PET) is associated with multiple domains of cognition independently of amyloid.
- Amyloid PET is not associated with any cognitive domains independently of tau.
- Apolipoprotein E (APOE) ε4 strengthens tau PET associations with memory independently of amyloid.
- APOE ε4 genotype and tau interactions persist among amyloid negative individuals.

RESEARCH IN CONTEXT

1. **Systematic review**: A literature review was conducted using traditional sources (eg, PubMed). Although existing research has not focused on the relationship between tau and apolipoprotein E (APOE) genotype independently of amyloid, there are a number of studies examining this independent relationship in animal models, as well as tau positron emission tomography (PET) more generally in the context of Alzheimer's disease (AD), which have been cited.
2. **Interpretation**: Our results indicated that tau PET was most strongly associated with memory in APOE ε4-carriers independently of amyloid beta (Aβ) PET level, and these effects persisted even among Aβ-negative individuals. These findings suggest that tau pathology may have a primary deleterious role on cognition within the AD prodrome.
3. **Future directions**: Our findings warrant future studies that (1) replicate the current analyses in a more demographically diverse sample; (2) examine alternative genetic risk factors, including AD polygenic risk, on PET-cognition associations; and (3) identify other polypathologic (eg, TDP-43) interactions with APOE.

2 | METHODS

2.1 | Participants

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. This research was approved by the Institutional Review Boards of all participating sites, and written informed consent was obtained for all study participants. Two-hundred ninety-seven articipants without dementia (n = 209 cognitively normal [CN]; n = 88 with MCI) from ADNI were selected based on the availability of tau and Aβ PET data acquired within 12 months of each other, as well as APOE genotype data.

3 | PET processing

Processing methods for ADNI Aβ PET (^{18}F-AV-45, florbetapir) and tau PET (^{18}F-AV-1451, flortaucipir) have been previously described elsewhere.[18,19] Based on extant processing recommendations, regional standardized uptake values (SUVs) were intensity normalized using the whole cerebellum[18,20] (Aβ PET) or inferior cerebellar gray[19,21] (tau PET) to create SUV ratios (SUVRs). Tau PET data were partial volume corrected using the geometric transfer method.[22] For Aβ PET, a cortical summary measure was created by averaging across FreeSurfer-derived frontal, cingulate, lateral parietal, and lateral temporal regions of interest to capture early vulnerable regions for Aβ deposition.[18] For tau PET, a Braak stage I/II composite region was created by averaging across FreeSurfer-derived hippocampal and entorhinal regions of interest to recapitulate tau progression in early Braak stages.[19,21]

Although previous work has determined positivity thresholds via differing methods,[23-25] positivity thresholds in this study were derived using conditional inference decision tree regression with the ctree() function from the party package in R (https://cran.r-project.org/) in order to: (1) remain consistent with prior derivations of tau PET thresholds in ADNI;[21,26] (2) maintain comparable methods in the derivation of optimal thresholds for both Aβ and tau; and (3) independently derive thresholds for Aβ and tau, rather than determining thresholds for one based on discrimination of the other biomarker.[23-25] Thresholding methods have been described in detail elsewhere.[27] Briefly, thresholds were determined using binary classification of individual SUVRs based on global cognitive function. A larger sample of individuals (n = 523) spanning all diagnostic categories (ie, CN, MCI, dementia) with tau PET data and a subset with Aβ PET data (n = 350) were included for threshold derivation. A threshold of SUVR > 1.14 was determined for cortical Aβ positivity (A+/A−), which is generally consistent with other commonly used Aβ thresholds (>1.11).[18,28] For tau PET, thresholds were first determined for higher Braak composite stages (ie, >1.96 for stage V/VI and >1.51 for stage III/IV), with individuals surpassing the positivity threshold for higher stages iteratively removed during derivation of lower-stage thresholds, as described elsewhere.[26,27] Ultimately, a threshold of SUVR > 1.18 was determined for tau Braak I/II (ie, MTL) positivity (T+/T−), largely consistent with a previously derived threshold using similar methods (>1.13).[21]

4 | Cognitive testing

Participants underwent neuropsychological testing that included measures from the following domains: attention/executive function (Trail-Making Test Parts A and B); language (confrontation naming [ie, Boston Naming Test or Multilingual Naming Test] and animal fluency); and memory (Wechsler Memory Scale–Revised Logical Memory Story A Immediate and Delayed Recall). All raw scores were converted to z-scores based on predicted values from regression equations adjusting for age, sex, and education derived within a robust normal control group (ie, CN throughout their duration in ADNI) based on the entire ADNI sample. Z-scores were then averaged within domains to create attention/executive, language, and memory composites. Trail-Making Test Parts A and B were reverse coded such that higher scores indicate better performance.

MCI was diagnosed using actuarial neuropsychological criteria.[29,30] Participants were diagnosed with MCI if they (1) had two impaired scores in one cognitive domain or (2) had one impaired score across all three cognitive domains. We combined CN participants and participants with MCI given that we were interested in the association between biological and cognitive changes along the prodromal AD continuum, to increase the range of observed cognitive scores, and to retain statistical power for models assessing interactive and polynomial effects. However, we have included sensitivity analyses split by cognitive diagnosis in Tables S6–S10 in supporting information.

5 | APOE genotyping

All participants had APOE ε4 genotyping data available. ε4-carriers and non-carriers were determined based on presence of at least one ε4 allele. Of the 297 participants overall, 99 (33%) were categorized as ε4-carriers (heterozygotes n = 82; homozygotes n = 17) and 198 (67%) as non-carriers. Notably, one participant had an ε2/ε4 genotype. This individual was classified as an ε4-carrier given recent evidence that individuals with this genotype have a three-fold increased risk for AD and higher amyloid load relative to ε3/ε3 individuals.[31]

6 | Statistical analyses

Cognitive domain z-scores were shifted to a positive scale and Box-Cox transformed to improve normality. Tau PET SUVRs were also Box-Cox transformed to improve normality. Figures depict untransformed values to facilitate interpretation. Chi-squared tests and *t* tests assessed for differences in demographic variables, PET values, and cognitive composite scores between ε4-carriers and non-carriers and between CN and MCI groups. Regression equations predicted demographically adjusted and Box-Cox transformed cognitive z-scores as a function of cortical Aβ PET SUVRs while controlling for MTL tau PET SUVRs (model 1) and MTL tau PET SUVRs while controlling for cortical Aβ PET SUVRs (model 2). Both models included linear and quadratic SUVR-of-interest main effects controlling for APOE ε4 status and, in separate models, interactions with APOE ε4 status. For any statistically significant linear or quadratic interactions, follow-up analyses examined these interactions stratified by PET positivity (eg, tau PET and ε4 interactions separately for A− and A+ individuals). All analyses and figures were generated in R version 3.5.0 (https://cran.r-project.org/) using the following packages: QuantPsyc, dplyr, psych, sjPlot, olsrr, ggplot2.

7 | Role of the funding source

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8 | RESULTS

8.1 | Sample characteristics

Group differences in demographic, PET, and cognitive variables between ε4-carriers and non-carriers are presented in Table 1.

TABLE 1 Apolipoprotein E ε4-carrier and non-carrier group differences in demographic and PET variables

	ε4 carriers (n = 99)	Non-carriers (n = 198)	Test statistic	*P* value
Age (mean[SE])	74.28 (.72)	76.50 (.52)	t = 2.50	*P* = .01
Sex (% female)	53.5% female	46.5% female	$\chi^2 = 1.05$	*P* = .30
Education (mean[SE])	16.51 (.27)	16.83 (.17)	t = 1.05	*P* = .29
Aβ status (% A+)	50.5% A+	23.7% A+	$\chi 2 = 20.30$	*P* < .001
Tau status (% T+)	72.7% T+	71.7% T+	$\chi^2 = .002$	*P* = .96
Cortical amyloid SUVR (mean[SE])	1.21 (.02)	1.09 (.01)	t = 5.07	*P* < .001
MTL tau SUVR (mean[SE])	1.39 (.03)	1.32 (.02)	t = 2.13	*P* = .03
Attention/executive (mean[SE])	−.45 (.13)	−.25 (.08)	t = 1.37	*P* = .17
Language (mean[SE])	−.46 (.14)	−.38 (.09)	t = .49	*P* = .62
Memory (mean[SE])	−.65 (.14)	−.43 (.08)	t = 1.41	*P* = .16

Abbreviations: Aβ, amyloid beta; MTL, medial temporal lobe; PET, positron emission tomography; SE, standard error; SUVR, standard uptake value ratio.

TABLE 2 Diagnostic (cognitively normal versus mild cognitive impairment) group differences in demographic characteristics, cognition, and PET measures

	Cognitively normal (n = 209)	Mild cognitive impairment (n = 88)	Test statistic	*P* value
Age (mean[SE])	75.07 (.49)	77.04 (.80)	t = 22.14	*P* = .03
Sex (% female)	51.4% female	43.8% female	$\chi^2 = 1.16$	*P* = .28
Education (mean[SE])	16.92 (.17)	16.16 (.29)	t = 2.40	*P* = .02
APOE status (% e4+)	29.2% e4+	43.2% e4+	$\chi^2 = 4.85$	*P* = .03
Aβ status (% A+)	26.4% A+	48.3% A+	$\chi^2 = 12.65$	*P* < .001
Tau status (% T+)	68.3% T+	79.8% T+	$\chi^2 = 3.46$	*P* = .06
Cortical amyloid SUVR (mean[SE])	1.11 (.01)	1.18 (.02)	t = 2.57	*P* = .01
MTL tau SUVR (mean[SE])	1.28 (.01)	1.49 (.04)	t = 6.31	*P* < .001
Attention/executive (mean[SE])	.01 (.05)	−1.08 (.17)	t = 8.11	*P* < .001
Language (mean[SE])	−.10 (.08)	−1.11 (.14)	t = 6.29	*P* < .001
Memory (mean[SE])	−.05 (.06)	−1.56 (.13)	t = 11.44	*P* < .001

Abbreviations: Aβ, amyloid beta; APOE, apolipoprotein E; MTL, medial temporal lobe; PET, positron emission tomography; SE, standard error; SUVR, standard uptake value ratio.

Participants' sex distribution and years of education did not differ between carriers and non-carriers, but ε4-carriers were younger. APOE ε4-carriers had a higher average cortical Aβ SUVR and a higher proportion of A+ individuals relative to non-carriers. Further, ε4-carriers had a higher average MTL tau SUVR relative to non-carriers. APOE ε4-carriers and non-carriers did not differ on average scores in any cognitive domain. Group differences in these variables between CN and MCI participants can be found in Table 2. Notably, MCI participants were older, had lower education, higher proportions of A+ and ε4+ individuals, higher amyloid and tau SUVRs, and poorer cognitive scores across all domains. Across the entire sample, cortical amyloid and MTL tau PET were correlated at $r = .29$, $P < .001$. Figure 1 depicts distributions of amyloid (1A) and tau (1B) PET SUVRs split by tau and amyloid positivity, respectively.

8.2 | APOE by Aβ interaction on cognition

In models adjusting for MTL tau PET SUVR and ε4 status, there was no linear or quadratic main effect of Aβ on cognitive performance in any domain (all $ts < |1.44|$, $Ps > .15$; see Table S1A-C and Figure S1 in supporting information). Notably, when tau was removed from the model, Aβ was significantly linearly associated with attention/executive ($P = .003$) and memory domains ($P = .04$). Further, no moderating effect of

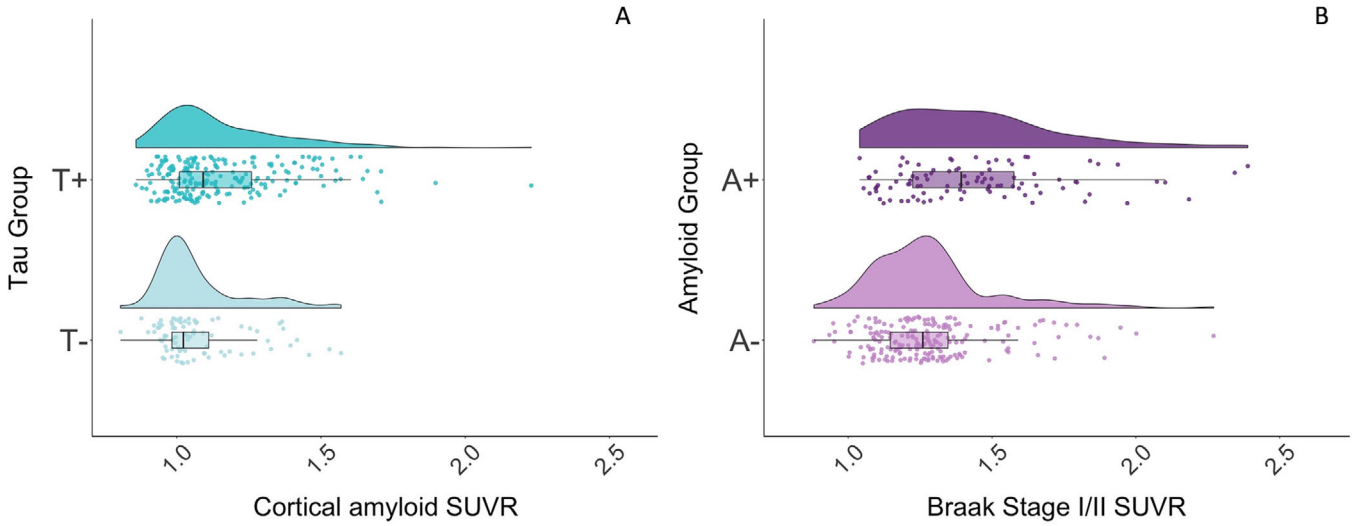

FIGURE 1 Amyloid and tau positron emission tomography (PET) distributions. Raincloud plots depicting standard uptake value ratio distributional properties for cortical amyloid PET split by tau positivity (A) and medial temporal lobe tau PET split by amyloid positivity (B)

ε4 status was observed for linear or quadratic associations between cortical Aβ and any cognitive domain (all *ts* < |1.23|, *Ps* > .21) while controlling for tau (see Table S3A-C in supporting information). All interactions remained non-significant when tau was removed from the model.

8.3 | APOE by tau interaction on cognition

In models adjusting for cortical Aβ PET SUVR and ε4 status, there was a linear main effect of tau for attention/executive performance ($\beta = -3.55$, $t = -3.47$, $P = .001$) such that higher tau was associated with poorer attention/executive function (see Table S2A and Figure S2 in supporting information). There was also a quadratic main effect of tau for language ($\beta = -3.33$, $t = -3.46$, $P = .001$) and memory ($\beta = -2.31$, $t = -2.45$, $P = .02$) such that higher tau was associated with worse performance and this negative association was disproportionately stronger at higher levels of tau (see Table S2B and S2C, respectively, and Figure S2). Further, a moderating effect of ε4 status was observed for the association between quadratic tau and memory ($\beta = -7.35$, $t = -3.54$, $P < .001$) such that ε4-carriers exhibited a disproportionately stronger negative association between tau and memory at higher levels of tau (see Figure 2 and Table S4C in supporting information). An examination of main effects revealed that there was a significant linear association between tau and memory for non-carriers ($P = .002$) and a highly significant quadratic association between tau and memory for ε4-carriers ($P < .001$). Notably, the moderating effect of ε4 status on quadratic MTL tau-memory associations was upheld even among individuals who had not yet reached Braak stage III/IV ($\beta = -6.34$, $t = 2.91$, $P = .004$). There were no moderating effects of ε4 status for the associations between tau and language or attention/executive function (all *ts* < |1.59|, *Ps* > .11; see Table S4A and S4B in supporting information).

Follow-up stratified analyses were conducted for the interaction between ε4 status and MTL tau on memory to examine the effects separately for A− and A+ individuals. Among A+ individuals, a moderating effect of ε4 status on linear tau and memory was observed ($\beta = -4.02$, $t = -2.19$, $P = .03$) such that higher levels of tau were more strongly associated with poor memory performance among ε4-carriers (see Figure 3A and Table S5 in supporting information). However, unlike in the full sample, no quadratic interaction was observed ($\beta = -1.43$, $t = -.79$, $P = .43$). In contrast, among A− individuals, a moderating effect of ε4 status on quadratic tau and memory was observed ($\beta = -5.70$, $t = -2.12$, $P = .04$) such that a negative association between tau and memory emerged only for higher levels of tau among ε4-carriers (see Figure 3B and Table S5).

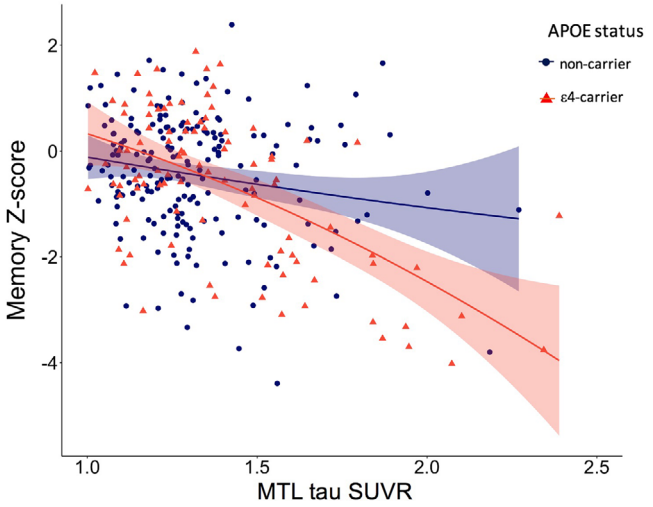

FIGURE 2 Apolipoprotein E ε4, tau positron emission tomography (PET), and memory. Quadratic moderating effect of ε4-carrier status on the association between medial temporal lobe tau and memory performance

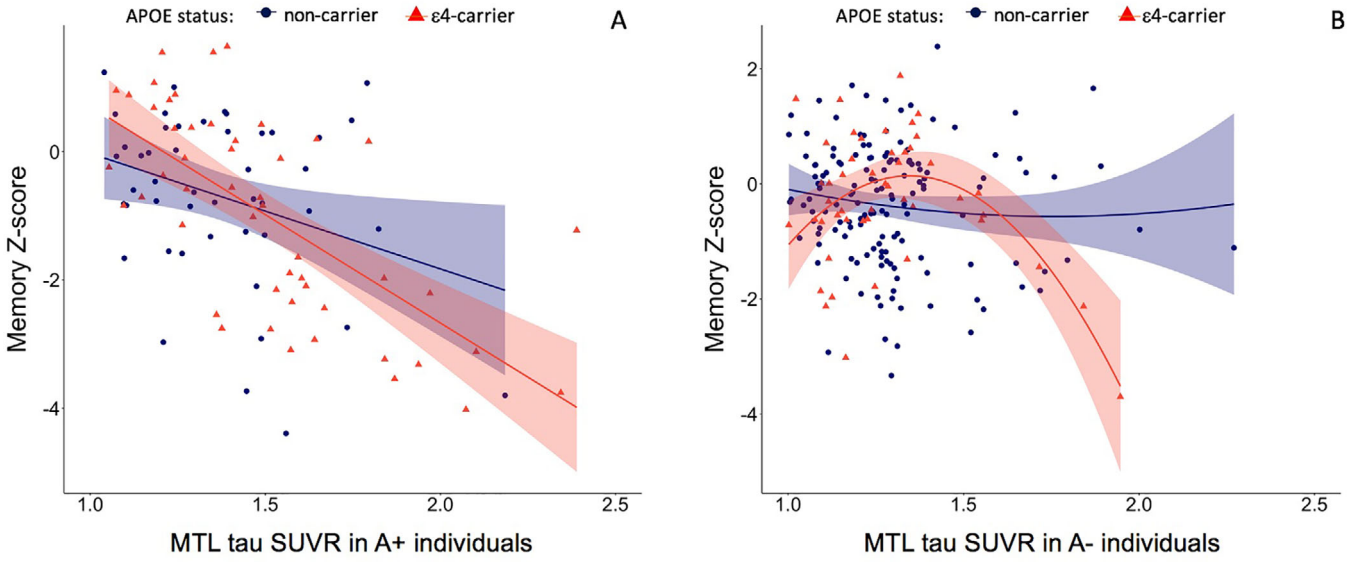

FIGURE 3 Apolipoprotein E (APOE) ε4, tau positron emission tomography (PET), and memory stratified by amyloid beta (Aβ) positivity. A, Linear moderating effect of ε4-carrier status on the association between medial temporal lobe tau and memory performance among Aβ-positive individuals. B, Quadratic moderating effect of ε4-carrier status on the association between medial temporal lobe tau and memory performance among Aβ-negative individuals

9 | DISCUSSION

Moderating effects of ε4 status on the association between AD PET biomarkers and cognition were observed only for tau–memory associations, such that higher levels of tau were more strongly associated with poorer memory among ε4 carriers, and this effect was disproportionately strong at higher levels of tau. Notably, this interaction was observed independently of Aβ as measured either on a continuous scale or via a threshold method. Further, independently of Aβ and ε4 status, tau was negatively associated with both language and attention/executive performance. In contrast, when adjusting for tau, no main effects of Aβ or moderating effects of ε4 status on cognition were observed. Although main effects of Aβ on attention/executive function and memory were observed when tau was removed from the model, the fact that these associations were absent when tau was included in the model indicates that tau accounts for a significant portion of the amyloid-cognition associations. Overall, these findings suggest that tau interacts with APOE ε4 independently of Aβ to exert negative influences on cognition, warranting a primary role for tau within the preclinical AD framework.[32,33]

There is accumulating evidence in support of a continuum hypothesis in which tau pathology accumulates in the brainstem and propagates to transentorhinal cortex independently of and—importantly—prior to Aβ.[34-37] Further, tau PET has consistently been linked to neurodegenerative processes and cognitive dysfunction, with effects strengthened in the presence of pathologic Aβ yet persisting even in its absence.[38-41] Accordingly, research on Aβ-independent mechanisms of pathologic tau formation, propagation, and neurodegenerative consequences are warranted, including the interaction between tau and APOE ε4 genotype. Such research may have important implications for updated nosology regarding the pathogenesis of AD and for novel treatment targets in AD-related clinical trials.

A recent study using a transgenic mouse model of tauopathy with APOE allelic differences assessed their combined effects on neurodegeneration.[7] Results indicated that, independent of Aβ, ε4 genotype exacerbated the association between tau pathology and neurodegeneration, and a follow-up study has demonstrated that this neurodegeneration occurs primarily through enhanced microglial activation.[8] Our findings of a moderating effect of APOE ε4 status on tau and memory associations independent of Aβ, which persists among A– individuals, provides converging translational evidence for Aβ-independent interactions of tau pathology and APOE.

The mechanisms by which APOE ε4 exerts its deleterious effects are incompletely understood, although both Aβ-dependent and -independent avenues have been explored. In addition to its role in the aggregation and clearance of Aβ, APOE has been implicated in neuroinflammatory processes, cerebrovascular alterations, and synaptic plasticity,[11] but its effects on tau pathology remain unclear. Evidence suggests that misfolding and aggregation of tau may be directly influenced by APOE-relevant processes.[13] Further, mouse models of tauopathy expressing different APOE genotypes demonstrated that ε4 knock-in mice had, in addition to higher tau levels, higher microglial reactivity and tumor necrosis factor alpha (TNF-α) secretion.[7,8,11] Thus, our findings may reflect APOE-moderated neuroinflammatory processes exacerbating tau-mediated neurodegeneration, resulting in the observed associations with cognition.

Given findings that APOE regulates clearance of Aβ,[42,43] one may speculate its involvement in the clearance of tau as well. Although

pathologic tau aggregates intraneuronally to form large fibrillar tangles, smaller soluble oligomers exist both intra- and extra-cellularly. These toxic oligomeric tau species spread through neighboring cells in a transsynaptic process to seed intraneuronal tangles,[44] and they may exacerbate inflammatory processes[45] as well as inhibit postsynaptic proteins, reduce gliotransmitter release, and impair memory independently of Aβ.[12,46] Reduced clearance of these tau oligomers in ε4-carriers may potentiate these negative effects, resulting in the observed strengthened associations between tau and memory among ε4-carriers.

Notably, the interaction between tau PET and ε4 status was only significant within the memory domain. Several studies have noted increased atrophy,[47,48] tau PET uptake,[9] and bioenergetic changes[49] specifically within the MTL in the presence of the ε4 allele. Importantly, we examined the effect of Braak stage I/II (ie, MTL) tau on cognition given the importance of this region early in the AD pathologic continuum. As the primary substrate of memory, MTL tau is most likely to have an effect on this domain, particularly within the CN and MCI individuals sampled in the current study.

When stratifying the tau–memory associations based on Aβ positivity, differential patterns of ε4 moderation were observed. Among A– individuals, ε4-carriers exhibited a quadratic effect such that a negative association between tau and memory emerged only at higher levels of tau. In contrast, among A+ individuals, a linear interaction was observed such that the negative association between all levels of tau and memory was stronger in ε4 carriers. Importantly, the moderating effect of ε4 status among A– individuals appears to primarily be driven by a small group of individuals with high levels of tau, and therefore this interaction should be interpreted with caution. However, it is noteworthy that these specific ε4+/A– individuals with high tau did not represent a subthreshold amyloid group, as their average amyloid level (.98) was well below the average for the entire ε4+/A– group (1.05) and certainly lower than the Aβ positivity threshold of 1.14.

It is conceivable that, in the context of high Aβ, tau is associated with poorer memory even at relatively lower tau levels because the combined effects of Aβ and ε4 status on neuroinflammatory processes lower the threshold such that less tau is needed to initiate neurodegeneration and cognitive dysfunction. Instead, when Aβ levels fall below the positivity threshold, a higher amount of tau in combination with ε4-associated processes may be needed to exert a negative effect on memory, explaining the observed quadratic effect among A– individuals. Given the quadratic nature of the interaction such that effects on memory were most prominent at higher levels of MTL tau, analyses were re-run among only individuals negative for Braak stage III/IV; the ε4 interaction on quadratic MTL tau-memory associations was retained, suggesting that the strengthened effect for high MTL tau is not driven by individuals who have reached Braak stage III/IV.

We conducted sensitivity analyses stratified by diagnostic group (eg, CN and MCI). Notably, no main effects of tau PET on cognition were retained within the control group, although quadratic effects at $P < .10$ were observed for language and memory. Further, linear effects of tau PET were significant within the MCI group for these domains. Amyloid PET was not significant for any cognitive domain for either CN or MCI groups, although there was a linear effect at $P < .10$ for memory among MCI participants. These stratified effects indicate that tau PET may impact cognition in different ways between CN and MCI groups. Individuals with MCI may exhibit a linear association between tau PET and cognition such that cognition is equally impacted at all levels of tau PET due to the more advanced clinical stage of this group, similar to effects observed in A+ individuals. In contrast, CN individuals follow a quadratic pattern in which tau PET is more strongly associated with cognition at higher levels of tau, as observed in A– individuals.

The primary strength of this study was the investigation of the moderating effects of APOE ε4 on both Aβ and tau PET independently of the other, resulting in the novel finding that the quadratic association between tau PET and memory was retained in ε4 carriers even among A– individuals. Further, assessing multiple cognitive domains broadened the scope of investigation beyond memory to demonstrate robust main effects of MTL tau on language and attention/executive function independent of Aβ level. However, generalizability is limited given that this study was conducted in a racially/ethnically homogeneous, clinic-based sample with few medical comorbidities. Replication of these findings in a more representative sample will better inform the range of pathologic and associated cognitive changes in AD. Further, the limited sampling of cognitive domains with the few existing tests within ADNI warrants replication of our findings in a dataset with a more robust and comprehensive neuropsychological battery. Additionally, extending analyses to other regions of tau deposition and other pathologies such as TDP-43 and cerebrovascular changes will provide more insight into the possible polypathologic nature of AD and the widespread influence of APOE genotypic variations on disease expression.

Our findings suggest that APOE may exert deleterious effects on cognition through specific interactions with tau pathology and that these effects may occur independently of and prior to the amyloidosis of AD. This relationship has important implications for models of AD pathogenesis by supporting an Aβ-independent role of APOE and tau during the preclinical period of AD and warranting a targeted approach toward early stage tau pathology in clinical trials for AD.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

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

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