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Tau Pathology in the Medial Temporal Lobe and Neocortex: Implications for Cognitive Unimpaired in Cognitively Unimpaired Older Adults

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Background: The accumulation of proteins such as amyloid-beta and tau, which disrupt normal cellular processes, characterizes Alzheimer's disease (AD). Cognitive decline is strongly linked to tau pathology, which initially manifests in the medial temporal lobe (MTL).

Aims: To investigated the association between cognitive performance and regional tau accumulation, as measured by positron emission tomography (PET) imaging, in cognitively normal older adults. Understanding this relationship is critical for early intervention before noticeable cognitive decline emerges.

Study Design: Retrospective study.

Methods: Tau PET scans were conducted on 440 participants enrolled in the anti-amyloid treatment in asymptomatic Alzheimer's (A4) study. The participants, aged 65-85, were cognitively unimpaired and had complete demographic and genetic profiles. Tau levels in the MTL and temporal neocortex (NEO) was quantified using composite metrics. Cognitive function was evaluated using the preclinical Alzheimer's cognitive composite (PACC) and its individual components. Multiple linear regression models were applied to determine the associations between tau burden and cognitive outcomes, including interaction terms to evaluate the moderating roles of sex and apolipoprotein E (APOE)-ε4 genotype.

Results: The average participant age was 71.8 years (standard deviation = 4.84), with females comprising 58% of the sample. Greater tau accumulation in both tau_{MTL} and tau_{NEO} regions was significantly associated with lower cognitive scores. Specifically, reduced PACC scores ($p < 0.001$) corresponded with higher tau levels in both regions, primarily influenced by declines in Delayed Logical Memory and Free and Cued Selective Reminding test scores. Additionally, tau_{NEO} levels were modestly linked to Mini-Mental State Examination scores. The effects of sex and APOE-ε4 status were minimal.

Conclusion: Elevated tau deposition in the MTL and NEO is associated with diminished cognitive function, particularly in memory and processing speed domains. Notably, tau accumulation in the MTL showed a strong association with poorer outcomes on memory-related cognitive measures. The limited influence of sex and APOE-ε4 genotype highlights tau pathology as a key contributor to early cognitive decline in preclinical AD.

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD) are frequently marked by the buildup of misfolded or aggregated proteins.[1] While these proteinopathies-conditions resulting from the accumulation of abnormally folded or aggregated proteins that impair normal cellular processes-were historically diagnosed through post-mortem brain analysis, detecting the presence of these proteins at an early age is essential for initiating treatments aimed at altering disease progression before significant neuronal damage occurs.[1] Studies investigating the brain's memory-related architecture have identified two primary cortical memory systems: the posterior-medial and the anterior-temporal networks. These systems are involved in distinct aspects of episodic memory and are closely linked to the hippocampus.[2,3] Neurofibrillary tangles develop early in medial temporal lobe (MTL) subregions associated with the anterior-temporal system, while early amyloid-beta (Aβ) accumulation is observed in areas of the posterior-medial system, including the posterior cingulate cortex and the precuneus.[4] Specifically, neurofibrillary tangles have been shown to initially form in the entorhinal cortex and transentorhinal region, a part of the MTL that approximately aligns with Brodmann area 35.[4] This progression is significant as it aligns with the cognitive deficits seen in AD. Greater tau accumulation in the MTL is linked to localized atrophy and reduced functional connectivity, which in turn impacts memory abilities even in individuals who have not yet shown cognitive symptoms.[4]

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Tau imaging represents a recent advancement among non-invasive techniques for assessing neurodegenerative proteinopathies. Although individuals with AD typically show elevated levels of both Aβ and tau[5-7], tau is found at significantly lower concentrations than Aβ within the same regions of deposition in AD.[1] While abnormal amyloid accumulation is considered an early step in the AD pathological cascade[8] tau pathology is believed to propagate through the MTL and subsequently extend into the temporal neocortex (NEO), following amyloid buildup, and is more directly linked to the emergence of clinical dementia symptoms.[9] Nevertheless, the exact order of these pathological processes, along with the mechanisms which amyloid and tau aggregates impair neuronal function and lead to clinical symptoms, remains uncertain. Current biomarker research aims to clarify the temporal progression of these pathologies and their influence on the course of AD.[9,10] Tau pathology demonstrates a strong association with cognitive function, particularly in relation to memory performance in AD.[11-13] Moreover, a relatively recent meta-analysis of a Pittsburgh compound B positron emission tomography (PET) study indicates that the overall effect of Aβ on cognition in cognitively normal individuals is relatively limited.[14] Although much attention has been directed toward Aβ, understanding tau's contribution to cognitive decline is equally essential.

This study aimed to examine the relationship between regional tau accumulation, as measured by PET imaging, and cognitive performance in older adults without cognitive impairment. Specifically, our objectives were to (I) determine whether tau burden in the MTL and NEO is associated with differences in cognitive function, including memory and executive abilities, in individuals without clinical dementia, and (II) gain a clearer understanding of how tau pathology may influence cognitive performance prior to the onset of clinically meaningful decline. Recognizing that tau_{MTL} is among the earliest indicators of AD pathology, we (III) concentrated on tau deposition in both the MTL and NEO and (IV) analyzed how tau burden in these areas is related to outcomes on various cognitive assessments, including the preclinical Alzheimer's cognitive composite (PACC), Free and Cued Selective Reminding test (FCSRT), Digit Symbol Substitution (DSS), Delayed Logical Memory (DLM), and the Mini-Mental State Examination (MMSE). These analyses were conducted using multiple models that accounted for potential confounding variables such as sex and apolipoprotein E (APOE)-ε4 status. Through these objectives, we aimed to enhance understanding of the influence of tau pathology on cognitive performance in cognitively normal older adults and its relevance for early detection of AD.

MATERIALS AND METHODS

Participants

The anti-amyloid treatment in asymptomatic Alzheimer's (A4) study is a double-blind, placebo-controlled clinical trial designed to evaluate whether the anti-amyloid monoclonal antibody solanezumab can slow memory decline in AD.[15] Conducted across 67 sites in the United States of America, Australia, Japan, and Canada, the study received approval from the Institutional Review Board at each location, and all participants provided written informed consent. Managed by the Alzheimer's Therapeutic Research Institute at the University of Southern California, the study data were available through the university's Laboratory for Neuro Imaging.[16]

Participants were confirmed to be cognitively unimpaired based on a global Clinical Dementia Rating score of 0, an MMSE score between 25 and 30, and a Logical Memory II delayed recall score ranging from 6 to 18 on the Wechsler Memory Scale-Revised.[17] The A4 trial enrolled individuals with elevated amyloid levels as detected through PET imaging. Those who met all inclusion criteria except for elevated amyloid were enrolled in the LEARN study, which investigates biological, clinical, and cognitive changes in this population. A total of 4,486 individuals underwent ^{18}F-florbetapir PET amyloid imaging[18,19], and a subset also received ^{18}F-flortaucipir tau PET imaging. Previous findings indicate that cognitively normal individuals with increased cerebrospinal fluid (CSF) tau and AD-like imaging characteristics are likely accumulating Aβ.[11] This analysis focuses on a subset of 440 participants who had tau PET standardized uptake value ratio (SUVR) data along with complete demographic and genetic information (Figure 1).

Magnetic resonance imaging (MRI)

Functional connectivity and volumetric MRI data were collected as part of the study. To further assess fibrillar amyloid accumulation, additional ^{18}F-florbetapir PET imaging was conducted at the conclusion of the trial. Internal processing scripts were employed to extract and analyze tau and amyloid PET data using FreeSurfer software.[20]

Amyloid PET imaging

Participants received ^{18}F-florbetapir PET scans approximately 50-70 minutes after the administration of 10 mCi of ^{18}F-florbetapir.[21] A central laboratory evaluated amyloid burden using a dual approach: quantitative measurement of the SUVR and qualitative visual interpretation.[22] An SUVR cutoff of 1.15, using the whole cerebellum as the reference region, served as the main criterion for determining amyloid positivity. This quantitative method, which is particularly sensitive to detecting early amyloid buildup, was prioritized over visual interpretation alone. In cases where SUVR values ranged between 1.10 and 1.15, participants were considered amyloid-positive only if there was a consensus-positive visual read.[22] This approach is particularly suited for identifying early amyloid accumulation during the preclinical phase of AD.[23]

Tau PET imaging

Tau PET status was evaluated using two composite metrics representing the MTL and the NEO. For the MTL, the tau PET value was calculated as the unweighted average of the bilateral entorhinal cortex and amygdala, while for the NEO, it was calculated as the weighted average of the bilateral middle and inferior temporal gyri. Since the entorhinal cortex, although smaller than the amygdala, plays a central role in the early stages of tau accumulation[24], an unweighted average was applied for the MTL region of interest (ROI). In alignment with the well-characterized progression of tau

pathology from the MTL to the lateral temporal cortex, the MTL and NEO ROIs were adapted from a previously established temporal meta-ROI.[25] Tau-PET positivity thresholds were defined separately for T_{MTL} (1.30 SUVR) and T_{NEO} (1.31 SUVR), using a validated method derived from the A4 trial cohort.[11] These thresholds were determined as the mean + 2 standard deviation (SD) of tau uptake in cognitively unimpaired, Aβ-negative participants.

The APOE genotype

The APOE genotype is the only genetic risk factor for both early- and late-onset AD that has been consistently validated across a wide range of studies.[26] In this our study, we examined APOE-ε4 status by categorizing participants based on the number of ε4 alleles they carried (0, 1, or 2) and included this variable categorically in our models to control for its potential impact on study outcomes.

Cognitive assessments

This study examined cognitive test scores in relation to regional and composite tau measures, with primary emphasis on the PACC.

PACC, which serves as the principal objective outcome measure in the first preclinical AD trial[21], includes the following four components:[16]

MMSE: A 30-item assessment of general cognitive function, with scores ranging from 0 to 30. A score of 23 or below is typically indicative of cognitive impairment.

DLM: A standardized measure of episodic narrative memory, scored from 0 to 25. Higher scores reflect stronger recall capabilities.

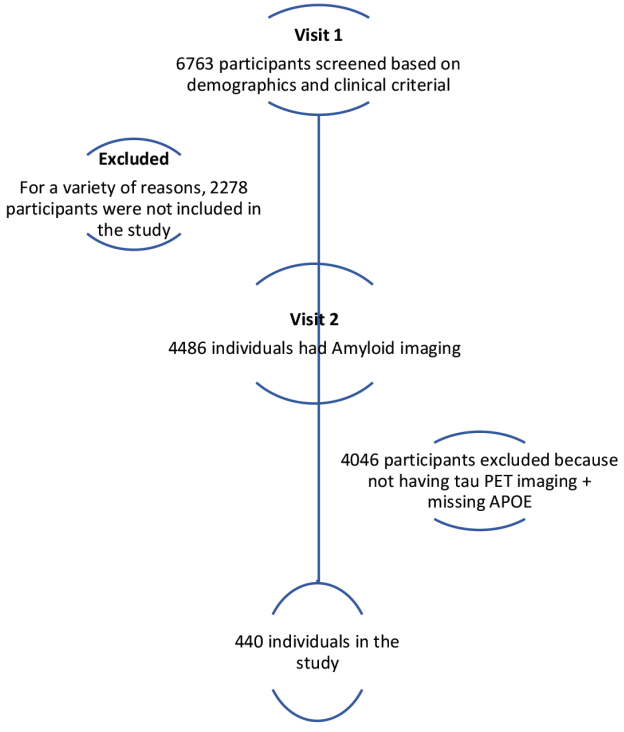

FIG. 1. Participants' flow chart for the study.
APOE, apolipoprotein E.; PET, positron emission tomography

DSS: A paper-and-pencil test presented on a single sheet, primarily evaluating memory retention, processing speed, and executive function. The maximum (max) score is 91, with higher scores indicating better cognitive function

FCSRT: A multimodal associative memory assessment that uses both visual and semantic category cues to facilitate learning. It provides two primary scores: (I) Free recall, which is the total number of items recalled without cues (max 48), and (II) Total recall, the combined number of freely and cued recalled items (max 48). The extended FCSRT96 score (ranging from 0 to 96) encompasses both free and cued recall, reflecting different aspects of associative memory function in preclinical AD. Higher scores on both metrics suggest stronger memory performance.

Statistical analysis

Independent t-tests were used to examine the relationships between age, sex, education, cognitive scores (such as PACC, FCRST96, etc.), and the groups defined by T_{MTL} (negative/positive) and T_{NEO} (negative/positive). Chi-squared tests were applied to assess amyloid status, APOE-ε4 carrier status, and sex distribution within each T_{MTL} and T_{NEO} group. Subsequently, T_{MTL} and T_{NEO} groups were categorized as negative or positive based on the established cutoff values, and similar analyses were conducted for these stratified tau groups. To test hypotheses regarding the effects of sex, APOE-ε4, and their interaction with tau_{MTL} and tau_{NEO} on cognitive performance, multiple linear regression models were employed.

RESULTS

Demographics

A total of 440 participants were included, with a mean age of 71.8 years (SD = 4.84); 58% were female, the average education level was 16.2 years (SD = 2.8), and 53.2% were APOE-ε4 positive. Tau groups were defined based on tau SUVR values for each region as T_{MTL} ± and T_{NEO} ±. When stratified by tau status, participants in the T_{MTL}+ group (72.78 ± 4.84 years) and the T_{NEO} + (72.81 ± 5.17 years) were significantly older than those in their respective negative groups (p = 0.005 and p = 0.048). There were no significant differences in sex distribution or education levels between groups. APOE-ε4 positivity was significantly more frequent in both T_{MTL}+ (69.4%) and T_{NEO}+ (71.6%) groups compared to their negative counterparts ($p < 0.001$ for both). Amyloid and tau levels were significantly elevated in the T_{MTL}+ group (amyloid, 1.38 ± 0.20; tau_{NEO}, 1.29 ± 0.13; tau_{MTL}, 1.39 ± 0.14) and the T_{NEO}+ group (amyloid, 1.41 ± 0.22; tau_{NEO}, 1.39 ± 0.13; tau_{MTL}, 1.40 ± 0.18) ($p < 0.001$ for all) (Table 1).

Cognitive performance was significantly lower in both T_{MTL} + and T_{NEO} + groups. Individuals in the T_{MTL}+ groups scored significantly worse on the PACC, DLM, and FCSRT96 tests ($p < 0.001$ for all). Similarly, those in the T_{NEO}+ group showed reduced cognitive scores, particularly in PACC and DLM ($p < 0.001$), as well as in FCSRT96 (p = 0.016) and DSS (p = 0.007). MMSE scores were also lower in both T_{MTL}+ and T_{NEO}+ groups compared to their negative counterparts (p = 0.031 and p = 0.006, respectively) (Table 1).

TABLE 1. Sample Characteristics for the Whole Sample and for Subgroups Stratified by T_{MTL} and T_{NEO} Status.

		Stratified by T_{MTL} status			Stratified by T_{NEO} status		
	Full dataset	Negative	Positive	*p*	Negative	Positive	*p*
	440	306	134		366	74	
Age (years)	71.80 (4.84)	71.37 (4.78)	72.78 (4.84)	**0.005**	71.59 (4.75)	72.81 (5.17)	**0.048**
Female	58.00%	57.20%	59.70%	0.623	57.01%	62.20%	0.421
Education (years)	16.20 (2.80)	16.12 (2.91)	16.43 (2.67)	0.307	16.18 (2.89)	16.41 (2.58)	0.530
APOE (+)	53.2%	46.1%	69.4%	**< 0.001**	49.5%	71.6%	**< 0.001**
Amyloid	1.28 (0.20)	1.23 (0.18)	1.38 (0.20)	**< 0.001**	1.25 (0.18)	1.41 (0.22)	**< 0.001**
tau_{NEO}	1.20 (0.12)	1.16 (0.08)	1.29 (0.13)	**< 0.001**	1.16 (0.06)	1.39 (0.13)	**< 0.001**
tau_{MTL}	1.21 (0.15)	1.13 (0.07)	1.39 (0.14)	**< 0.001**	1.17 (0.11)	1.40 (0.18)	**< 0.001**
PACC	-0.38 (2.78)	-0.02 (2.77)	-1.19 (2.66)	**< 0.001**	-0.13 (2.68)	-1.62 (2.97)	**< 0.001**
DLM	11.61 (3.39)	11.99 (3.41)	10.75 (3.19)	**< 0.001**	11.84 (3.39)	10.46 (3.15)	**0.001**
DSS	42.62 (9.44)	43.17 (9.24)	41.37 (9.79)	0.066	43.16 (9.41)	39.95 (9.17)	**0.007**
FCSRT96	75.78 (6.26)	76.40 (5.95)	74.38 (6.73)	**0.002**	76.10 (6.09)	74.19 (6.87)	**0.016**
MMSE	28.65 (1.30)	28.74 (1.28)	28.45 (1.33)	**0.031**	28.73 (1.27)	28.27 (1.40)	**0.006**

tau_{MTL}: tau standardized uptake value ratios in medial temporal lobe. From the threshold, tau SUVR split to positive and negative for medial temporal lobe (T_{MTL}) and neocortex (T_{NEO})
FCSRT, free and cued selective reminding test (range, 0-96); DSS, Digit Symbol Substitution (maximum score, 91); DLM, Delayed Logical Memory (range, 0-25); MMSE, Mini-Mental State Examination (range, 0-30), APOE, apolipoprotein E; PACC, preclinical Alzheimer's cognitive composite.

Tau PET SUVR association with cognitive performance

The associations between tau_{MTL} and cognitive performance, as well as tau_{NEO} and cognitive performance, were examined using four different statistical models for comparison. Tables 2-6 present the associations between tau_{MTL} and five cognitive measures across these models, with the later models incorporating interaction terms for sex and APOE-ε4 status.

Tau_{MTL} showed a significant association with lower cognitive performance on the PACC (β = -0.182, $p < 0.001$), FCSRT (β = -0.181, $p < 0.001$), and DLM (β = -0.191, $p < 0.001$). However, when interaction terms were added, the significance of tau_{MTL} diminished and its effect size was reduced (e.g., for PACC in model 2, β = -0.070, $p = 0.339$). Despite this, the interaction terms themselves remained significant (Tables 2-6).

Tau_{NEO} was also significantly associated with decreased cognitive performance on the PACC (β = -0.168, $p < 0.001$), FCSRT (β = -0.092, $p = 0.045$), and DLM (β = -0.127, $p = 0.008$). These associations were generally weaker and less consistent than those observed with tau_{MTL}. After adjusting for sex and APOE-ε4, the associations between tau_{NEO} and cognitive measures were further reduced, with only marginal significance remaining for PACC (β = -0.087, $p = 0.233$) and DLM (β = -0.126, $p = 0.108$) in some models. Similar to tau_{MTL}, tau_{NEO} was not significantly associated with MMSE or DSS scores (Supllement Tables 11, 15).

Association of tau_{MTL} with cognitive performance in the T_{MTL}+ groups

Further analysis of stratified tau groups, T_{NEO} and T_{MTL}, showed that none of the cognitive tests reached statistical significance in either T_{NEO} (±) groups or in the T_{MTL}- participants.

According to Table 7 and Supplement Tables 16-20, was significantly linked to poorer cognitive performance on the PACC, FCSRT96, and DLM tests, but not on the MMSE or DSS. For example, in model 1, was significantly associated with lower PACC scores (β = -0.266, $p = 0.003$) and lower FCSRT96 scores (β = -0.340, $p < 0.001$). Similarly, was significantly related to reduced DLM scores in model 1 (β = -0.269, $p = 0.004$).

The effects of sex and APOE-ε4 on these associations were minimal. Although interaction terms for sex and APOE-ε4 were included in the models, they generally did not significantly alter the relationship between and cognitive performance for most tests. For instance, with PACC, the interaction terms in models 2-4 did not significantly change the association between tau_{MTL} and PACC scores (p -values ranging from 0.312 to 0.837).

Sex differences in tau and cognitive performance

A comparative analysis was performed by plotting tau SUVR against cognitive test scores separately for male and female participants. The plot shows a strong association between tau levels and cognitive performance, with higher tau associated with lower scores across all five cognitive tests. Importantly, female participants consistently had lower scores in all cognitive domains compared to males. While both Figures 2, 3 displayed similar patterns, the sex difference was more pronounced for tau_{MTL}, suggesting that tau pathology in the MTL may have a greater impact on cognitive function in females. Further studies are needed to clarify the mechanisms and clinical significance of these findings. In addition, predicted interactions between tau levels and sex, stratified by APOE-ε4 status, were plotted across various cognitive outcomes. Notably, the slopes of predicted cognitive scores varied between males and females, especially among APOE-ε4 carriers, indicating a sex-specific influence of tau on cognition (Supplement Figure 1).

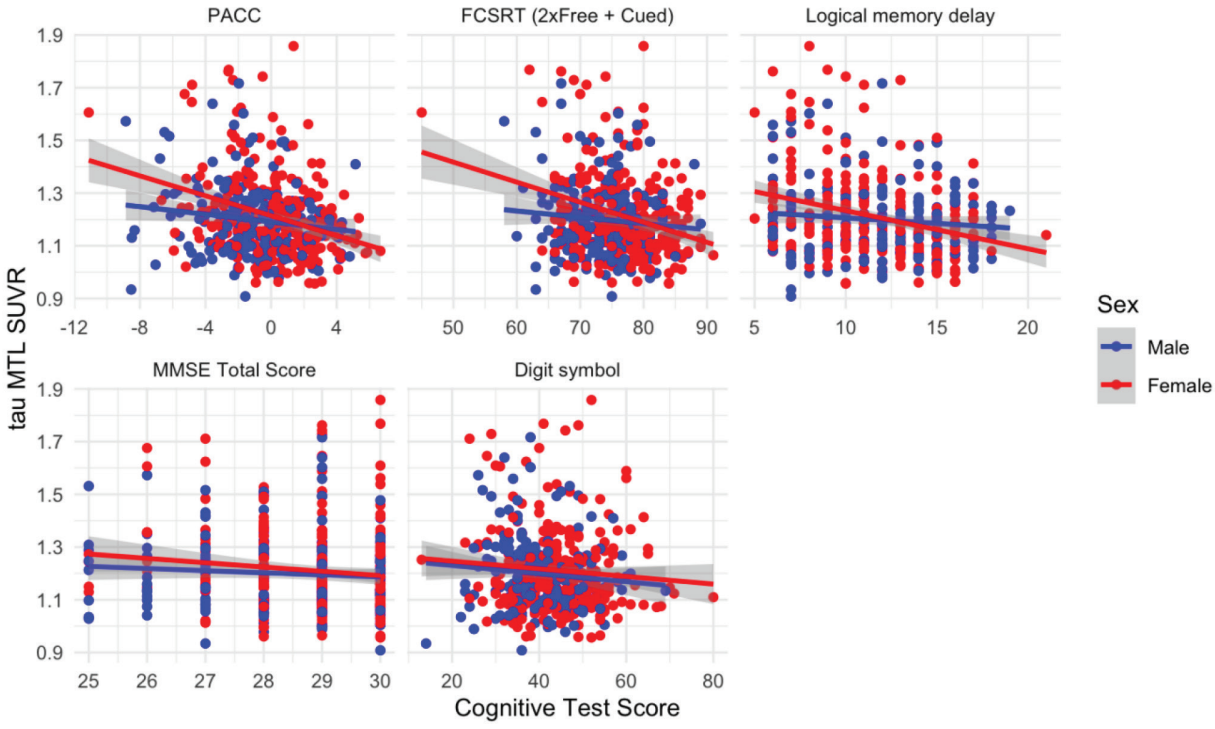

FIG. 2. TauMTL vs. cognitive test scores for sex differences.

MTL, medial temporal lobe; SUVR, standardized uptake value ratio; MMSE, Mini-Mental State Examination; FCSRT, free and cued selective reminding test; PACC, preclinical Alzheimer's cognitive composite

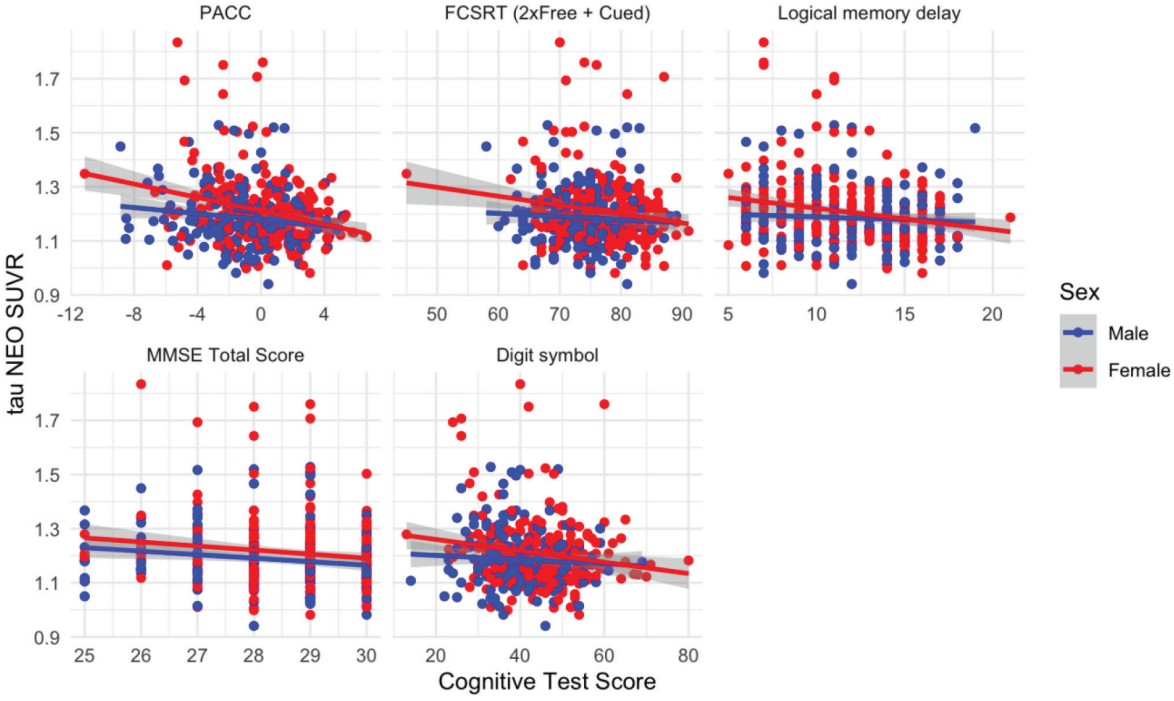

FIG. 3. TauNEO vs. cognitive test scores for sex differences.

NEO, neocortex; SUVR, standardized uptake value ratio; MMSE, Mini-Mental State Examination; FCSRT, free and cued selective reminding test; PACC, preclinical Alzheimer's cognitive composite

TABLE 2. Linear Regression Models Predicting PACC scores from Demographic Variables, APOE Status, Tau Pathology (tau_{MTL}), and their Interactions.

	Model 1			Model 2			Model 3			Model 4		
Predictors	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***
(Intercept)	-0.176	0.082	**0.033**	-0.171	0.082	**0.038**	-0.149	0.084	0.078	-0.142	0.084	0.091
Age	-0.316	0.044	**< 0.001**	-0.317	0.044	**< 0.001**	-0.321	0.044	**< 0.001**	-0.322	0.044	**< 0.001**
Sex	0.447	0.089	**< 0.001**	0.447	0.088	**< 0.001**	0.448	0.088	**< 0.001**	0.449	0.088	**< 0.001**
Education	0.148	0.043	**0.001**	0.157	0.043	**< 0.001**	0.152	0.043	**< 0.001**	0.162	0.043	**< 0.001**
APOE (+)	-0.156	0.088	0.078	-0.160	0.088	0.071	-0.173	0.089	0.052	-0.177	0.089	**0.046**
tau_{MTL}	-0.182	0.044	**< 0.001**	-0.070	0.073	0.339	-0.084	0.077	0.278	0.038	0.098	0.702
Sex*tau_{MTL}				-0.171	0.089	0.055				-0.177	0.089	**0.047**
APOE*tau_{MTL}							-0.145	0.093	0.12	-0.153	0.093	0.101
R^2	0.234			0.240			0.238			0.245		
R^2 adjusted	0.225			0.230			0.227			0.233		

APOE, apolipoprotein E; SE, standard error; PACC, preclinical Alzheimer's cognitive composite.

TABLE 3. Linear Regression Models Predicting FCSRT Scores from Demographic Variables, APOE Status, Tau Pathology (tau_{MTL}), and their Interactions.

	Model 1			Model 2			Model 3			Model 4		
Predictors	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***
(Intercept)	-0.255	0.086	**0.003**	-0.249	0.086	**0.004**	-0.236	0.088	**0.008**	-0.229	0.088	**0.009**
Age	-0.216	0.046	**< 0.001**	-0.217	0.045	**< 0.001**	-0.219	0.046	**< 0.001**	-0.221	0.045	**< 0.001**
Sex	0.497	0.092	**< 0.001**	0.498	0.092	**< 0.001**	0.498	0.092	**< 0.001**	0.499	0.092	**< 0.001**
Education	0.058	0.045	0.197	0.069	0.045	0.128	0.061	0.045	0.177	0.072	0.045	0.111
APOE (+)	-0.063	0.092	0.497	-0.067	0.092	0.469	-0.074	0.093	0.425	-0.079	0.093	0.393
tau_{MTL}	-0.181	0.046	**< 0.001**	-0.051	0.076	0.506	-0.113	0.081	0.162	0.026	0.103	0.799
Sex*tau_{MTL}				-0.198	0.093	**0.033**				-0.202	0.093	**0.030**
APOE*tau_{MTL}							-0.100	0.098	0.304	-0.109	0.097	0.261
R^2	0.164			0.173			0.166			0.175		
R^2 adjusted	0.155			0.162			0.155			0.162		

APOE, apolipoprotein E; SE, standard error, FCSRT, free and cued selective reminding test.

TABLE 4. Linear Regression Models Predicting DLM Scores from Demographic Variables, APOE Status, Tau Pathology (tau_{MTL}), and their Interactions.

	Model 1			Model 2			Model 3			Model 4		
Predictors	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***
(Intercept)	0.077	0.09	0.395	0.082	0.09	0.362	0.088	0.092	0.341	0.095	0.092	0.303
Age	-0.152	0.048	**0.002**	-0.153	0.047	**0.001**	-0.154	0.048	**0.001**	-0.156	0.048	**0.001**
Sex	-0.021	0.097	0.827	-0.021	0.096	0.828	-0.021	0.097	0.831	-0.02	0.096	0.833
Education	0.118	0.047	**0.012**	0.128	0.047	**0.007**	0.12	0.047	**0.011**	0.13	0.047	**0.006**
APOE (+)	-0.121	0.097	0.211	-0.125	0.096	0.196	-0.128	0.097	0.19	-0.132	0.097	0.173
tau_{MTL}	-0.191	0.048	**< 0.001**	-0.067	0.08	0.399	-0.15	0.084	0.075	-0.019	0.107	0.856
Sex*tau_{MTL}				-0.188	0.097	0.053				-0.191	0.097	0.05
APOE*tau_{MTL}							-0.06	0.102	0.558	-0.068	0.102	0.503
R^2	0.087			0.095			0.088			0.096		
R^2 adjusted	0.077			0.083			0.075			0.081		

APOE, apolipoprotein E; SE, standard error; DLM, Delayed Logical Memory.

TABLE 5. Linear Regression Models Predicting DSS Scores from Demographic Variables, APOE Status, Tau Pathology (tau_{MTL}), and their Interactions.

	Model 1			Model 2			Model 3			Model 4		
Predictors	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***
(Intercept)	-0.208	0.087	**0.017**	-0.208	0.087	**0.017**	-0.189	0.089	**0.034**	-0.189	0.089	**0.035**
Age	-0.288	0.046	**< 0.001**	-0.288	0.046	**< 0.001**	-0.291	0.046	**< 0.001**	-0.291	0.046	**< 0.001**
Sex	0.404	0.093	**< 0.001**	0.404	0.094	**< 0.001**	0.405	0.093	**< 0.001**	0.405	0.094	**< 0.001**
Education	0.075	0.045	0.098	0.076	0.046	0.096	0.078	0.046	0.087	0.08	0.046	0.084
APOE (+)	-0.048	0.093	0.608	-0.048	0.093	0.606	-0.059	0.094	0.527	-0.06	0.094	0.524
tau_{MTL}	-0.047	0.047	0.321	-0.033	0.078	0.668	0.022	0.082	0.787	0.039	0.104	0.71
Sex*tau_{MTL}				-0.02	0.094	0.831				-0.024	0.094	0.797
APOE*tau_{MTL}							-0.101	0.099	0.305	-0.102	0.099	0.301
R^2	0.147			0.147			0.149			0.149		
R^2 adjusted	0.137			0.135			0.137			0.135		

APOE, apolipoprotein E; SE, standard error; DSS, Digit Symbol Substitution.

TABLE 6. Linear Regression Models Predicting MMSE Scores from Demographic Variables, APOE Status, Tau Pathology (tau_{MTL}), and their Interactions.

	Model 1			Model 2			Model 3			Model 4		
Predictors	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***	**Estimates**	**SE**	***p***
(Intercept)	-0.076	0.09	0.399	-0.075	0.09	0.407	-0.054	0.092	0.561	-0.052	0.092	0.575
Age	-0.176	0.048	**0.001**	-0.176	0.048	**0.001**	-0.18	0.048	**0.001**	-0.18	0.048	**0.001**
Sex	0.294	0.097	**0.003**	0.294	0.097	**0.003**	0.295	0.097	**0.002**	0.295	0.097	**0.002**
Education	0.137	0.047	**0.004**	0.139	0.047	**0.004**	0.14	0.047	**0.003**	0.143	0.048	**0.003**
APOE (+)	-0.177	0.097	0.067	-0.178	0.097	0.066	-0.191	0.097	0.05	-0.192	0.097	**0.049**
tau_{MTL}	-0.061	0.048	0.207	-0.033	0.08	0.683	0.020	0.084	0.815	0.053	0.108	0.624
Sex*tau_{MTL}				-0.043	0.097	0.657				-0.048	0.098	0.621
APOE*tau_{MTL}							-0.12	0.102	0.241	-0.122	0.102	0.234
R^2	0.085			0.086			0.088			0.089		
R^2 adjusted	0.075			0.073			0.075			0.074		

APOE, apolipoprotein E; SE, standard error; MMSE, Mini-Mental State Examination.

DISCUSSION

Our study investigated the relationship between regional tau deposition and cognitive performance in cognitively unimpaired older adults using data from the A4 study. We concentrated on tau pathology in the MTL and NEO regions, assessed by PET imaging, and examined its link to cognitive outcomes measured by the PACC and other tests. The results showed that increased tau in both regions was associated with worse cognitive performance, especially on the PACC, DLM, and FCSRT96. We also found notable sex differences, with female participants displaying a stronger connection between tau_{MTL} and cognitive decline compared to males, indicating that tau pathology in the MTL may have a greater impact on cognitive function in females.

Previous research has indicated that age plays a significant role in how tau pathology affects cognitive function. Wisse et al.[27] examined the involvement of the MTL in cognition and how tau pathology mediates age-related changes in MTL structure. Their results suggest that tau pathology may be a driving factor behind age-related alterations in the MTL, highlighting its important role in neurodegeneration and cognitive decline associated with aging. Our analysis showed that older age correlates with poorer cognitive performance, which is clinically important since age is a well-known risk factor for cognitive decline and dementia. Early detection of cognitive changes related to aging can help guide interventions to preserve cognitive health in older adults. Furthermore, research by Harrison et al.[28] supports this view by demonstrating that tau accumulation and spread, worsened by Aβ, progressively impair functional memory circuits-a process that becomes particularly evident with aging, causing disconnection in key MTL regions such as the hippocampus.

TABLE 7. Components of PACC (FCSRT96, MMSE, DLM, and DSS) - Stratified for T_{MTL}+ (n = 134).

		Model 1			Model 2			Model 3			Model 4		
	Variables					+			+			+	
	Predictors		SE	*p*	*β*	SE	*p*	*β*	SE	*p*	*β*	SE	*p*
PACC	tau_{MTL}	-0.266	0.087	**0.003**	-0.165	0.163	0.312	-0.178	0.168	0.293	-0.048	0.231	0.837
	Sex*tau_{MTL}				-0.139	0.19	0.466				-0.158	0.193	0.414
	APOE*tau_{MTL}							-0.121	0.197	0.539	-0.143	0.199	0.474
	R^2	0.207			0.211			0.210			0.214		
	R^2 adjusted	0.176			0.173			0.172			0.170		
FSCRT	tau_{MTL}	-0.340	0.101	**0.001**	-0.147	0.189	0.437	-0.142	0.195	0.466	0.111	0.266	0.678
	Sex*tau_{MTL}				-0.267	0.22	0.229				-0.307	0.222	0.168
	APOE*tau_{MTL}							-0.27	0.227	0.237	-0.312	0.229	0.174
	R^2	0.155			0.165			0.164			0.177		
	R^2 adjusted	0.122			0.125			0.125			0.131		
DLM	tau_{MTL}	-0.269	0.091	**0.004**	-0.337	0.17	0.05	-0.316	0.176	0.074	-0.402	0.242	0.099
	Sex*tau_{MTL}				0.094	0.199	0.638				0.104	0.201	0.606
	APOE*tau_{MTL}							0.065	0.205	0.753	0.079	0.208	0.704
	R^2	0.111			0.112			0.112			0.113		
	R^2 adjusted	0.076			0.071			0.070			0.064		
DSS	tau_{MTL}	-0.098	0.097	0.317	-0.014	0.183	0.941	0.015	0.188	0.935	0.13	0.259	0.618
	Sex*tau_{MTL}				-0.116	0.214	0.587				-0.139	0.216	0.522
	APOE*tau_{MTL}							-0.155	0.22	0.484	-0.174	0.223	0.437
	R^2	0.155			0.157			0.159			0.162		
	R^2 adjusted	0.123			0.118			0.119			0.115		
MMSE	tau_{MTL}	0.004	0.100	0.968	0.060	0.188	0.751	-0.025	0.194	0.896	0.035	0.267	0.896
	Sex*tau_{MTL}				-0.077	0.219	0.727				-0.073	0.222	0.743
	APOE*tau_{MTL}							0.04	0.226	0.86	0.03	0.229	0.896
	R^2	0.083			0.084			0.083			0.084		
	R^2 adjusted	0.047			0.041			0.040			0.033		

Age, sex, education, and have been used in all models as covariates. Regression coefficients (*β*), SE, standard error, and *p* -value are standardized for all cognitive test models, are reported for the , not interaction terms. (Detail version of this table can be found in Supllement Table 16-20). APOE, apolipoprotein E; SE, standard error; MMSE, Mini-Mental State Examination; DSS, Digit Symbol Substitution; DLM, Delayed Logical Memory; FCSRT, free and cued selective reminding test; PACC, preclinical Alzheimer's cognitive composite.

Our study presents strong evidence linking tau pathology, as indicated by tau SUVRs (tau_{MTL} and tau_{NEO}), to declines in cognitive performance, highlighting notable sex differences. The results show that higher tau SUVR levels correspond to decreased cognitive function across several domains, emphasizing the potential role of tau pathology in cognitive decline. Both tau_{MTL} and tau_{NEO} were related to reduced cognitive performance, especially in processing speed and memory. However, tau_{MTL} demonstrated stronger and more consistent associations with cognitive outcomes compared to tau_{NEO}. The effect of APOE-ε4 on these relationships was limited, reaching significance only for PACC and MMSE when interaction with tau pathology was considered, suggesting that tau pathology itself is the main factor influencing cognitive decline.

Notably, we found sex differences, with females consistently showing lower cognitive scores. Honarpisheh and McCullough[29] emphasized the importance of including sex as a biological variable in neurodegenerative research.[30] The stronger effect of tau_{MTL} SUVR on cognition in females suggests that regional tau accumulation may influence cognitive outcomes differently depending on sex.[31] Sohrabji[32] noted that hormone loss during menopause has become a significant risk factor for AD. The exact mechanisms behind these sex-specific effects are not yet fully understood but may involve hormonal, genetic, or environmental factors[33] that differently affect tau pathology and its impact on cognition. Our analysis showed that the adverse effect of tau_{MTL} on cognitive scores was greater in females, particularly for PACC scores. This finding is clinically important, underscoring the need for personalized strategies in

cognitive health that consider individual factors such as sex and genetic risk.

Our study has certain limitations. For instance, we relied on cross-sectional data, which restricts the ability to make causal conclusions and to monitor the progression of tau pathology over time. Longitudinal research is necessary to assess how tau deposition develops and its cognitive impact, especially concerning sex differences. Although SUVR offers a useful measure of tau burden, future studies should include additional methods, such as CSF biomarkers or advanced imaging techniques, to provide a more comprehensive understanding of tau-related neurodegeneration. Furthermore, the demographics of the study sample, including age and APOE-ε4, may limit the extent to which these findings can be generalized. Since the study focused on cognitively unimpaired older adults, it does not fully address the patterns of tau pathology in individuals with more advanced cognitive impairment, where tau accumulation likely has a stronger effect.

In conclusion, our study underscores the significance of cognitive performance and tau pathology, particularly tau_{MTL} in T_{MTL}+ individuals. This indicates that tau pathology in the MTL can substantially affect episodic memory and related cognitive functions before broader cognitive decline is detectable by measures like the MMSE. This highlights the need to use more sensitive, memory-focused assessments (such as PACC, FCSRT, and DLM) in the early stages of AD or other tauopathies, especially when early cognitive decline is suspected. The strong link between tau_{MTL} and memory performance supports the view that memory deficits, especially in episodic memory, may be among the earliest and most sensitive signs of neurodegenerative disease. Therefore, concentrating on memory-specific tasks can aid in identifying individuals at greater risk of progressing to AD or other tau-related disorders. Higher education levels correlate with better cognitive performance, which is clinically important as education is a modifiable factor. Promoting educational attainment and lifelong learning might help reduce cognitive decline in populations at risk. Lastly, it is important to consider sex differences in studies of tau pathology and cognitive decline. The role of the APOE-ε4 allele seems limited in this association, suggesting it is a potential genetic risk factor for AD. Further research is necessary to clarify the complex interactions among tau accumulation, sex, genetics, and cognitive outcomes, ultimately guiding the development of targeted interventions to enhance cognitive health in diverse populations.

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