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APOE differentially moderates cerebrospinal fluid and plasma phosphorylated tau181 associations with multi-domain cognition

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ABSTRACT

Biofluid markers of phosphorylated tau181 (p-tau181) are increasingly popular for the detection of early Alzheimer's pathologic changes. However, the differential dynamics of cerebrospinal fluid (CSF) and plasma p-tau181 remain under investigation. We studied 727 participants from the Alzheimer's Disease Neuroimaging Initiative with plasma and CSF p-tau181 data, apolipoprotein (APOE) ε4 carrier status, amyloid positron emission tomography (PET) imaging, and neuropsychological data. Higher levels of plasma and CSF p-tau181 were observed among APOE ε4 carriers. CSF and plasma p-tau181 were significantly associated with memory, and this effect was greater in APOE ε4 carriers. However, whereas CSF p-tau181 was not significantly associated with language or attention/executive function among ε4 carriers or non-carriers, APOE ε4 status moderated the association of plasma p-tau181 with both language and attention/executive function. These findings lend support to the notion that p-tau181 biofluid markers are useful in measuring AD pathologic changes but also suggest that CSF and plasma p-tau181 have unique properties and dynamics that should be considered when using these markers in research and clinical practice.

1. Introduction

Tau neurofibrillary tangles are one of the defining features of many neurodegenerative diseases including Alzheimer's disease (AD; Gao et al., 2018; Wang & Madelkow, 2016). Although traditionally identified through histological methods, advancements in biomarker technology now allow us to characterize these pathological changes to tau in vivo (Blennow & Zetterberg, 2018a; Blennow & Zetterberg, 2018b; Olsson et al., 2016). Biomarker methods are advantageous in several ways, including the ability to examine earlier pathologic and clinical stages as well as concurrent measurement of biomarkers with other measures such as neuropsychological data. Tau pathologic markers can be measured in vivo using neuroimaging (i.e. positron emission tomography [PET]) or biofluid markers (i.e. cerebrospinal fluid [CSF] and blood plasma).

There are relative costs and benefits to each of these methods; consideration of cost-effectiveness, scalability and ease of data collection, diagnostic and prognostic accuracy, and participant burden must be weighed when determining the ideal marker to use in any given situation (Alawode et al., 2021). In addition to these practical concerns, each marker offers unique value in its spatiotemporal measurement of tau pathology. Specifically, tau PET methods allow for assessment of the spatial distribution of tau to investigate patterns of regional deposition throughout the brain

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[#] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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(Lowe et al., 2018; Schöll et al., 2016). Research suggests that changes to tau phosphorylated at threonine 181 (i.e., phosphorylated tau181 [p-tau181]) measured through CSF may precede PET measurements of tau deposition by 4–8 years (Boerwinkle et al., 2021; Cogswell et al., 2022; Moscoso et al., 2022). Blood plasma measurements of p-tau follow a similar trajectory to CSF p-tau181 in terms of the temporal dynamics and emergence of biomarker abnormality (Guo et al., 2021; Moscoso et al., 2021), suggesting that these two biofluid measurements of tau may reflect a similar time course of pathologic change that precedes that measured by PET imaging.

Importantly, tau biomarkers have shown strong associations with clinical and cognitive outcomes (Digma et al., 2019; Lowe et al., 2019; Wang et al., 2021) that are not observed with amyloid-beta 1-42 (Biel et al., 2021; Brier et al., 2016) – the other primary pathologic AD marker. Our prior work demonstrated that tau PET in the medial temporal lobe was associated with neuropsychological outcomes across domains of memory, language, and attention/executive function, and these associations occurred independent of amyloid-beta 1-42 PET levels (Weigand et al., 2021). In this prior study, we also examined the moderating effect of the apolipoprotein (APOE) $\varepsilon 4$ genotype on tau PET and cognition associations given that this AD genetic susceptibility marker has been shown to exacerbate tau aggregation and neurodegeneration (Shi et al., 2017). We found that the association between tau PET and memory performance was stronger among $\varepsilon 4$ carriers such that memory performance decreased as tau increased, and that this negative association was strongest at higher levels of tau.

Examination of the moderating effect of APOE $\varepsilon 4$ carrier status on p-tau181 and multi-domain cognition has yet to be investigated using biofluid markers. Given that the dynamics of these tau biomarkers may differ from PET as well as from one another, we sought to assess (1) APOE $\varepsilon 4$ carrier group differences in levels of CSF and plasma p-tau181, (2) associations between CSF/plasma p-tau181 and multiple domains of cognition, and (3) the moderating effect of APOE $\varepsilon 4$ carrier status on these tau-cognition associations in a sample of highly educated and predominantly White older adults without dementia from the Alzheimer's Disease Neuroimaging Initiative.

2. Methods

2.1. Study design

Data used in the preparation of this article 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, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

2.2. Participants

A group of 727 participants without dementia from ADNI who had plasma measures of p-tau181, APOE genotype, amyloid PET, and neuropsychological data were included in this study. Of this sample, 661 participants also had CSF measures of p-tau181; for this variable, missing data were replaced using multiple imputation so all individuals with plasma data could be included. Multiple imputation was conducted using the *mice* package in R, which stands for multivariate imputation by chained equations and uses predictive mean matching based on Fully Conditional Specification. Demographic and biomarker descriptive statistics for both the imputed dataset (n = 727) and the incomplete dataset (n = 661) can be found in Table 1. For neuropsychological data, 727 participants had memory composite scores, 726 participants had language composite scores, and 720 participants had attention/executive function composite scores.

2.3. Biomarker data

2.3.1. Biofluid data

Measurements of CSF p-tau181 were analyzed using Roche Elecsys immunoassays as fully described in ADNI documentation (Shaw et al., 2022; Shaw et al., 2017). Measurement of plasma p-tau181 was analyzed with the Single Molecule array (Simoa) technique using an in-house immunoassay specific to the University of Gothenburg, Sweden as fully described in ADNI documentation (Zetterberg & Blennow, 2021).

2.3.2. Apolipoprotein $\varepsilon 4$ data

APOE $\varepsilon 4$ carrier status (i.e., positive or negative) was defined as the presence of at least one $\varepsilon 4$ allele. Participants who had an $\varepsilon 2/\varepsilon 4$ genotype were classified as APOE $\varepsilon 4$ positive given data demonstrating that this group has increased likelihood of progression to dementia relative to the $\varepsilon 3/\varepsilon 3$ reference genotype (Goldberg et al., 2020; Oveisgharan et al., 2018).

2.3.3. PET data

Cerebral amyloid burden was quantified using Florbetapir and Florbetaben PET imaging. Summary SUVR values were calculated across frontal, temporal, parietal, and cingulate regions and were intensity normalized to the whole cerebellum. To standardize values across the two PET tracers, all SUVRs were converted to centiloid units using previously published methods (Landau et al., 2021a; Landau et al., 2021b).

2.4. Neuropsychological data

Cognition was assessed using a neuropsychological battery comprised of memory (Auditory Verbal Learning Test delayed recall and yes/no recognition), language (naming [Boston Naming Test or Multilingual Naming Test] and animal fluency), and attention/executive function (Trail Making Test parts A and B). Z-scores were derived for each of these 6 measures using the formula (observed value – predicted value)/standard error of the estimate for which the predicted value and standard error came from a demographically (age-, sex-, and education-) adjusted regression formula. The regression weights for this formula were based on a group of "robust" cognitively unimpaired individuals (defined using ADNI's criteria; Petersen et al., 2010) who remained unimpaired throughout the duration of their participation in the study. Note that this "robust" group was not fully independent from the current study sample (i.e., 217 of the current sample were classified in this "robust" group), but the measures used to define cognitively unimpaired (CU) or mild cognitive impairment status (MCI) as described below were not used in ADNI's criteria to define CU and MCI status.

Cognitive classification (i.e. CU or MCI) for our sample of participants without dementia was determined using Jak/Bondi comprehensive neuropsychological criteria (Bondi et al., 2014; Jak et al., 2009; Thomas et al., 2019). These participants were categorized as having MCI if they met either of 2 criteria: (1) impairment on both measures in any of the 3 cognitive domains, or (2) impairment on at least one measure across each of the 3 cognitive domains. Impairment was defined as more than 1 standard deviation below the

Table 1
Descriptive statistics of demographic and biomarker variables between the incomplete dataset (left, not used in analyses) and the imputed dataset (right, used in analyses)

Variable	Incomplete dataset Mean(SD) or %	Imputed dataset Mean(SD) or %
Age	72.4(7.3)	72.5(7.3)
Sex	47.5% female	48.2% female
Education	16.3(2.6)	16.2(2.6)
Race	92.6% White	92.0% White
Ethnicity	95.5% non-Hispanic	95.4% non-Hispanic
APOE ε4 status	43.9% ε4+	43.1% ε4+
Cognitive status	38.7% MCI	37.8% MCI
Plasma p-tau181	2.7(.6) pg/mL	2.7(.6) pg/mL
CSF p-tau181	3.1(.5) pg/mL	3.1(.5) pg/mL
Amyloid PET	40.4(44.0) centiloids	39.2(43.5) centiloids

predicted mean (i.e., z < -1). These criteria were used to balance sensitivity and specificity of diagnostic categorization. Any participants who did not meet criteria for MCI were categorized as CU. Of the 443 participants classified as MCI using the original ADNI criteria, 215 were instead classified as CU using the Jak/Bondi criteria employed in the current study.

2.5. Statistical analysis

Per prior studies (Janelidze et al., 2020a; Karikari et al., 2021; Thijssen et al., 2021), plasma and CSF p-tau181 values underwent log transformation to improve normality. Language scores, attention/executive function scores, CSF amyloid-beta 1-42, and amyloid PET centiloids were rescaled to positive values if necessary (using the formula: 1 + variable – minimum value for variable) and underwent Box-cox transformation to improve normality (language $\lambda = 2.5$; attention/executive function $\lambda = 4.3$; amyloid PET centiloid $\lambda = 0.2$) using the boxcox function in R (from the MASS package), which selects the lambda value with the greatest log-likelihood. Memory composite scores were normally distributed and therefore were not transformed.

Correlations were conducted between CSF p-tau181 and plasma p-tau181, as well as each p-tau181 marker with amyloid PET centiloid values and age. APOE ε4 carrier groups were compared on levels of CSF and plasma p-tau181 using ANOVAs and ANCOVAs adjusting for age and cognitive classification. Associations between CSF/plasma p-tau181 and all cognitive domains (i.e., memory, language, attention/executive function) were assessed using multiple linear regression adjusting for age, sex, education, cognitive classification, and APOE ε4 carrier status. The moderating effect of APOE ε4 carrier status on associations between CSF/plasma p-tau181 and all cognitive domains was assessed using multiple linear regression adjusting for age, sex, education, and cognitive classification; models included simple effects of CSF/plasma p-tau181 and APOE ε4 carrier status as well as an interaction term between these two predictors. Models were also examined with an additional covariate of amyloid PET centiloid values. Finally, sensitivity analyses assessed the three-way interaction between cognitive classification, APOE ε4 carrier status, and CSF/plasma p-tau181 on cognition.

3. Results

3.1. Sample characteristics

Sample characteristics are presented in Table 1 for the imputed dataset as well as for the incomplete dataset. Independent-samples t-tests and 2-proportion z-tests indicated that the dataset with imputed values for CSF p-tau181 did not differ from the incomplete dataset (i.e., missing values for CSF p-tau181) on any demographic or biomarker variables and therefore the imputed dataset was used in all subsequent analyses. The racial breakdown of the sample was as follows: 92.0% White, 4.1% Black/African American, 1.6% more than 1 race, 1.3% Asian, 0.3% American Indian or Alaskan Native, and 0.3% Native Hawaiian or Other Pacific Islander, and 0.4% unknown. The ethnicity breakdown of the sample was as follows: 95.5% non-Hispanic, 4.0% Hispanic, and 0.5% unknown. Median (IQR) of untransformed p-tau181 values were 15.91 (10.70 – 23.00) pg/mL for plasma and 23.00 (16.54 – 32.57) pg/mL for CSF. There was a significantly higher proportion of APOE ε4 carriers among participants with MCI (50.7%) relative to CU participants (31.7%; $X^2 = 67.24$, $p < 0.001$).

3.2. Association between CSF and plasma p-tau181

In the overall sample, there was a significant positive correlation between CSF and plasma p-tau181 ($r = .34$, 95% CI[.27,.40], $p < 0.001$). There was a significant moderating effect of cognitive classification (B = .11, 95% CI[.006,.21], $t = 2.07$, $p = 0.04$) such that this association was stronger in participants with MCI ($r = .36$, 95% CI[.25,.46], $p < 0.001$) relative to CU participants ($r = .28$, 95% CI[.19,.36], $p < 0.001$). The association between CSF and plasma p-tau181 remained after adjusting for amyloid PET (B = .12, *partial* $r = .19$, 95% CI[.12,.26], $p < 0.001$). Additionally, when amyloid PET was dichotomized into biomarker positive and negative groups, the association between CSF and plasma p-tau181 was significant in both positive ($r = .29$, 95% CI[.18,.39], $p < 0.001$) and negative ($r = .10$, 95% CI[.008,.20], $p = 0.03$) amyloid PET groups, albeit stronger for the positive group (see Fig. 1). Both CSF p-tau181 ($r = .52$, 95% CI[.47,.57], $p < 0.001$) and plasma p-tau181 ($r = .36$, 95% CI[.29,.42], $p < 0.001$) were significantly positively correlated with amyloid PET, with stronger associations observed for CSF p-tau181 relative to plasma p-tau181. Both p-tau181 markers had a positive association with age: CSF ($r = .16$, 95% CI[.09,.23], $p < 0.001$) and plasma ($r = .20$, 95% CI[.13,.27], $p < 0.001$).

3.3. APOE ε4 group differences in CSF and plasma p-tau181

APOE ε4 groups significantly differed in levels of CSF p-tau181 ($t = 8.46$, Cohen's d = .63, 95% CI[.48,.77], $p < 0.001$) with mean(sd) values of 2.97(0.43) pg/mL for the ε4- group and 3.26(0.48) pg/mL for the ε4+ group. APOE ε4 groups also significantly differed in levels of plasma p-tau181 ($t = 5.81$, Cohen's d = .43, 95% CI[.28,.58], $p < 0.001$) with mean(sd) values of 2.54(0.68) pg/mL for the ε4- group and 2.82(0.58) pg/mL for the ε4+ group. These differences remained after adjusting for age and cognitive classification (CSF $t = 8.51$, $p < 0.001$; plasma $t = 5.90$, $p < 0.001$). These differences also remained after adjusting for amyloid PET levels (CSF $t = 3.54$, $p < 0.001$; plasma $t = 2.36$, $p = 0.02$). These group differences are depicted in Fig. 2.

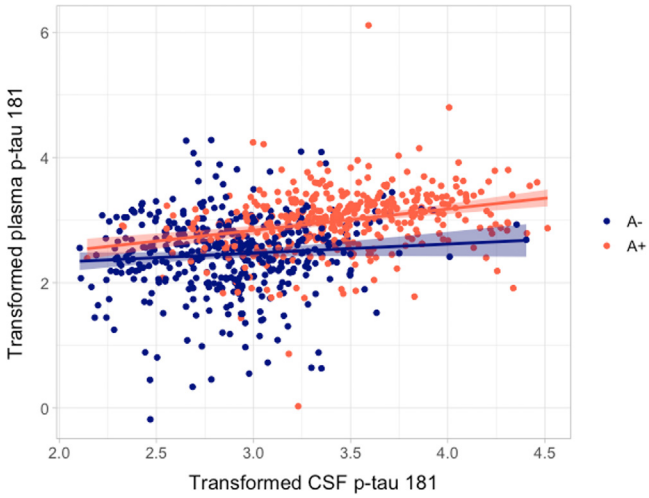

Fig. 1. Scatterplot depicting the association between CSF and plasma p-tau181 in individuals who are amyloid PET positive (red) and negative (navy). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

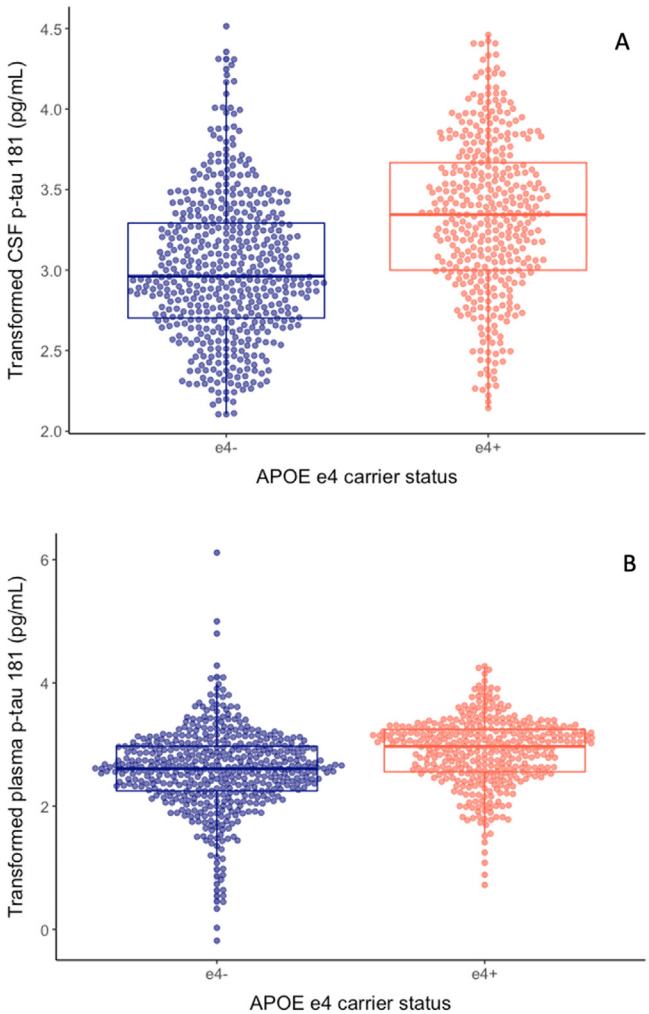

Fig. 2. Beeswarm plots depicting associations levels of CSF p-tau181 (A) and plasma p-tau181 (B) across APOE e4 carriers (+, red) and non-carriers (-, navy). APOE = apolipoprotein E. CSF, cerebrospinal fluid. P-tau, phosphorylated tau. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.4. APOE ε4, CSF p-tau181, and cognition

Adjusting for age, sex, education, cognitive classification, and APOE status, CSF p-tau181 was strongly associated with memory (B = -.38, 95% CI[-.52,-.24], t = -5.34, $p < 0.001$) such that as CSF p-tau181 increased, memory performance decreased. There was a significant moderating effect of cognitive classification (B = -.50, 95% CI[-.77,-.24], t = -3.74, $p < 0.001$) such that the association was driven by participants with MCI (B = -.72, 95% CI[-.97,-.48], t = -5.82, $p < 0.001$) compared to CU participants (B = -.11, 95% CI[-.27,.06], t = -1.27 p = 0.21). Adjusting additionally for amyloid PET, the association between CSF p-tau181 and memory remained statistically significant (B = -.35, 95% CI[-.50,-.19], t = -4.44, $p <$ 0.001). Adjusting for the same variables, there was not a significant association between CSF p-tau181 and language (B = -10.7, 95% CI[-29.88,8.49], t = -1.09, p = 0.27) or attention/executive function (B = 5.14, 95% CI[-123.78,134.06], t = 0.08, p = 0.94).

When examining the moderating effect of APOE status on associations between CSF p-tau181 and cognition, there was a significant effect for memory (B = -.28, 95% CI[-.56,-.01], t = =2.03, p = 0.04). Examination of the association between CSF p-tau181 and memory separately within each APOE group indicated that the effect of CSF p-tau181 on memory was stronger among ε4 carriers (ε4+ B = -.55, $p < 0.001$) relative to non-carriers (ε4- B = -.22, p = 0.02). There was no significant moderating effect of cognitive classification on the interaction between APOE status and CSF p-tau181 on memory (B = -.54, 95% CI[-1.11,.02], t = -1.90, p = 0.06). Adjusting for amyloid PET, there were similar significant effects (B = -.28, 95% CI[-.55,-.004], t = -1.99, p = 0.047). Adjusting for these same factors, there was no significant moderating effect of APOE status for language (B = -12.30, 95% CI[-30.57,19.99], t = -0.65, p = 0.52) or attention/executive function (B = -72.82, 95% CI[-133.12,207.75], t = -0.57, p = 0.57). See Fig. 3.

3.5. APOE ε4, plasma p-tau181, and cognition

Adjusting for age, sex, education, cognitive classification, and APOE status, plasma p-tau181 was associated with memory (B = -.11, 95% CI[-.21,-.01], t = -2.19, p = 0.03) such that as plasma p-tau181 increased, memory performance decreased. There was a significant moderating effect of cognitive classification (B = -.35, 95% CI[-.55,-.15], t = -3.44, $p < 0.001$) such that the association was driven by participants with MCI (B = -.42, 95% CI[-.62,-.22], t = -4.20, $p < 0.001$) compared to CU participants (B = .05, 95% CI[-.06,.15], t = 0.90 p = 0. 37). The effect of plasma p-tau181 on memory was no longer statistically significant after additionally adjusting for amyloid PET (B = -.08, 95% CI[-.18,.03], t = -1.46, p = 0.14). Adjusting for the same factors, there was not a significant association between plasma p-tau181 and language (B = -.06, 95% CI[-.17,.04], t = =1.17, p = 0.24) or attention/executive function (B = -.03, 95% CI[-.15,.10], t = -.40, p = 0.69).

When examining the moderating effect of APOE status on associations between plasma p-tau181 and cognition, there was a significant interaction effect for language (B = -32.94, 95% CI[-60.69,-5.18], t = -2.33, p = .02; see Fig. 3) and attention/executive function (B = 213.47, 95% CI[-401.03,-25.91], t = -2.24, p = 0.03; see Fig. 3). Examination of the association between plasma p-tau181 and memory separately within each APOE group indicated that the effect of plasma p-tau181 on language was only significant among ε4 carriers (ε4+ B = -25.44, p = 0.04; ε4- B = 5.17, p = 0.52), and the effect of plasma p-tau181 on attention/executive function was not significant in either group when stratified but quantitatively stronger among ε4 carriers (ε4+ B = -142.51, p = 0.09; ε4- B = 58.35, p = 0.29). There was no significant moderating effect of cognitive classification on the interaction between APOE status and

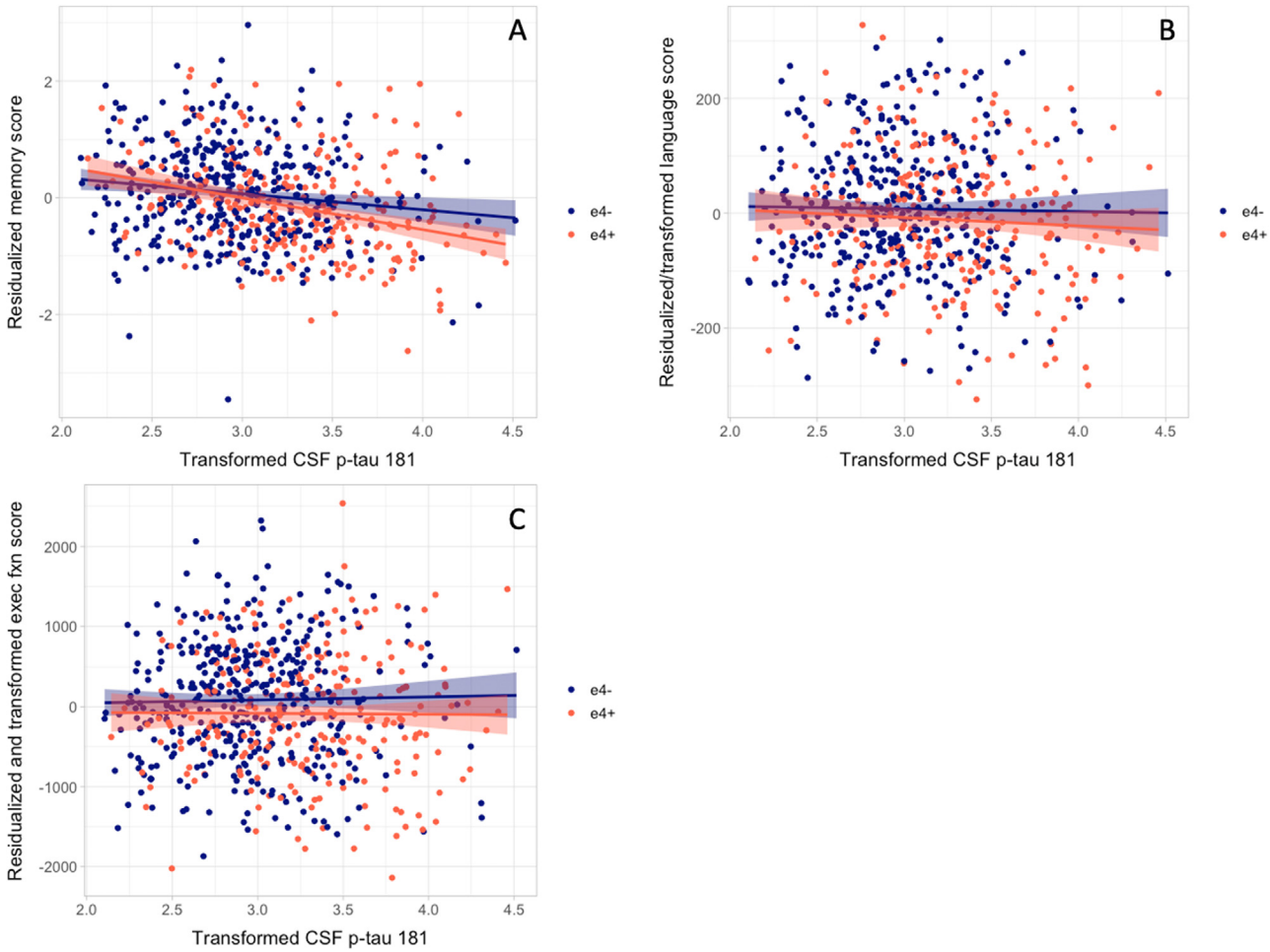

Fig. 3. Scatterplots depicting associations between CSF p-tau181 and memory (A), language (B), and attention/executive function (C, exec fxn) performance across APOE e4 carriers (+, red) and non-carriers (-, blue). Language and attention/executive function scores have been Box-cox transformed and all cognitive variables have been residualized for age, sex, education, and cognitive classification. APOE, apolipoprotein E. CSF, cerebrospinal fluid. P-tau, phosphorylated tau. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

plasma p-tau181 for language (B = -39.46, 95% CI[-98.93,20.01], t = -1.30, p = 0.19) or attention/executive function (B = -222.27, 95% CI[-627.36,182.82], t = -1.08, p = 0.28). Adjusting for amyloid PET, there were similar significant effects for language (B = -31.09, 95% CI[-59.02,-3.16], t = -2.19, p = 0.03) and attention/executive function (B = -198.79, 95% CI[-387.51,-10.08], t = -2.07, p = 0.04). Adjusting for the same factors, there was not a significant moderating effect of APOE status for memory (B = -.15, 95% CI[-.36,.05], t = -1.47, p = 0.14). See Fig. 4.

4. Discussion

Results indicated that CSF and plasma p-tau181 were associated with one another, as previously demonstrated (Janelidze et al., 2020b). However, in contrast to other previous research, our findings indicated that this association was significant even among amyloid PET negative participants, albeit the effect in this group was smaller relative to amyloid PET positive participants. APOE ε4 carriers had higher levels of p-tau181 measured using both CSF and plasma methods. When examining associations between p-tau181 and cognition as well as the moderating effect of APOE ε4 carrier status, interesting patterns emerged for CSF and plasma. CSF p-tau181 was associated only with memory performance, particularly among participants with MCI, and not with language or attention/executive function. Similarly, APOE ε4 carrier status moderated only this association with memory such that ε4 carriers showed a stronger negative association. Although plasma p-tau181 was also associated with memory performance (particularly among participants with MCI) and not with language or attention/executive function, the moderating effect of APOE ε4 carrier status on plasma p-tau181 was observed only for language and attention/executive function and not for memory. For language, APOE ε4 carriers demonstrated a negative association between plasma p-tau181 and cognition that was not present in non-carriers; for attention/executive function, the association between plasma p-tau and cognition was not significant in either APOE group, likely due to reduced statistical power, but was stronger among ε4 carriers. Notably, these effects were generally similar with and without adjustment for amyloid PET centiloids with the exception of the association between plasma p-tau181 and memory.

Neither CSF nor plasma p-tau181 was associated with language or attention/executive function across the sample. This result contrasts with our previous work using tau PET imaging, which demonstrated associations between tau PET and all 3 cognitive domains even after adjusting for amyloid PET (Weigand et al., 2021). Research has indicated that plasma and CSF changes to p-tau181 occur years prior to changes detected via tau PET imaging (Boerwinkle et al., 2021; Cogswell et al., 2022; Moscoso et al., 2022), which may explain the lack of associations of these biofluid markers with language and attention/executive function given that

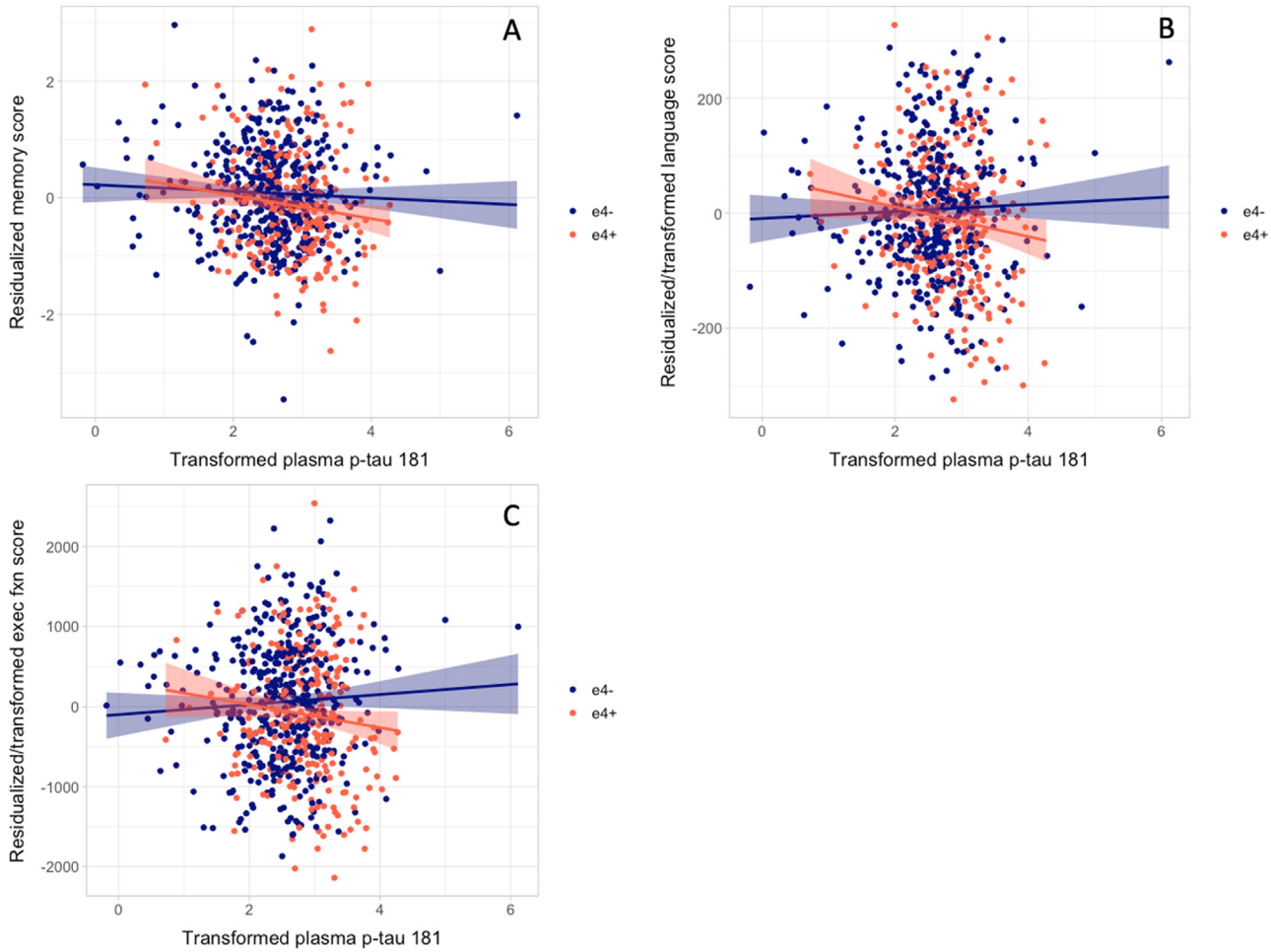

Fig. 4. Scatterplots depicting associations between plasma p-tau181 and memory (A), language (B), and attention/executive function (C, exec fxn) performance across APOE e4 carriers (+, red) and non-carriers (-, blue). Language and attention/executive function scores have been Box-cox transformed and all cognitive variables have been residualized for age, sex, education, and cognitive classification. APOE, apolipoprotein E. P-tau, phosphorylated tau. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

these cognitive abilities are typically affected in later AD-related clinical stages (Bondi et al., 2017). However, we additionally examined the moderating effect of APOE ε4 carrier status given that individuals with AD-genetic risk may show unique patterns of susceptibility within and beyond the memory domain.

In our prior PET study, APOE ε4 carrier status moderated only the association between tau PET and memory performance, but not language or attention/executive function, such that ε4 carriers demonstrated a stronger association between tau PET and memory (Weigand et al., 2021). A similar finding was observed in the current study when using CSF measures of p-tau181, such that APOE ε4 carrier status only moderated the association between CSF p-tau181 and memory. In contrast, using plasma measures of p-tau181, APOE ε4 carrier status moderated the association of plasma p-tau181 with language and attention/executive function, but *not* with memory. Notably, our prior PET study examined regional tau associations with cognition using a medial temporal lobe composite, which may have explained the specificity of APOE and memory interactions in that study. In contrast, the use of biofluid measures is limited in terms of measurement of regional tau accumulation, which is an important consideration when deciding what biomarker modality to use based on the research question under consideration.

This moderating effect of APOE status for plasma p-tau181 on non-memory domains may reflect increased sensitivity of this particular marker to "non-traditional" patterns of AD brain and cognitive changes in ε4 carriers. For example, the behavioral variant of AD exhibits primarily executive dysfunction with less of an effect on memory than observed in typical AD and greater tau PET deposition in frontal cortex (Ossenkoppele et al., 2022; Suárez-Calvet et al., 2021). It is possible that plasma p-tau181 reflects less regionally specific (i.e. medial temporal) pathologic changes to tau in ε4 carriers, instead capturing more widespread cortical tau pathology. This hypothesis stands in contrast to other findings that have demonstrated an association between plasma p-tau181 and hippocampal dysfunction only in ε4 carriers (Salami et al., 2022). Notably, that study did not examine structure or function of other brain regions, and future research examining more widespread brain changes may elucidate additional insight into the potential interactions between APOE ε4 status and plasma p-tau181 across the heterogeneous typical and atypical AD pathologic and clinical spectrum.

Different properties of plasma p-tau181 relative to CSF and PET may also explain the observed APOE ε4 interactions on non-memory measures using plasma p-tau181. Specifically, the dynamic range of these different biofluid markers or the possible impact of peripheral factors on plasma, but not CSF or PET, may be of relevance to the current findings. For example, the movement of pathologic tau substrates from the central nervous system to plasma is influenced by vascular factors

(Zetterberg & Burnham, 2019). Vascular pathology such as increased blood-brain barrier permeability may result in a greater efflux of pathologic tau into the blood compartment (Fossati et al., 2019), increasing the levels of p-tau181 in plasma; indeed plasma p-tau181 has been associated with brain white matter hyperintensity volume (Mielke et al., 2021; Wang et al;, 2021), an indicator of cerebrovascular risk, whereas CSF p-tau181 may not be associated with this marker of vascular pathology (Soldan et al., 2020; van Waalwijk et al., 2021). Individuals with such vascular pathology often exhibit cognitive changes primarily in attention and executive function (Ganguli et al., 2014; Villeneuve et al., 2009); thus, exacerbation of this vascular risk in ε4 carriers (Bangen et al., 2013; Montagne et al., 2020) may explain the observed association between plasma p-tau181 (but not CSF or PET) with attention/executive function in this ε4 positive group.

These potential explanations for the observed effects are speculatory and future research is needed to replicate these findings. Specifically, research in community-based, representative samples is needed given demonstrated differences in biomarker profiles in minoritized racial/ethnic groups (Barnes et al., 2015); our sample was 92% White with an average 16 years of education, a highly homogenous group to which our findings may be specific. Notably, however, at least one study has indicated the utility of plasma p-tau181 across racial/ethnic groups (Brickman et al., 2021; Brickman et al., 2022). However, the high mean level of education in this sample also introduces the complex notion of cognitive reserve and a community-based sample with a broader range of educational attainment and educational quality may yield different findings. In this ADNI sample, there may be a somewhat restricted range of p-tau181 values relative to community-based samples given evidence from a prior study which demonstrated that there was less age-related change in CSF AD biomarkers among individuals with higher cognitive reserve (Almeida et al., 2015). Similarly, there is likely a broader range of cognitive scores in a community-based sample, particularly in non-memory domains, which may allow for the emergence of associations between CSF p-tau181 and language or attention/executive function that were not observed in the current study. Research on the effects of cognitive reserve on cognitive outcomes as a function of APOE status is mixed, with some studies demonstrating a protective effect of cognitive reserve in APOE ε4 carriers (López et al., 2017) and others indicating that this protective effect is only present among ε2 carriers (Pettigrew et al., 2013). It is possible that the moderating effects of APOE status observed in the current study were somewhat attenuated by the high mean educational attainment of the sample, and the differential effects of CSF/plasma p-tau181 and cognition between ε4 carriers and non-carriers may be even more pronounced in a community-based sample, although future research is needed to investigate this.

Given that the current study was limited to p-tau181, future studies examining other pathologic tau biofluid markers such as p-tau 217 or p-tau 231 may yield different findings (Suárez-Calvet et al., 2020). Additionally, our study was limited to the examination of cross-sectional biomarker and neuropsychological measures and yielded some relatively weak effects, but investigation of longitudinal changes could expand our knowledge of the temporal dynamics of tau pathology and its interaction with APOE ε4. Finally, it should be noted that although qualitatively different patterns were observed in our sample for CSF and plasma p-tau181 associations with cognition and APOE status, our results do not explicitly address whether these patterns statistically differ.

Increasing use of biofluid markers of tau highlights their utility and availability in the investigation and characterization of AD pathologic changes. Importantly, biofluid markers (particularly plasma) provide cost-effective and scalable measures of AD pathology relative to neuroimaging metrics, and thus may be more easily implemented in clinical trials and, eventually, in diagnostic and prognostic decision-making in clinical settings. The current study demonstrates that biofluid markers of tau pathology are associated with memory performance in older adults without dementia, and that plasma p-tau181 in particular may be a sensitive marker of non-memory performance in individuals at genetic risk for AD. CSF and plasma p-tau181 levels, alone or in combination with cognitive measures (Palmqvist et al., 2021; Thomas et al., 2021), may serve as a useful criteria for screening into clinical trials to identify individuals at highest risk for progression to dementia who may benefit most from early disease-modifying treatment, particularly among APOE ε4 carriers. Continued investigation of tau biomarkers and their interaction with APOE ε4 genotype is needed to better understand mechanisms by which tau pathology contributes to cognitive and clinical function in the AD continuum.

On behalf of myself and our co-authors, I attest that all authors have contributed to the work and agree with the presented findings, and that the work is based on original research that has not been previously published or submitted for concurrent consideration of publication elsewhere. A poster based on this manuscript was presented at the 2022 Alzheimer's Association International Conference. As senior author, I take full responsibility for the data, the analyses and interpretation, and the conduct of the research. All co-authors agree to the submission of this manuscript.

Declaration of Competing Interest

Dr Galasko is a consultant for Biogen, Esai, GE Healthcare, Fujirebio, Generian and Amprion, and serves on a DSMB for Cognition Therapeutics. Dr. Bondi receives royalties from Oxford University Press. All other study authors report no conflicts of interest.

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