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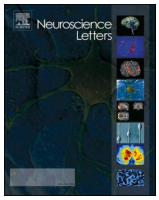

Research article

APOE ε4 status and plasma p-tau181 interact to influence cognitive performance among non-demented older adults

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A B S T R A C T

Objective: In this study, we aimed to investigate the relationships among plasma p-tau181, APOE ε4, and cognitive performance in non-demented elderly individuals.
Methods: We used individuals (n = 630) with cognitive normal (CN, n = 182) and mild cognitive impairment (MCI, n = 448). Multiple linear regression models were performed to test the effects of APOE ε4 × plasma p-tau181 interaction on MMSE, CDR-SOB, ADAS-cog13, and RAVLT immediate recall. All models adjusted for age, sex, and education.
Results: In total, our study comprised 630 samples including 364 APOE ε4 non-carriers and 266 APOE ε4 carriers. In APOE ε4 carriers, plasma p-tau181 was significantly associated with MMSE (B = −0.04, $p = 0.003$), ADAS-Cog13 (B [unstandardized coefficient] = 0.21, $p < 0.001$), CDR-SB (B = 0.02, $p = 0.003$) and RAVLT immediate recall ((B = −0.17, $p = 0.035$). After correcting for Aβ status and diagnosis, the interaction between APOE ε4 and plasma p-tau181 was significant or marginally significant associations for RAVLT immediate recall ($p = 0.076$), MMSE ($p = 0.011$), CDR ($p = 0.008$), and ADAS-Cog13 ($p < 0.001$).
Conclusions: Our findings suggested that plasma p-tau181 levels predicted cognitive performance among non-demented older adults, but only in the APOE ε4 carriers.

1. Introduction

Amyloid β (Aβ) and tau pathology are the defining neuropathological features of Alzheimer's disease (AD) [5,6]. Traditionally, the reliable measurement of Aβ and tau pathology have been restricted to histopathological examination post-mortem, positron emission tomography (PET) and cerebrospinal fluid (CSF) markers in vivo [1,5,24]. Despite being highly accurate and specific for AD diagnosis, both neuroimaging and CSF biomarkers are limited by high costs and invasiveness [14]. Blood-based biomarkers may hold promise to address these challenges. The detection of tau phosphorylated at threonine181 (p-tau181) in blood has recently emerged as a simple, accessible, relatively non-invasive, and cost-effective tool for screening and diagnosis of AD [11,12]. Prior studies have found that plasma p-tau181 accurately predicts in-vivo tau tangles and β-amyloid as assessed with PET [11] and amyloid plasma assays [17,22]. Moreover, the previous report has shown that blood p-tau181 increases along the AD dementia continuum in cognitively unimpaired and MCI individuals [8]. More recently, increased blood p-tau181 was also associated with higher rates of clinical progression to dementia and greater memory decline among non-demented elderly individuals [29].

APOE ε4 risk alleles play an important role in the metabolism of CSF Aβ42, total tau, and p-tau [2,4,26]. APOE ε4 and β-amyloid also interact to influence the decline of cognition [15]. Compared to APOE ε4 non-carriers, AD and MCI participants with APOE ε4 have greater hippocampal area atrophy, particularly in the CA1 subfield [15,21].

In this study, we aimed to study the relationships among plasma p-tau181, APOE-ε4, and cognitive performance in non-demented elderly individuals. Given the importance of APOE ε4 to AD neuropathology [2,4,26], we hypothesized that the association of plasma p-tau181 with cognitive performance may vary by APOE 4 status.

2. Methods

2.1. Participants and data

Cross-sectional data were downloaded on 16 April 2021 from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Recruitment procedures have been described [18] (https://www.loni.usc.edu/ADNI), and eligibility criteria of ADNI are

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[1] 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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showed at adni.loni.usc.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf.

Our analyses were restricted to non-demented subjects who met the criteria for normal cognition (CN) and mild cognitive impairment (MCI) and had baseline plasma p-tua181 samples and APOE ε4 data. A total of 630 individuals were analyzed, including 182 with CN and 448 with MCI. Our inclusion and exclusion criteria were showed in Fig. 1. ADNI CN subjects had a Clinical Dementia Rating (CDR) of 0, and Mini-Mental State Examination (MMSE) ≥ 24 at the baseline. ADNI MCI subjects had a CDR of 0.5, Mini-Mental State Examination (MMSE) ≥ 24, and the absence of dementia. For more details regarding the ADNI diagnostic criteria, refer to www.adni-info.org [18].

The submitted data were available at www.adni.loni.usc.edu/data-samples/access-data/.

2.2. APOE ε4 genotyping

APOE ε4 data of this analysis were extracted from the ADNI database. Further procedures have been reported [18] (http://adni.loni.usc.edu/methods/documents/). Participants with at least one APOE 4 allele were classified as APOE ε4 carrier or APOE ε4+, whereas no APOE ε4 allele defined participants as APOE ε4 noncarriers or APOE ε4−.

2.3. Plasma p-tau181 levels

Plasma samples were collected, processed and stored according to the ADNI document [10]. The plasma p-tau181 was measured using the Single Molecule array technique on the Simoa HD-1 (Quanterix) as shown previously [11]. We obtained the plasma p-tau181 data from the ADNI database in April 2021.

2.4. Neuropsychological assessments

Neuropsychological tests included the following: Mini-Mental State Examination (MMSE) [3], Alzheimer's Disease Assessment Scale-cognitive 13 [7,13], Clinical Dementia Rating (CDR-SOB) [16], and Rey Auditory Verbal Learning Test (RAVLT) immediate recall [23].

2.5. Statistical analyses

Sample characteristics (demographic and clinical outcomes) and variables of interests were compared between APOE ε4 risk alleles in non-demented group using the *t* test for continuous variables and the chi-square test for categorical variables. To examine the cross-section relationship between plasma p-tau181 and cognitive performance, the correlation analysis was constructed in APOE ε4 carriers and non-carriers. To investigate the contributions of APOE ε4 and plasma p-tau181 to cognitive performance, we implemented multiple regression models for each cognitive outcome adjusting for age, education, and sex. To further test the interaction term between APOE ε4 and plasma p-tau181, sensitivity analysis was performed correcting for baseline age, education, sex, diagnosis, and amyloid status. The level of statistical significance is set at $p < 0.05$. The level of marginally significant is set at $p < 0.1$. All the statistical methods were performed in R version 4.0.4.

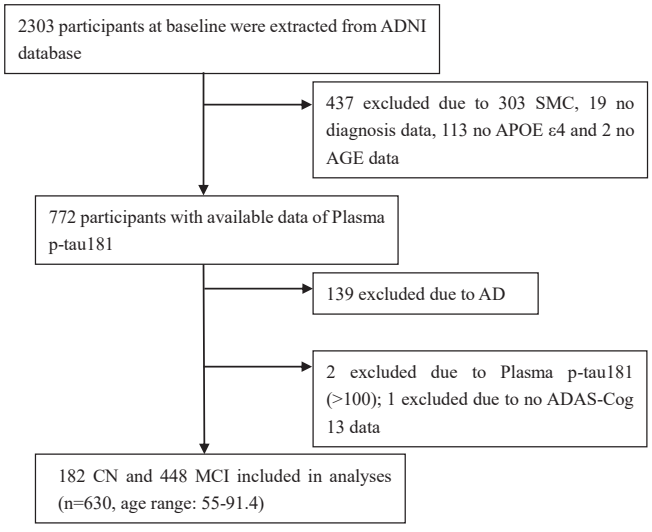

Fig. 1. Flowchart. Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; APOE = apolipoprotein E; ADAS-Cog 13 = Alzheimer's Disease Assessment Scale-cognitive 13.

3. Results

3.1. Sample characteristics

In total, our study comprised 630 samples including 364 APOE ε4 non-carriers and 266 APOE ε4 carriers (Fig. 1 and Table 1). Overall, APOE ε4 non-carriers were older ($p = 0.004$) and less likely to be MCI ($p < 0.001$) compared to 266 APOE ε4 carriers. There were no significant differences in education and gender ($p > 0.05$). As shown in Table 1, plasma p-tau181 levels were significantly higher in the individuals with APOE ε4 alleles ($p < 0.001$). As expected, there were significant differences in MMSE, CDR-SOB, ADAS-cog13 and RAVLT immediate recall across the two groups ($p < 0.001$).

3.2. Linear regression results

The correlation of plasma p-tau181 levels with cognition would vary by APOE ε4 carrier status was supported by the result of a significant plasma p-tau181 × APOE ε4 status interaction for MMSE ($B = -0.04$, $p = 0.003$), ADAS-Cog13 (B [unstandardized coefficient] = 0.21, $p < 0.001$), CDR-SB ($B = 0.02$, $p = 0.003$) and RAVLT immediate recall ($B = -0.17$, $p = 0.035$; Table 2 and Fig. 2). All models adjusted for age, sex, and education. Moreover, we did a sensitivity analysis to examine the influence of Aβ and diagnosis on the APOE ε4 × plasma p-tau181 interaction. After correcting for Aβ status and diagnosis, the interaction between APOE ε4 and plasma p-tau181 was significant or marginally significant associations for RAVLT immediate recall ($p = 0.076$), MMSE ($p = 0.011$), CDR ($p = 0.008$), and ADAS-Cog13 ($p < 0.001$).

Table 1
Demographic and Clinical Characteristics of the Non-demented Individuals (n = 630).

Characteristics	APOE ε4 noncarriers (n = 364)	APOE ε4 carriers (n = 266)	*p* Value
Age[a], y, range	72.8 ± 7.2	71.1 ± 7.2	0.004[b]
Education[a], y, range	16.4 ± 2.5	16.1 ± 2.7	0.19[b]
Sex (female), n (%)	175 (48.1)	124 (46.6)	0.72[c]
MCI, n (%)	233 (64)	215 (80.8)	<0.001[c]
MMSE[a], scores	28.6 ± 1.5	28 ± 1.8	<0.001[b]
RAVLT immediate recall[a]	41.4 ± 11.6	37.4 ± 11.2	<0.001[b]
CDR-SB[a]	0.9 ± 0.9	1.3 ± 1.0	<0.001[b]
ADAS-Cog13[a]	11.9 ± 6.0	14.9 ± 7.2	<0.001[b]
Plasma p-tau181[a], pg/mL	15.1 ± 10.1	20 ± 11.1	<0.001[b]

Abbreviations: APOE = apolipoprotein E; MCI = Mild cognitive impairment; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; CDR-SB = Clinical Dementia Rating Sum of Boxes; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive 13; p-tau181 = tau phosphorylated at threonine 181, SD = standard deviation.

[a] mean ± SD.

[b] *t*-test for continuous variables.

[c] $\chi 2$ test for categorical variables.

Table 2
Results of multivariable linear regression analyses modeling the independent and interactive effects of APOE4 status and Plasma p-tau181 on cognitive performance.

Sample/ outcome	Multivariable linear regression models					
	Model 1: No interactions in model				Model 2: Interaction included in model, APOE ε4 status × Plasma p-tau181	
	APOE ε4 (non-carriers vs carriers)		Plasma p-tau181			
	B (SE)	*p* Value	B (SE)	*p* Value	B (SE)	*p* Value
RAVLT immediate recall	−3.55 (0.87)	<0.001	−0.17 (0.04)	<0.001	−0.17 (0.08)	0.035[a]
MMSE	−0.57 (0.13)	<0.001	−0.01 (0.006)	0.05	−0.04 (0.01)	0.003[a]
ADAS-Cog13	2.77 (0.51)	<0.001	0.10 (0.02)	<0.001	0.21 (0.05)	<0.001[a]
CDR-SOB	0.34 (0.08)	<0.001	0.01 (0.004)	0.002	0.02 (0.007)	0.003[a]

Abbreviations: APOE = apolipoprotein E; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; CDR-SB = Clinical Dementia Rating Sum of Boxes; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive 13; p-tau181 = tau phosphorylated at threonine 181; B = unstandardized regression coefficient.
All analyses were adjusted for age, education, and sex.
[a] Significant.

3.3. Correlations of plasma p-tau181 with MMSE, ADAS-Cog13, CDR-SOB and RAVLT immediate recall

Higher plasma p-tau181 was associated with poorer RAVLT immediate recall in both the APOE ε4 non-carriers (r = −0.162, $p = 0.002$) and APOE ε4 carriers (r = −0.320, $p < 0.001$; Table 3). We further investigated the relationship between plasma p-tau181 and cognitive performance. Among non-demented individuals with APOE ε4 risk allele, an inverse relationship between plasma p-tau181 and MMSE was observed (r = −0.223, $p < 0.001$). In addition, strong positive correlations between plasma p-tau181 and CDR scores, and ADAS-cog13 were found (r = 0.236, $p < 0.001$; r = 0.375, $p < 0.001$, respectively). In contrast, no significant correlations were showed between plasma p-tau181 and other cognitive performances (MMSE, CDR and ADAS-cog13) in the APOE ε4 non-carriers ($p > 0.05$).

4. Discussion

In the present study, we investigated the effects of plasma p-tau181, APOE ε4 status, and their interaction on cognitive performance in a non-

Table 3
Correlations between Plasma p-tau181 levels and cognitive tests.

Groups	APOE ε4 non-carriers (n = 364)		APOE ε4 carriers (n = 266)	
	r	*p*	r	*p*
MMSE	−0.028	0.590	−0.223	<0.001
RAVLT immediate recall	−0.162	0.002	−0.320	<0.001
CDR-SB	0.006	0.911	0.236	<0.001
ADAS-Cog13	0.070	0.180	0.375	<0.001

Abbreviations: APOE = apolipoprotein E; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; CDR-SB = Clinical Dementia Rating Sum of Boxes; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive 13; p-tau181 = tau phosphorylated at threonine 181.
Pearson's correlation for analyses.

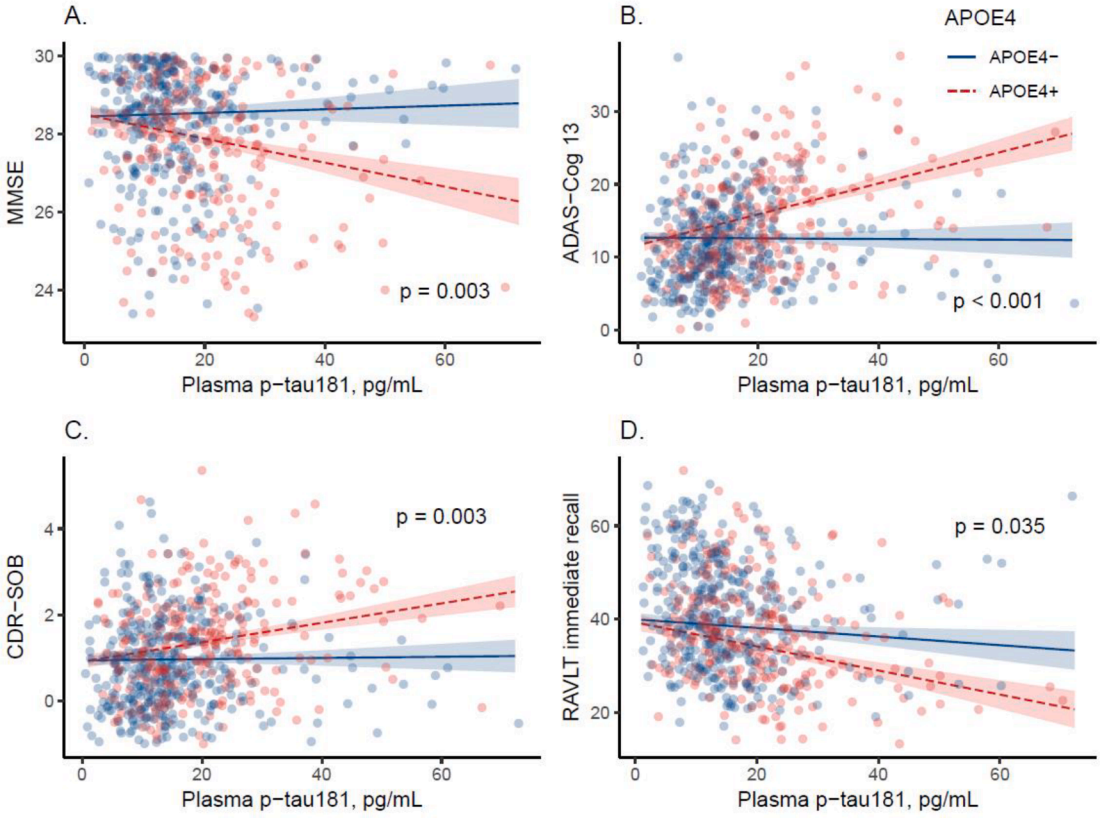

Fig. 2. Relationship between Plasma p-tau181 and neuropsychological outcomes in APOE ε4 non-carriers and carriers. For changes in MMSE score (A) and RAVLT immediate recall score (D), lower scores represent cognitive decline and a decrease in memory. For changes in ADAS-Cog 13 (B) and CDR-SOB (C), higher scores represent cognitive impairment and an increase in dementia severity.

demented sample. We found that increased plasma p-tau181 were more strongly related to worse cognitive manifestations among individuals with APOE ε4, whereas for APOE ε4 non-carriers the correlations in plasma p-tau181 and cognition were absent except memory ($p = 0.002$). In addition, the interaction between blood p-tau181 levels and APOE ε4 status on cognition were significant in non-demented older adults. Taken together, we suggested that the results were driven by interaction between plasma p-tau181 and APOE ε4 in non-demented elderly adults, where plasma p-tau181 levels predicted cognition, but not in APOE ε4 non-carriers.

Cognitive decline is associated with decreases in one's daily function, quality of life, and increased cost of living [9,19]. Recent studies showed that blood p-tau181 was related to MMSE scores [11] and other cognitive domains [28]. A recent longitudinal multicenter study presented evidence for the potential clinical utility of plasma p-tau181 [27]. Consistent with the broader evidence [11,27,28], we found that higher blood p-tau181 levels were related to poor cognition. Here, we observed that APOE ε4 non-carriers had no significant relationship between plasma p-tau181 and cognitive performance (MMSE, CDR-SOB and ADAS-cog13). We further expanded on those studies by revealing that the correlation between blood p-tau181 and cognition were APOE ε4 dependent among non-demented older individuals. It has been suggested that the associations between blood biomarkers of p-tau181 and cognitive function may diminish without APOE ε4 risk alleles, whereas previous studies only showed that plasma p-tau181 may keep rising along with the declines of cognitive performance [27,28].

Blood biomarkers have been expected as a better predictor of AD and Aβ PET compared with CSF biomarkers. The APOE ε4 has been reported as the strongest genetic risk factor for sporadic AD. Furthermore, APOE ε4 and its isoforms are also significantly involved in Aβ and tau pathologies [25]. A recent study reported the effects of APOE ε4 and higher plasma p-tau181 on preclinical AD and hippocampal function [20].

The changes of plasma p-tau181 levels in association with increased local hippocampal connectivity and reduction of hippocampus encoding-related activity might be APOE ε4 status mediated [20]. In this study, we highlight the interactive effects of APOE ε4 status and plasma p-tau levels, and we predict that these modifications might impact cognitive performance.

There are several study limitations in this study. The first limitation is that the cross-sectional study may be insufficient to fully capture interactive effects of plasma p-tau181 and APOE ε4 status on cognitive impairment. The possibility of the lack of an effect of plasma p-tau181 by APOE ε4 status interaction on longitudinal cognition decline in non-demented individuals might be due to a cross-sectional sample that cannot be ruled out. Longitudinal studies are needed to solidify our findings that APOE ε4 status may vary the association between plasma p-tau181 and cognition in future study. Secondly, investigations of apolipoprotein E (APOE) are meaningful to yielding insights into the differential associations of APOE-ε2/3/4 alleles with cognitive performance. Although the sample size of this study was large for a multicenter study, the number of subjects with APOE ε2 was still limited among APOE ε4 noncarriers, which may have lowered the statistical power to detect more subtle associations with cognitive performance. Therefore, more analyses based on specific data with APOE alleles need to be performed.

In conclusion, our findings showed that plasma p-tau181 levels predicted cognitive performance among non-demented older adults, but only in the APOE ε4 carriers.

CRediT authorship contribution statement

Shanshan Wang: Conceptualization, Methodology, Software, Writing – original draft. **Shaofa Ke:** Visualization, Investigation. **Suzhi Liu:** Writing – original draft. **En Wang:** Validation. **Tengwei Pan:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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