Original Article

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Regional tau Burden and Multidomain Cognitive Function in Clinically Unimpaired Older Adults: Evidence from the A4 Study

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Abstract

Aim: We aimed to evaluate how modifiable risk factors influence these relationships and to better understand the drivers of early cognitive changes in regional tau burden in the medial temporal lobe (MTL) versus the neocortex (NEO) during the preclinical stages of Alzheimer's disease (AD).

Methods: In this cross-sectional study, 447 participants in the A4 study (anti-amyloid treatment in asymptomatic AD) underwent tau-positron emission tomography-standardized uptake value ratio evaluations. Cognitive abilities were assessed using the Preclinical Alzheimer's Cognitive Composite (PACC). Depression, anxiety, and lifestyle factors were analyzed using t-tests, chi-square tests, and multiple linear regression models.

Results: The tau-positive cohort was notably older ($p=0.002$) and significantly more likely to carry APOE4 ($p<0.001$). Tau-positive groups demonstrated poorer cognitive performance. Negative correlations between tau accumulation and cognitive performance for PACC and its components, with tauMTL/tauNEO associated with worse outcomes. Females were associated with better objective performance but worse informant-reported function, suggesting an early loss of self-awareness. Higher education was protective; depression was linked to decreased memory and executive function, whereas anxiety showed no association.

Conclusion: Regional tau pathology is robustly associated with functional decline detectable by informants prior to clinical emergence. The significant interaction between tau and modifiable factors such as depressive symptoms underscores the importance of multifaceted, informant-based assessments in preclinical AD screening.

Keywords: Cognitive dysfunction, Alzheimer's disease, tau proteins, temporal lobe, depression, risk factors

Introduction

Cognitive decline (CD) is a significant concern in age-related diseases, especially in neurodegenerative disorders such as Alzheimer's disease (AD) related dementias (ADRDs) (1). Individuals experiencing CD often report higher levels of depression and anxiety, which further exacerbate reductions in their perceived quality of life (2). Multiple studies indicate that demographic and lifestyle factors influence subjective CD (SCD), a self-reported cognitive difficulty. Cognitive lifestyle factors, such as education, career, and social engagement, are associated with slower CD and offer protective benefits (3,4). Additionally, demographic factors such as age and sex may influence the onset and progression of SCD, thereby affecting the risk of developing AD (5).

The medial temporal lobe (MTL), particularly the hippocampus, is often among the earliest regions affected by AD (6,7). Studies indicate that individuals with SCD may exhibit reduced MTL volumes, which correlate with AD pathology (8). The neocortex (NEO), involved in higher cognitive functions, also exhibits atrophy in individuals with

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CD, further supporting the view that SCD may precede more pronounced cognitive deficits (9). Elevated tau levels in cerebrospinal fluid are associated with AD, and the N-224 tau fragment has shown promise in differentiating AD from SCD, suggesting its potential as an early biomarker (10,11). Lifestyle choices also play a critical role in modulating CD. Regular exercise is associated with improved cognitive function and may delay the onset of dementia; physical activity is also linked to better cognitive outcomes (12). Conversely, alcohol consumption negatively impacts cognitive health, contributing to neuroinflammation and cognitive impairments, particularly in older adults.

In this study, we hypothesized that tau accumulation in the tau accumulation in the neocortex (tau_{NEO}) and tau accumulation in the medial temporal lobe (tau_{MTL}) would be associated with CD in individuals at risk for neurodegenerative diseases. This study represents one of the limited analyses within the A4 cohort that simultaneously evaluates regional tau burden (MTL vs. NEO) using both objective cognitive assessments and informant-based functional measures. Participants from the A4 study were stratified according to neuroimaging findings into groups with positive and negative tau accumulation in each region. In addition, we investigated the potential influence of demographic characteristics, health-related variables, and lifestyle factors on tau accumulation and their associations with cognitive outcomes across multiple assessment domains. By examining the relationship between regional tau pathology and cognitive performance, this study aims to provide a more comprehensive understanding of how tau accumulation contributes to early changes in memory and functional abilities. Furthermore, we explored whether demographic and lifestyle factors may act as potential moderators of this relationship, thereby offering further insights into the complicated interaction between biological mechanisms and modifiable risk factors in cognitive health.

Materials and Methods

Study Design

This study was designed as a cross-sectional secondary analysis of the A4 study dataset. The analysis did not require additional Institutional Review Board (IRB) approval because it used previously collected and fully de-identified data from a study that had already received IRB approval. The dataset used in this analysis was fully de-identified and contained no direct or indirect personal identifiers. As the researchers had no interaction with human subjects and no access to identifiable private information, the study does not meet the regulatory definition of human subjects research. It is therefore exempt from additional IRB review.

Participants

The A4 study, which began in 2014, was conducted at 67 sites across the United States, Japan, Australia, and Canada, and participant randomization was completed by the end of 2017. All locations obtained approval from their IRBs. Before joining the trial, participants provided informed consent. The Alzheimer's Therapeutic Research Institute at University of Southern California handled the management of the A4/LEARN Study, with data sourced from the university's Laboratory for Neuro Imaging (13). The study followed the ethical principles outlined in the Declaration of Helsinki, and all individuals gave written informed consent before participating. The analysis used previously deidentified individual-level data.

A total of 6,763 cognitively healthy participants aged between 65 and 85 years entered the study. To be eligible, participants needed to show no cognitive impairment. They must meet specific standards, including a score of 0 on the clinical dementia rating, a mini-mental state examination (MMSE) score ranging from 25 to 30, and a delayed paragraph recall (LM-IIa) subscale score on the Wechsler Memory Scale-Revised ranging from 6 to 18 (14). The A4 study was open to participants who had a significant amyloid burden, as demonstrated by positron emission tomography (PET) imaging. Those without high amyloid levels who were eligible for the A4 Study were referred to the LEARN Study. Subsequently, ^{18}F-florbetapir PET scans were conducted on 4,486 individuals (15,16).

Additionally, some participants in the research underwent ^{18}F-flortaucipir PET scans for tau PET imaging. A total of 447 individuals who received PET tau assessments were included in this study. Participants were divided into positive and negative groups for each region based on their tau standardized uptake value ratio (SUVr) values, which referred to tau SUVr in the tau_{MTL} and in the tau_{NEO} (Figure 1).

Magnetic Resonance Imaging

Throughout the study, volumetric magnetic resonance imaging scans and functional connectivity assessments were conducted. To assess the effects of fibrillar amyloid buildup, ^{18}F-florbetapir PET amyloid imaging was performed at the trial's conclusion. The PET data for tau and amyloid are analyzed using FreeSurfer (17).

Amyloid and tau Status

^{18}F-florbetapir was performed 50 to 70 minutes following the administration of 10 mCi of the tracer to obtain Amyloid PET imaging (18). The presence of amyloid deposits, classified as either high (Aß+) or low (Aß-), was assessed by the SUVr and by visual assessment at a leading research laboratory. Non-elevated amyloid status (Aß-) was defined using an average cortical SUVr,

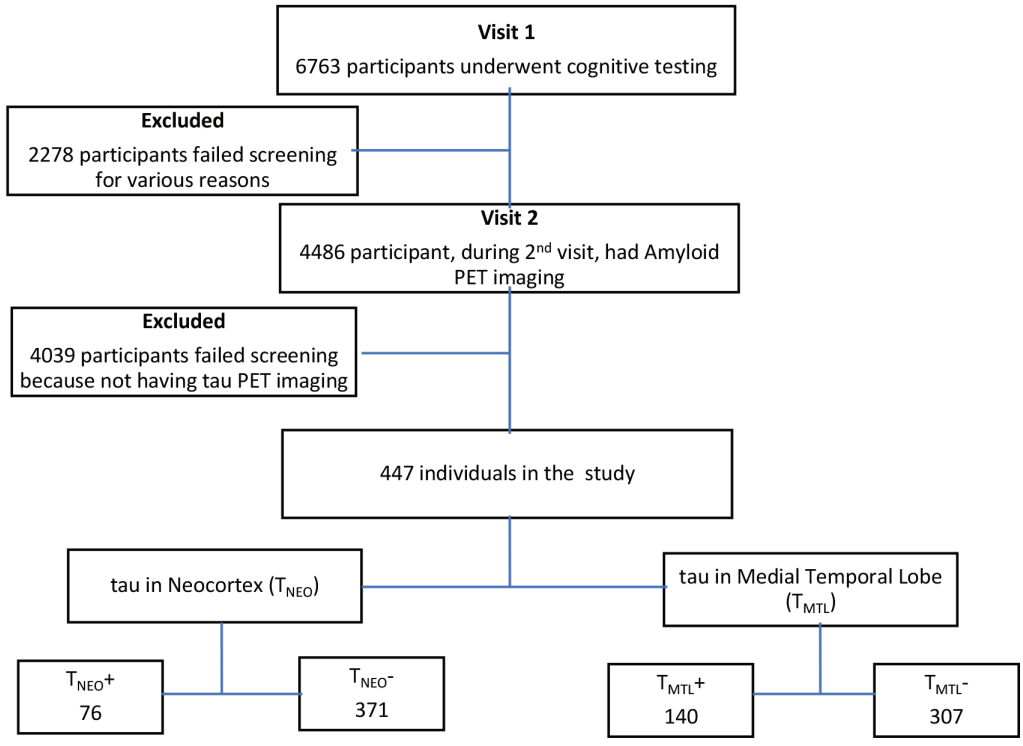

Figure 1. Participant selection flowchart and tau PET results. Of 6,763 initially tested, 447 met all criteria. Tables show number of participants with tau burden (SUVr*) in neocortex (left) and medial temporal lobe (right)
PET: Positron emission tomography, SUVr: Standardized uptake value ratio

with the entire cerebellum as the reference region and a threshold of <1.15 applied. This is considered a highly effective technique for detecting early amyloid deposits in the preclinical stage of AD (19).

In the A4 study, some participants underwent 18F-flortaucipir PET scans, performed 90 to 110 minutes after injection. The assessment of tau SUVr levels focused on the tau_{MTL}, a region encompassing the amygdala and entorhinal cortex bilaterally (20). Although the entorhinal cortex is smaller than the amygdala, it plays a critical role in the early stages of tau accumulation (7) for these two structures. The MTL region was defined based on an established temporal meta-region of interest that captures the typical pattern of tau spread (21,22). The criteria for grouping tau status in the MTL as positive or negative were established based on the mean tau level plus 2 standard deviations observed among all Aß-negative participants in the A4 study (20). For tau deposition in the tau_{MTL} and in the tau_{NEO}, the cut-off values were found to be 1.25 and 1.28, respectively.

Self-Assessment of Lifestyle Habits

The A4 study's self-report questionnaire consists of 8 questions. It was designed to assess participants' current lifestyle habits. It covers physical activity, sleep patterns, and substance use. It asks about the frequency of aerobic exercise (average hours spent swimming, jogging, or cycling per week), the average sleep duration per night, and the average daily alcohol consumption. However, no dietary questions were included (23,24).

Geriatric Depression Scale and State Anxiety Inventory

The GDS is a self-reported tool designed to examine depression among older adults. It consists of 15 questions with dichotomous (yes/no) answers and focuses primarily on the emotional and psychological symptoms of depression, making it an effective tool for identifying depressive symptoms in older adults (25). A higher score on the scale indicates more significant concerns (24).

The State Anxiety Inventory (STAI) is a widely used instrument for measuring anxiety levels (26). The 6-item version of STAI is designed to measure state anxiety, which refers to the temporary feelings of anxiety or nervousness that a person may experience in a particular situation (27).

Cognitive Assessments and Outcome Measures

This study compared various cognitive assessments and their relationships with regional and composite measures. They are used as outcome measures in regression analysis.

The following tests were included:

The main objective of the Preclinical Alzheimer's Cognitive Composite (PACC) is to measure outcomes in the first preclinical AD trial (13). It includes four key components designed to assess different aspects of cognitive function (28):

- Free and cued selective reminding test (FCSRT): A memory test that assesses associations through visual and semantic prompts. It yields two scores: free recall (items remembered independently) and total recall (a combination of free and cued recall), with higher scores (0-96) indicating better memory performance.

- Mini-mental state examination: The MMSE is a test comprising 30 items that evaluates overall cognitive function, covering orientation, attention, memory, naming, and simple drawing tasks. A score of 23 or below suggests cognitive impairment.

- Digit symbol substitution (DSS): A task in which participants match symbols with numbers to evaluate cognitive speed, memory recall, and executive functioning. Higher scores (0 to 91) signify improved cognitive abilities.

- Delayed logical memory (DLM): This test measures episodic memory by asking participants to recall a short story immediately, followed by a delayed recall 20–30 minutes later. Higher scores (0-25) indicate better memory retention.

The cognitive function index: Cognitive function index (CFI), developed by the Alzheimer's Disease Cooperative Study, is used to monitor changes in cognitive function over 1 year (29-31). To participate, individuals must be proficient in English, Japanese, or Spanish and have adequate hearing and vision for the assessments. Each participant needs a study partner to provide weekly insights into their cognitive function via phone, email, or in person.

The CFI has two editions: One for the participant to assess their own cognitive skills and another for the study partner to share their viewpoint (19). Both versions are mailed four weeks before the annual evaluation, with clear instructions for independent completion. Study partners are prohibited from discussing the questionnaire with the participant, though they may consult others if necessary. The CFI comprises 14 questions, which are the same for both the participant and study-partner versions, plus one additional question in the A4 study asking whether the participant has consulted a doctor regarding memory issues (29). Responses are scored as "Yes" (2), "Maybe" (1), or "No" (0) (19), and a higher score indicates more deleted significant severe subjective cognitive complaints (32). A "not applicable" option is provided for questions about driving, money, or job performance; when this option is chosen, the average of the other answers is used (16).

Statistical Analysis

Demographic data from all participants were compiled for the overall sample. Continuous variables were characterized using means and standard deviations, and Independent Samples t-tests were used to evaluate group differences in age, education, cognitive scores (e.g., PACC, FCRST96), and the difference between tau_{MTL} (negative/positive) and tau_{NEO} (negative/positive) groups. For categorical variables, analyses were performed using the chi-square test and Fisher's exact test. Chi-square tests were used to examine differences in amyloid eligibility, APOE ε4 status, and sex distribution between the tau_{MTL} and tau_{NEO} groups. We also assessed the independent relationships between tau_{MTL}, tau_{NEO}, and cognitive scores overall. We used multiple regression analysis across various models to test our hypotheses regarding the effects of demographics and habits and their interactions with tau_{MTL} and tau_{NEO} on cognitive function. R version 4.3.2 was used in the study (33).

Results

Demographics and Group Comparisons

Total 447 participants were included in the study, divided into tau_{NEO} and tau_{MTL} groups based on tau PET SUVr from neuroimaging. Regarding demographic characteristics, there were no significant differences in age between the tau-positive and tau-negative groups in the TNEO region. However, the tau_{MTL} positive group was significantly older than the comparison group [72.88 (4.83) vs. 71.36 (4.78), p=0.002]. Sex distribution was similar across all groups, with no significant differences observed for either the tau_{NEO} (p=0.756) or TMTL (p=0.557) groups. The prevalence of the APOE4 allele was significantly higher in tau-positive groups than in their respective tau-negative groups in both regions. Tau deposition was markedly elevated in the tau-positive groups across both regions, as indicated in Table 1.

The scores on the STAI and the GDS showed no discernible differences between the groups. Even if alcohol consumption was higher among TNEO+ participants, there were no significant differences. Similarly, weekly hours of aerobic activity were lower in tau-positive groups, but this difference was not statistically significant. Similarly, the proportion of participants living with a study partner was comparable across groups, with no significant differences observed.

Cognitive performance was significantly worse in the tau-positive groups at both levels. Participants with higher tau accumulation had significantly lower scores on several cognitive assessments. The PACC score was significantly lower in the tau-positive groups in both the TNEO and TMTL levels (p<0.001 for both). Likewise, MMSE scores

Table 1. The characteristics of the sample and subgroups							
		Stratified by tau_{NEO} Status			Stratified by tau_{MTL} Status		
Variables	**Full Dataset**	**Negative**	**Positive**	**p-value**	**Negative**	**Positive**	**p-value**
N	447	371	76		307	140	
Age (yrs), mean (SD)	71.84 (4.84)	71.65 (4.77)	72.76 (5.11)	0.067	71.36 (4.78)	72.88 (4.83)	**0.002**
Sex (F)	257 (57.5%)	211 (56.9%)	46 (60.5%)	0.557	175 (57.0%)	82 (58.6%)	0.756
Race - white (%)	409 (91.5%)	337 (90.8%)	72 (94.7%)	0.622	281 (91.5%)	128 (91.4%)	0.967
Education (yrs), mean (SD)	16.22 (2.84)	16.18 (2.88)	16.42 (2.59)	0.496	16.13 (2.91)	16.42 (2.67)	0.309
APOE4 - N (%)	234 (53.2%)	181 (49.5%)	53 (71.6%)	**<0.001**	141 (46.1%)	93 (69.4%)	**<0.001**
Amyloid (Aß)	1.28 (0.20)	1.25 (0.18)	1.41 (0.22)	**<0.001**	1.23 (0.18)	1.38 (0.20)	**<0.001**
tau_{MTL}	1.21 (0.15)	1.17 (0.11)	1.41 (0.18)	**<0.001**	1.13 (0.07)	1.39 (0.14)	**<0.001**
tau_{NEO}	1.20 (0.12)	1.16 (0.06)	1.39 (0.13)	**<0.001**	1.16 (0.08)	1.29 (0.13)	**<0.001**
Alcohol (day)	0.76 (0.93)	0.75 (0.95)	0.78 (0.86)	0.836	0.79 (0.98)	0.69 (0.80)	0.332
Aerobic (week)	2.90 (3.48)	2.92 (3.53)	2.82 (3.24)	0.814	3.04 (3.62)	2.60 (3.13)	0.216
Depression (total)	1.05 (1.44)	1.04 (1.47)	1.11 (1.33)	0.722	1.06 (1.51)	1.04 (1.28)	0.932
Anxiety (total)	10.17 (3.04)	10.17 (3.00)	10.18 (3.22)	0.976	10.13 (3.08)	10.28 (2.96)	0.625
CFI_p - mean (SD)	0.16 (0.15)	0.15 (0.14)	0.22 (0.18)	**<0.001**	0.14 (0.13)	0.19 (0.17)	**<0.001**
CFI_{sp} - mean (SD)	0.10 (0.13)	0.09 (0.12)	0.17 (0.18)	**<0.001**	0.10 (0.12)	0.12 (0.16)	**0.039**
PACC	-0.42 (2.79)	-0.16 (2.68)	-1.70 (3.00)	**<0.001**	-0.02 (2.76)	-1.29 (2.67)	**<0.001**
MMSE	28.64 (1.31)	28.71 (1.27)	28.26 (1.42)	**0.006**	28.74 (1.28)	28.41 (1.34)	**0.015**
LMD	11.59 (3.38)	11.83 (3.37)	10.38 (3.16)	**<0.001**	11.98 (3.40)	10.71 (3.16)	**<0.001**
DSS	42.56 (9.39)	43.12 (9.36)	39.82 (9.09)	**0.005**	43.17 (9.23)	41.22 (9.63)	**0.042**
FCSRT	75.69 (6.28)	76.05 (6.09)	73.96 (6.92)	**0.008**	76.40 (5.94)	74.13 (6.72)	**<0.001**

Bold values indicate statistically significant results (p<0.05).
Note: Using t-tests or continuous variables and chi-square test for categorical variables.
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical Memory Delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

were lower in tau-positive groups (TNEO: p=0.006, TMTL: p=0.015). On the Logical Memory Delayed (LMD) test, which assesses verbal memory, the tau-positive groups also performed worse (p<0.001 for both groups). Additionally, tau-positive participants had significantly lower FCSRT scores, indicating impaired memory performance (TNEO: p=0.008; TMTL: p<0.001). Furthermore, the functional decline was more pronounced in the tau-positive groups. The DSS scores were significantly lower in the tau-positive groups, reflecting more significant functional impairment in those with higher tau levels (TNEO: p=0.005; TMTL: p=0.042). Finally, Tau-positive groups had higher CFI scores not only for participants but also for study partners for TNEO (p<0.001; p<0.001) and TMTL (p<0.001; p=0.039) groups (Table 1).

Factors Influencing tau Accumulation

To investigate the impact of lifestyle, health, and demographic variables on tau_{MTL} and tau_{NEO} and their correlation with cognitive function, we used multiple linear regression analyses. Separate regression models were employed for tau_{MTL} and tau_{NEO} (Tables 2 and 3), with an additional model assessing the interaction between tau_{MTL} and tau_{NEO} (Table S1). This allowed a comparison of how each form of tau deposition and its combined effect relate to cognitive outcomes.

Associations Between tau_{MTL} & Cognitive Function and tau_{NEO} & Cognitive Function

Higher tauMTL deposition was associated with poorer performance on the PACC (ß=-0.224, p<0.001), FCSRT (ß=-0.210, p<0.001), LMD (ß=-0.220, p<0.001), and MMSE (ß=-0.099, p=0.066) and with higher (worse) scores on the CFI participant and study-partner reports (ß=0.024 & 0.023, both p<0.001). It was not associated with DSS. Older individuals performed worse on the PACC, FCSRT, LMD, and MMSE (all p≤0.003). Female participants were associated with better performance on the PACC, FCSRT, DSS, and MMSE (all p<0.001), but with worse study-partner ratings on the CFI (ß=-0.043, p=0.004). Higher education was associated with better performance on the PACC (ß=0.161, p<0.001) and the LMD (ß=0.128, p=0.016). Geriatric Depression Scale were associated with worse PACC and FCSRT performance (ß=-0.099, p_FDR=0.061 & ß=-0.127, p=0.017) and worse CFI ratings (both p≤0.03),

but not with DSS, LMD, or MMSE. Neither the STAI, daily alcohol use, nor weekly aerobic activity showed significant associations with any cognitive measure (Table 2).

Similarly, Higher tau_{NEO} deposition was associated with poorer performance on the PACC (ß=-0.192, p<0.001), FCSRT (ß=-0.109, p=0.033), LMD (ß=-0.150, p=0.004), DSS (ß=-0.102, p=0.047), and MMSE (ß=-0.145, p=0.005), but with higher scores on the CFI participant and study-partner reports (ß=0.019, p=0.011 & ß=0.024, p<0.001). Older age was negatively associated with PACC, FCSRT, LMD, and MMSE performance (all p≤0.005). Females performed better on the PACC, FCSRT, DSS, and CFI study partner (all p<0.002). Higher education was associated with better performance on the PACC (ß=0.154, p<0.001), LMD (ß=0.121, p=0.027), and MMSE (ß=0.152, p=0.004). Geriatric Depression Scalewere associated with worse PACC and FCSRT performance (ß=-0.098, p=0.066; ß=-0.126, p=0.023) and worse CFI ratings (both p≤0.031). Daily alcohol use showed a minor negative association with PACC performance (ß=-0.087, p=0.084). However, no significant correlation was found between any cognitive measure and either weekly aerobic exercise or STAI. Every p-value has been corrected for false discovery rate (FDR) (Table 3).

Tau Region Interaction and Relation to Cognitive Performance

When examining the interaction between tau_{MTL} and tau_{NEO}, we found that tau_{MTL} retained significant negative associations with PACC (ß=-0.150, p=0.026), FCSRT (ß=-0.224, p<0.001), and LMD (ß=-0.200, p=0.007), whereas tau_{NEO} lost significance across cognitive measures. Notably, the interaction between tau_{MTL} and tau_{NEO} was slightly associated with performance on PACC (ß=-0.067, p=0.080) and FCSRT (ß=-0.062, p=0.109), indicating that the joint influence of both tau types may exacerbate CD in some domains. All p-values are FDR-adjusted (Table S1).

Age, sex, and education showed similarly significant associations with cognitive outcomes. Average daily alcohol use remains substantial only with respect to the global cognitive measure (PACC).

Discussion

This study is one of the rare A4 analyses that simultaneously evaluates regional tau burden (MTL vs. NEO) using both objective cognitive tests and informant-based functional measures. Notably, tau pathology in the tau_{MTL} was strongly linked to cognitive functioning, emphasizing its critical role in AD progression (20,34). Additionally, differences in cognitive functioning by sex highlighted the importance of considering self- and informant-reported measures (35). The protective effect of education on cognitive function was evident (36), and

Table 2. Associations between cognitive function and covariates with tau_{MTL} for the whole sample

	CFIp		CFIsp		PACC		FCSRT		LMD		DSS		MMSE	
Variables	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**
(Intercept)	0.167	**<0.001**	0.129	**<0.001**	-0.238	**0.001**	-0.266	**<0.001**	0.031	0.708	-0.225	**0.004**	-0.167	**0.050**
Sex-female	-0.012	0.491	-0.043	**0.004**	0.414	**<0.001**	0.462	**<0.001**	-0.054	0.635	0.392	**<0.001**	0.290	**0.008**
Age (yrs)	0.008	0.366	0.005	0.563	-0.304	**<0.001**	-0.209	**<0.001**	-0.140	**0.008**	-0.283	**<0.001**	-0.171	**0.001**
Education (yrs)	-0.004	0.635	0.010	0.168	0.161	**0.001**	0.061	0.252	0.128	**0.016**	0.081	0.138	0.153	**0.004**
tau_{MTL}	0.024	**0.001**	0.023	**<0.001**	-0.224	**<0.001**	-0.210	**<0.001**	-0.220	**<0.001**	-0.061	0.252	-0.099	0.066
Alcohol	0.006	0.450	0.013	0.080	-0.093	0.061	-0.063	0.236	-0.085	0.127	-0.028	0.626	-0.067	0.236
Aerobic	0.000	0.957	0.000	0.957	-0.014	0.779	-0.034	0.552	-0.043	0.479	-0.002	0.957	0.042	0.481
STAI	0.010	0.246	0.004	0.635	0.082	0.132	0.034	0.564	0.072	0.236	0.036	0.563	0.074	0.235
GDS	0.047	**<0.001**	0.017	**0.030**	-0.099	0.061	-0.127	**0.017**	-0.084	0.159	-0.028	0.635	-0.023	0.705

Bold values indicate statistically significant results (p<0.05)
Associations were examined using multiple linear regression models adjusted for relevant covariates. Bonferroni correction was applied to account for multiple comparisons. Coefficients represent standardized beta estimates.
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical Memory Delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: Standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

Table 3. Associations between cognitive function and covariates with tauNEO for the whole sample

	CFI_p		CFI_{sp}		PACC		FCSRT		LMD		DSS		MMSE	
Variables	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**
(Intercept)	0.167	**<0.001**	0.131	**<0.001**	-0.248	**<0.001**	-0.265	**<0.001**	0.027	0.712	-0.235	**0.001**	-0.179	**0.013**
Sex - female	-0.014	0.326	-0.045	**0.001**	0.431	**<0.001**	0.461	**<0.001**	-0.047	0.635	0.408	**<0.001**	0.311	**0.001**
Age (yrs)	0.009	0.183	0.005	0.384	-0.315	**<0.001**	-0.227	**<0.001**	-0.154	**0.001**	-0.281	**<0.001**	-0.169	**<0.001**
Education (yrs)	-0.003	0.653	0.011	0.077	0.154	**<0.001**	0.052	0.245	0.121	**0.011**	0.081	0.074	0.152	**0.001**
tau_{NEO}	0.019	**0.004**	0.024	**<0.001**	-0.192	**<0.001**	-0.109	**0.015**	-0.150	**0.001**	-0.102	**0.022**	-0.145	**0.002**
Alcohol	0.006	0.371	0.012	**0.050**	-0.087	**0.041**	-0.057	0.201	-0.079	0.090	-0.027	0.545	-0.064	0.162
Aerobic	0.001	0.892	0.000	0.990	-0.018	0.671	-0.039	0.385	-0.047	0.311	-0.003	0.94	0.041	0.374
STAI	0.011	0.132	0.005	0.484	0.074	0.104	0.028	0.555	0.064	0.198	0.033	0.496	0.069	0.163
GDS	0.047	**<0.001**	0.016	**0.013**	-0.098	**0.031**	-0.126	**0.009**	-0.083	0.097	-0.027	0.568	-0.022	0.655

Bold values indicate statistically significant results (p<0.05)
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical memory delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: Standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

the sensitivity of PACC in detecting cognitive changes across multiple domains was underscored by its numerous significant associations (13). The intriguing finding that alcohol consumption was significantly associated with PACC and study-partner-reported CFI, but not with other cognitive measures, suggests that its impact on cognition might be more subtle and better perceived by external observers (14,24).

Our finding that tau_{MTL} deposition shows a robust, specific association with informant-reported functional decline (CFI study partner) more than with global cognitive screens like the MMSE carries significant clinical implications. First, it indicates that functional changes in daily life emerge as an early and sensitive consequence of pathology, potentially preceding detectable impairment on standard cognitive tests. This positions the study partner not as a secondary source but as a primary sensor of early disease impact, leveraging a continuous, real-world observational perspective and an 'external observer advantage' rooted in social perception. Second, the notable discrepancy we observed—where female participants demonstrated better objective test performance but partners reported greater functional concerns—suggests a critical early clinical phenomenon. This divergence may represent a prodromal or subclinical form of anosognosia (loss of self-awareness). Affected individuals may lose the subtle metacognitive ability to monitor their functional lapses in daily life, even while retaining the capacity to perform well on focused cognitive tests. The study-partner CFI therefore may capture the earliest behavioral signature of this evolving lack of insight, marking a key transition from preclinical pathology to prodromal clinical disease.

Among the cognitive tests used in this study, FCSRT, MMSE, DLM, and DSS did not show any association between alcohol consumption and cognitive performance, whereas the PACC and CFI revealed a key relationship between alcohol consumption and cognitive performance. This implies that alcohol's effects on cognitive function could be more intricate and less straightforward for outside observers to detect. The findings could mean that alcohol's effect is more pronounced in everyday functioning and social contexts, which are captured by the PACC and the CFI study partner. Additionally, the PACC is a composite measure specifically designed to detect subtle changes in cognitive functioning in the early stages of AD and other neurodegenerative conditions (37). It includes tests that assess episodic memory, processing speed, and executive function, all of which are cognitive domains that are highly susceptible to disruption by alcohol use, particularly with chronic or daily consumption (38). Alcohol affects these domains early in its use, impairing episodic memory (especially recall), attention, and executive function (including decision-making and processing speed) (38).

On the other hand, the CFI might place more emphasis on global cognitive scores or a broader range of domains. In contrast, alcohol's impact might be more pronounced in certain cognitive functions (such as episodic memory or executive function), which are better captured by measures such as PACC (14).

The MTL plays a crucial role in memory formation, particularly in episodic memory. The MTL is also highly sensitive to alcohol-related neurodegeneration, which can impair memory (39). Tau deposition in the neocortex (NEO), on the other hand, may reflect more widespread cognitive involvement that affects multiple cognitive domains (40). Alcohol may influence these broader functions in a more diffuse or complex manner. This could explain why tau deposition in the MTL was significantly associated with cognitive performance measures such as PACC, whereas tau in the NEO showed a less pronounced association. Study partners are often more attuned to subtle changes in mental functioning because they observe the participant in everyday settings and may notice memory lapses, impaired judgment, or slower processing speed that the participant might not report. As other studies have shown, the CFI study partner captures these external observations and may be more sensitive to the early effects of daily alcohol use because study partners may report cognitive changes that participants do not recognize (16,24). This might explain why alcohol was significant for the CFI study partner but not for the CFI participant.

Study Limitations

One limitation of this study is its cross-sectional design, which provides only a snapshot of cognitive function and tau deposition, thereby limiting the ability to establish causal relationships. The exact role of alcohol use was unclear, since the study evaluated it without explicitly measuring its effects on tau accumulation or CD. Because the sample was drawn from a secondary prevention study and included older individuals without cognitive impairment, it might not be representative of larger groups, particularly those with severe cognitive impairment or other medical issues. Although tau PET imaging helps identify tau accumulation, it cannot distinguish between tau associated with Alzheimer's disease and that related to other neurodegenerative diseases (20). Potential confounding factors, such as comorbidities, could not be accounted for in the analysis, which may lead to skewed results and limit the generalizability of the findings to populations with varying health conditions. Another limitation is its low ethnic diversity and high educational attainment. These limitations highlight the necessity for extended research involving a more diverse participant pool and comprehensive methodologies to assess tau accumulation, cognitive function, and lifestyle factors.

Despite these limitations, the use of high-fidelity PET imaging in a large, well-characterized cohort of clinically normal individuals provides powerful evidence for the role of regional tau. By incorporating both objective and informant-based metrics, this study captures a more holistic view of early CD than traditional clinical assessments alone provide.

Conclusion

Our study provides compelling evidence that regional tau pathology, particularly in the MTL, may represent an early neurobiological correlate of cognitive and functional decline in asymptomatic older adults. While traditional screening often relies on global cognitive tests or self-reports, our findings demonstrate a clear "informant advantage" whereby study partners are more sensitive to the early functional effects of tau pathology than participants themselves. This discrepancy suggests that subclinical anosognosia may be an early behavioral marker of preclinical AD (41). From a clinical perspective, these results underscore the need to move beyond global cognitive screens, such as the MMSE, in the initial work-up of older adults. Clinicians ought to prioritize informant-based functional assessments (e.g., the CFI study partner) in conjunction with regional tau-PET imaging to ascertain individuals at the highest risk for progression.

Furthermore, the significant association between depressive symptoms and cognitive performance suggests that mood assessments must be carefully integrated into the diagnostic process, as depression may mimic or exacerbate the earliest stages of neurodegeneration. These findings emphasize the need for longitudinal studies that track how the interplay between regional tau accumulation and modifiable lifestyle factors, such as alcohol use and education, influences the rate of decline. Shifting toward a multimodal assessment framework that incorporates biological markers, mood profiles, and external observations will be essential for developing the precision screening tools required for early intervention and targeted clinical trials.

Ethics

Ethics Committee Approval: This study was designed as a cross-sectional secondary analysis of the A4 study dataset. The analysis did not require additional Institutional Review Board (IRB) approval because it used previously collected and fully de-identified data from a study that had already received IRB approval. The dataset used in this analysis was fully de-identified and contained no direct or indirect personal identifiers. As the researchers had no interaction with human subjects and no access to identifiable private information, the study does not meet the regulatory definition of human subjects research. It is therefore exempt from additional IRB review.

Informed Consent: All individuals gave written informed consent before participating.

Footnotes

Authorship Contributions

Concept: I.D., Design: I.D., A.O., Data Collection or Processing: I.D., Analysis or Interpretation: I.D., A.O., Literature Search: I.D., A.O., Writing: I.D., A.O.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

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Data Availability: The data is freely available on https://ida.loni.usc.edu/login.jsp.

Supplementary Table Link: https://d2v96fxpocvxx.cloudfront.net/66b874bd-7aaa-4f61-9199-52f558d61c0d/content-images/b1e3c8ab-5e64-468e-919c-0b8bd6aac622.pdf

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