Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease

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Key Points

Question: Do plasma levels of tau phosphorylated at threonine 217 (p-tau217) predict accumulation of pathology in the brain and cognitive performance in individuals with autosomal dominant Alzheimer's disease?

Findings: In this cohort study of 24 presenilin-1 E280A carriers and 20 non-carriers from the same kindred, plasma p-tau217 was elevated in cognitively unimpaired carriers as compared to non-carriers. Higher plasma p-tau217 was associated with greater subsequent cortical amyloid burden and regional tau pathology measured via positron emission tomography, along with worse memory performance.

Meaning: Baseline levels of plasma p-tau217 may predict subsequent pathology burden and memory performance in autosomal dominant Alzheimer's disease.

Abstract

Introduction: Plasma-measured tau phosphorylated at threonine 217 (p-tau217) is a potential non-invasive biomarker of Alzheimer's disease (AD). We investigated whether plasma p-tau217 predicts subsequent cognition and positron emission tomography (PET) markers of pathology in autosomal dominant AD.

Methods: We analyzed baseline levels of plasma p-tau217 and its associations with amyloid PET, tau PET, and word list delayed recall measured 7.61 years later in non-demented age- and education-matched presenilin-1 E280A carriers (n = 24) and non-carrier (n = 20) family members.

Results: Carriers had higher plasma p-tau217 levels than non-carriers. Baseline plasma p-tau217 was associated with subsequent amyloid and tau PET pathology levels and cognitive function.

Discussion: Our findings suggest that plasma p-tau217 predicts subsequent brain pathological burden and memory performance in presenilin-1 E280A carriers. These results provide support for plasma p-tau217 as a minimally invasive diagnostic and prognostic biomarker for AD, with potential utility in clinical practice and trials.

Highlights: Non-demented presenilin-1 E280A carriers have higher plasma tau phosphorylated at threonine 217 (p-tau217) than do age-matched non-carriers. Higher baseline p-tau217 is associated with greater future amyloid positron emission tomography (PET) pathology burden. Higher baseline p-tau217 is associated with greater future tau PET pathology burden. Higher baseline p-tau217 is associated with worse future memory performance.

Keywords: autosomal dominant Alzheimer's disease; blood biomarkers; dementia; presenilin-1; tau pathology.

Introduction

In vivo imaging of tau neurofibrillary tangle accumulation via positron emission tomography (PET) has improved the study, diagnosis, and monitoring of early Alzheimer's disease (AD)[1]. Measuring tau via cerebrospinal fluid (CSF) samples has similarly shown utility as an early and specific measure of AD pathology[2]. However, there is a critical need for sensitive, cost-effective, and minimally invasive biomarkers of AD. Plasma-based measures of phosphorylated tau (p-tau), which are less costly and invasive compared to PET or CSF, increase early in the disease process and reliably discriminate between AD and other neurodegenerative diseases[3]. Further research is needed to determine the utility of plasma p-tau as a preclinical biomarker.

Plasma-measured tau phosphorylated at site threonine 217 (p-tau217) has emerged as a particularly promising and specific AD biomarker[3–6]. Growing evidence shows elevated plasma p-tau217 across preclinical to clinical disease stages[5,7–9], particularly in adults with high β-amyloid (Aβ)[5,10–12]. Further, p-tau217 may have better diagnostic ability than other plasma biomarkers in early stages (e.g., p-tau181, neurofilament light, Aβ40, Aβ42)[5,13,14]. We previously showed in a kindred with autosomal dominant Alzheimer's disease (ADAD) due to a mutation on the presenilin-1 (*PSEN1*) gene that increased levels of plasma p-tau217 were able to distinguish carriers from age-matched non-carriers 20 years prior to their estimated age of symptom onset[15]. When directly compared to plasma neurofilament light, p-tau217 was more sensitive at discriminating the groups at earlier ages[15].

The association between tau measured through plasma and PET is important to characterize, as tau-PET remains the gold standard for *in vivo* quantification of tau pathology for research and clinical purposes. Plasma p-tau217 is correlated with concurrent tau-PET in individuals with high Aβ, mild cognitive impairment, and AD[5,15–17]. Notably, a recent study found increased plasma p-tau217 in cognitively unimpaired individuals with positive Aβ-PET imaging and negative tau-PET, suggesting that plasma p-tau217 levels become abnormal before accumulation is detectable via tau-PET[15].

Less is known, however, about the association between plasma p-tau217 and subsequent tau-PET accumulation. In sporadic AD (e.g., older adults with high Aβ), one study reported an association between plasma p-tau217 and increasing tau-PET in the entorhinal cortex on average 1.6 years later[15]. A second study, similarly examining measurements one to two years from baseline, reported an association with increasing medial temporal lobe tau-PET[18]. Further research into this association is critical to determine whether p-tau217 may serve as an early marker of AD pathology and aid in early detection. If plasma p-tau217 can predict future tau-PET at a longer interval, clinical trials may be able to enroll individuals at an earlier stage.

In this study, we leveraged a cohort of carriers of the *PSEN1* E280A mutation for ADAD to examine whether baseline levels of plasma p-tau217 are associated with subsequent PET-based markers of AD pathology in the brain, measured on average 7.61 years following plasma collection. Secondarily, we examined the association between plasma p-tau217 and subsequent cognition. These findings would inform the use of plasma p-tau217 as a biomarker for the selection, monitoring, and evaluation in clinical trials and other investigations.

Methods

Study design and participants

This cohort study included 24 *PSEN1* E280A mutation carriers and 20 age- and education-matched non-carriers from the same kindred, enrolled in the Massachusetts General Hospital (MGH) COLBOS (Colombia-Boston) longitudinal biomarker study. Participants were recruited from the Alzheimer's Prevention Initiative (API) registry of familial AD, which currently includes more than 6,000 living members of the kindred and approximately 1,200 mutation carriers[19]. Characteristics of this kindred have been well characterized[20–22]. Notably, the onset of clinical impairment occurs in midlife, with the median age of onset of mild cognitive impairment (MCI) at 44 years old and dementia at 49 years old[21].

Participants with a diagnosis of dementia at the time of blood sample collection or with a significant medical, psychiatric, or neurological disorder (e.g., stroke, seizures, substance abuse, and other disorders that affect motor, visuospatial or cognitive abilities) were excluded. Neither the participants nor raters were informed of the genetic status of the individuals. This study was approved by the institutional ethics review boards of the University of Antioquia in Medellin, Colombia, and the MGH in Boston, MA, USA. All participants provided written informed consent before inclusion in the study.

Blood sampling was collected at baseline. Neuroimaging and cognitive memory assessment were completed at follow-up (mean = 7.61 ± 4.05 years). All participants were cognitively unimpaired at baseline. At follow up, all non-carriers and 18 carriers were cognitively unimpaired, and six carriers progressed to MCI. Participants were considered cognitively unimpaired if they had a Mini-Mental State Examination (MMSE)[23] score ≥26 and a Functional Assessment Staging Test (FAST)[24] score of 1 or 2. Impaired carriers were defined as having a FAST score of 3.

Plasma p-tau217 assay

Plasma was collected in the morning (without fasting) at the University of Antioquia in aliquots of 1 mL. Samples were stored at –80°C. Concentrations of plasma p-tau217 were measured using immunoassays at Lilly Research Laboratories, using the MSD platform (Meso Scale Discovery) as previously described[7]. Biotinylated-IBA493 was used as a capture antibody and SULFO-TAG-4G10-E2 (anti-Tau) as the detector. Additional details of the plasma P-tau217 analysis are described in Palmqvist et al., 2020, Supplemental Material.

Clinical and cognitive assessments

Clinical assessments were performed at the University of Antioquia. Participants underwent a clinical interview and were administered the MMSE, FAST, and a Spanish version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list, which has been adapted for this Colombian population[25]. Cognitive measures were administered in Spanish by a neuropsychologist or a psychologist trained in neuropsychological assessment. Neurological examinations were performed by a neurologist or by a general practitioner trained in assessing neurodegenerative disorders.

Image acquisition and processing

All participants in this study traveled from Colombia to Boston (USA) for positron emission tomography (PET) at the MGH. PET data were acquired on a Siemens ECAT HR+ (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution; 2.4 mm slice interval).

11C-Pittsburgh compound B (11C-PiB) PET was acquired with an 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12x15 seconds, 57x60 seconds). 11C-PiB PET data were expressed as the distribution volume ratio (DVR) with cerebellar grey as a reference region; regional time-activity curves were used to compute regional DVRs for each region of interest (ROI) using the Logan graphical method applied to data obtained between 40 and 60 minutes after injection[25]. 11C-PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal, and retrosplenial cortices as described previously[26].

[F18] Flortaucipir (FTP) was acquired between 80 and 100 minutes after a 9.0 to 11.0 mCi bolus injection in 4 separate 5-minute frames. [F18] FTP-specific binding was expressed in FreeSurfer ROIs as the standardized uptake value ratio (SUVR) to the cerebellum. The spatially transformed SUVR PET data were smoothed with an 8mm Gaussian kernel to account for individual anatomic differences[26]. SUVR values were represented graphically on vertices at the pial surface. A priori ROIs were inferior temporal cortex, entorhinal cortex, and precuneus[27,28].

Genotyping

Genomic DNA was extracted from the blood by standard protocols, and *PSEN1* E280A characterization was done at the University of Antioquia using methods previously described[29]. Genomic DNA was amplified with the primers PSEN1-S 5′ AACAGCTCAGGAGAGGAATG 3′ and PSEN1-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme *Bsm*I for restriction fragment length polymorphism analysis. Each participant was classified as a *PSEN1* E280A carrier or non-carrier.

Statistical analysis

Analyses and visualizations were performed in R (version 4.0.3) and used a significance threshold of $p < .05$. Group differences in continuous variables were compared using independent sample *t*-tests (Levene's test used for equality of variances). Chi-square tests were used for categorical variables. Pearson correlation was used to test associations between continuous variables in the whole sample, reported in the main text. Correlations were additionally conducted within each group and presented in the supplementary materials. Pearson correlation was used in exploratory analyses of plasma p-tau217 and vertex-wise Aβ- and tau-PET within carriers. PET images were normalized to standard (MNI) space and projected onto the average surface, and vertex-wise values were sampled at the midpoint of the gray matter. Partial volume correction was applied using the extended Muller-Gartner method implemented in FreeSurfer[30]. Results were displayed as –log10(p), significant at cluster-wise p<0.05 (minimum cluster extent = 100 mm^2) after false discovery rate (FDR) correction for multiple comparisons. Clustering and multiple comparisons corrections were performed using FreeSurfer tools.

Results

Baseline sample characteristics and plasma p-tau217 levels

A total of 24 *PSEN1* E280A carriers and 20 non-carriers were included in analyses (Table 1). Carriers and non-carriers did not differ in age at baseline, years of education, or sex. Carriers had higher plasma p-tau217 levels than non-carriers. Neuroimaging occurred on average 7.61 years after plasma sample collection, with a significantly longer interval for non-carriers than for carriers.

[Insert Table 1 here]

Group differences in biomarkers at follow-up assessment

Of the 24 carriers, 18 remained cognitively unimpaired and six converted to MCI at follow-up. Carriers exhibited elevated neuroimaging biomarkers at follow-up (Table 2), namely higher cortical Aβ DVR and regional tau-PET SUVR in the entorhinal cortex, inferior temporal cortex, and precuneus. CERAD word list delayed recall and MMSE scores were lower in carriers than non-carriers.

[Insert Table 2 here]

Associations between plasma p-tau217 levels and age, cortical Aβ, regional tau, and cognition

To assess the utility of plasma p-tau217 as an early AD biomarker, we examined its associations with various concurrent and subsequent markers of AD in the whole sample. Older age at baseline was associated with higher levels of plasma p-tau217, r = 0.50, p = .005 (Fig. 1A). Higher delayed recall at follow-up was associated with lower baseline plasma p-tau217 (r = -0.70, p < .001; Fig. 1B). Higher baseline plasma p-tau217 was also associated with higher subsequent PET measures of cortical Aβ (r = 0.60, p < .001; Fig. 1C) and tau in all ROIs: inferior temporal cortex (r = 0.72, p < .001; Fig. 1D), entorhinal cortex (r = 0.65, p < .001), and precuneus (r = 0.75, p < .001). We additionally examined these relationships separately for carriers and non-carriers, finding that associations between p-tau217 and age, PET pathology, and memory were only significant for carriers (Table S1).

[Insert Figure 1 here]

Associations between plasma p-tau217 and whole-brain Aβ- and tau-PET in *PSEN1* carriers

Finally, we assessed the relationship between plasma p-tau217 and vertex-wise PET pathology in mutation carriers. Plasma p-tau217 was positively correlated with Aβ burden in frontal, lateral temporal, parietal, and retrosplenial cortices. Correlations with tau-PET were strongest in temporal and parietal regions and to a lesser extent in the frontal regions (Fig. 2). When limiting analyses to cognitively unimpaired carriers only (Fig. 3), Aβ- and tau-PET correlations with plasma p-tau217 were observed to a smaller extent, primarily in the left lateral temporal cortices.

[Insert Figures 2, 3 here]

Discussion

The primary aim of this study was to examine whether plasma p-tau217 is associated with subsequent PET-based markers of AD pathology in the brain and cognitive performance. We examined this association in a cohort of *PSEN1* E280A carriers, who will develop dementia by midlife, and non-carrier family members, using plasma p-tau217 and neuroimaging markers collected on average 7.61 years apart. Consistent with our hypotheses, plasma p-tau217 was elevated in cognitively unimpaired *PSEN1* carriers as compared to non-carrier family members. Critically, baseline p-tau217 levels were associated with subsequent Aβ- and tau-PET deposits and lower memory performance. Together, our results suggest that plasma p-tau217 is a promising biomarker for early AD detection and progression.

In our sample, carriers had higher plasma levels of p-tau217 than non-carriers prior to the onset of cognitive impairment, and, within carriers, higher p-tau217 was associated with older age. The median age of onset of MCI in this kindred is 44 years[21], over a decade older than the average age of carriers in this sample at the time of plasma collection. Although these data are not longitudinal, due to the well-characterized clinical trajectory of the mutation carriers and near complete penetrance of the mutation, age serves as a proxy for time until clinical onset and provides a model for disease progression. As such, these associations provide evidence that plasma p-tau217 may be an early marker of preclinical AD and related to disease progression, potentially increasing as clinical onset approaches. Consistent results have been previously reported from this kindred[7] and from studies of sporadic AD, using comparisons of unimpaired older adults with high- versus low-Aβ[15,31]. However, longitudinal studies are required to describe the trajectory of plasma p-tau217 across disease stage.

Although converging findings indicate this early change in plasma p-tau217, little has been reported about its associations with subsequent PET-based pathology, the current gold standard in measuring *in vivo* AD pathology. Prior findings in older adults at risk for sporadic AD found an association between plasma p-tau217 and concurrent Aβ-PET[17]and tau-PET imaging[5,16,17,32]; however, only two studies, to our knowledge, have examined the relationship with future tau-PET. In these prior studies, with measurements conducted approximately one to two years apart, found a relationship between plasma p-tau217 and subsequent medial temporal lobe tau-PET[15,18]. Our study expands on these results by showing an association with widespread Aβ and tau pathology 7.61 years after plasma collection. Regional analyses revealed an association with mean cortical Aβ and regional tau-PET in three key anatomical regions: interior temporal cortex, entorhinal cortex, and precuneus. Our findings in inferior temporal cortex and entorhinal cortex are consistent with prior findings in plasma-PET investigations[5,15,18,32], and we additionally show this association with precuneus, a region previously shown to be early impacted by AD pathology in this kindred[28,33]. Further, our study is the first to conduct whole-brain analyses, revealing the correlations between plasma and tau-PET mirror the known progression of early tau pathology accumulation[27,28]. As expected early in the course of the disease, the correlations were limited to the temporal cortices in the cognitively unimpaired carriers. In contrast, when including the carriers with MCI, the spatial extent was much greater, including parietal and frontal cortices.

In addition to pathological markers, elevated plasma p-tau217 was associated with lower subsequent delayed recall, consistent with prior reported findings in this kindred[7]. In sporadic AD, longitudinal increases in plasma p-tau217 were associated with worse cognition[12]. However, another study found that tau-PET had a stronger association with cognition than did plasma p-tau217[32]. More work is needed to clarify the association between plasma p-tau217 and cognition and the extent it can predict declines in specific domains versus global cognitive changes.

This study has several strengths and limitations. A primary strength of this study is the kindred with a single variant mutation for autosomal dominant AD, whose clinical trajectory is well-characterized[20,21]. Due to the early median age of onset for MCI in this kindred, typical age-related confounds prevalent in studies of older adults are mitigated in this sample. This is particularly important for studies of tau pathology, which can accumulate with age in the absence of other AD pathology[34]. Another strength is the 7.61-year interval between plasma collection, at which time all participants were cognitively unimpaired, and neuroimaging

measures, at which time only six participants converted to MCI, thereby highlighting the utility of early plasma p-tau217 for predicting pathology prior to conversion to dementia. Despite the advantages provided by studying this kindred, our sample size is relatively small for a biomarker study, and the extent to which these findings can be generalized to sporadic AD is unknown. Future studies in additional autosomal dominant and sporadic AD populations are needed. Additionally, analysis of blood samples was not available at follow-up. Future studies would benefit from longitudinal collection of both plasma p-tau217 and tau-PET to assess the trajectory of each biomarker, as well as investigate potential differences in the plasma-PET association at varying follow-up intervals.

Conclusion

In sum, our results show that baseline levels of plasma p-tau217 predict subsequent levels of amyloid and tau burden and worse future memory performance in *PSEN1* E280A carriers. These findings add to the growing literature suggesting that plasma p-tau217 is an early marker for AD by demonstrating an association between plasma and PET measures of pathology. Our results provide support for plasma p-tau217 as a potential minimally invasive diagnostic and prognostic biomarker of AD pathology and cognition, with promising utility in clinical practice and trials.

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Disclosures

HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Alector, ALZPath, Annexon, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). OH has acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer, and Roche. In the past 2 years, he has received consultancy/speaker fees from Amylyx, Alzpath, BioArctic, Biogen, Cerveau, Fujirebio, Genentech, Novartis, Roche, and Siemens.

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Table 1. Baseline demographic and plasma p-tau217 data

	Non-carriers (n=20)	Carriers (n=24)	*p* value
Age at baseline (years)	27.55±6.99	31.13±6.81	.094
Education (years)	11.25±4.10	9.38±4.63	.167
Sex (Male/Female)	11/9	10/14	.378
p-tau217 (pg/ml)	2.53±1.39	5.27±4.69	.011
Time between blood samples and PET scans (years)	8.95±4.19	6.50±3.65	.044

Note: Means and standard deviations given for age, education, p-tau217, and follow-up time.

Table 2. Follow-up neuroimaging and cognitive data

	Non-carriers (n=20)	Carriers (n=24)	*p* value
11C PiB-PET (DVR)	1.11±0.04	1.69±0.39	< .001
Entorhinal cortex FTP (SUVR)	1.02±0.12	1.52±0.45	<.001
Inferior temporal FTP (SUVR)	1.21±0.13	1.56±0.68	.023
Precuneus FTP (SUVR)	1.05±0.13	1.72±1.02	.004
Mini Mental State Examination	29.00±0.97	26.67±3.50	.004
CERAD delayed recall	7.85±1.18	5.17±3.21	< .001

Note: Means and standard deviations give for all variables.

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; DVR, distribution volume ratio; FTP, flortaucipir; PiB, Pittsburgh Compound B; SUVR, standardized uptake value ratio.

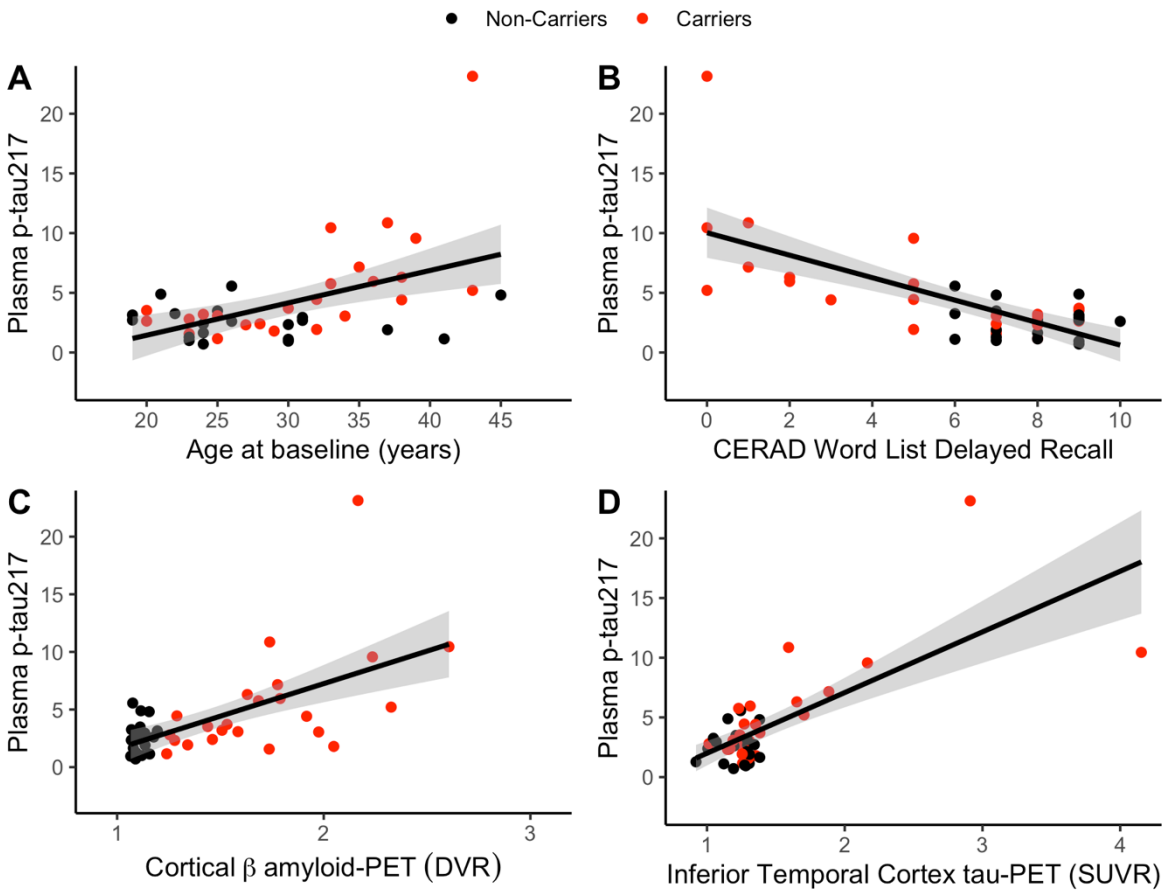

Figure 1. Plasma p-tau217 levels (picograms per milliliter) and its associations in the whole sample. Scatterplots with simple regression line and standard error showing the association between plasma p-tau217 and (**A**) age at baseline, (**B**) Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list delayed recall, (**C**) mean cortical β amyloid-PET, and (**D**) inferior temporal cortex tau-PET. DVR = distribution volume ratio, SUVR = standardized uptake value ratio

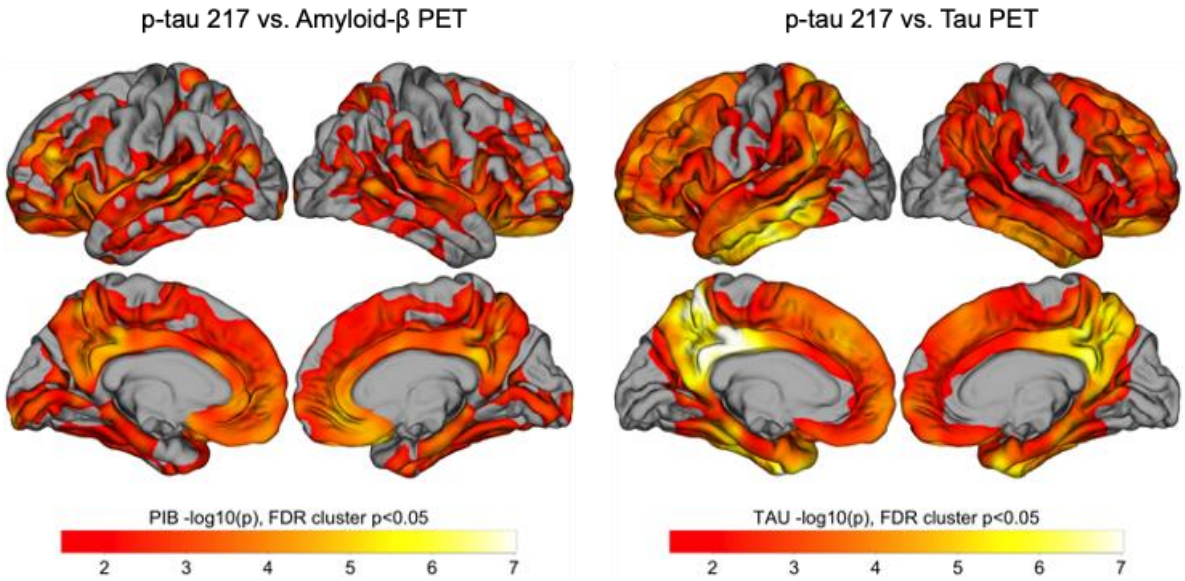

Figure 2. Whole-cortex analysis of Aβ- and tau-PET versus plasma p-tau217 in all *PSEN1* E280A carriers (n = 24). Pearson correlations were performed between p-tau217 concentrations and Aβ- (*left*) and tau- (*right*) PET. Results are displayed as -log10(p), significant at cluster p < .05 after false discovery rate (FDR) correction.

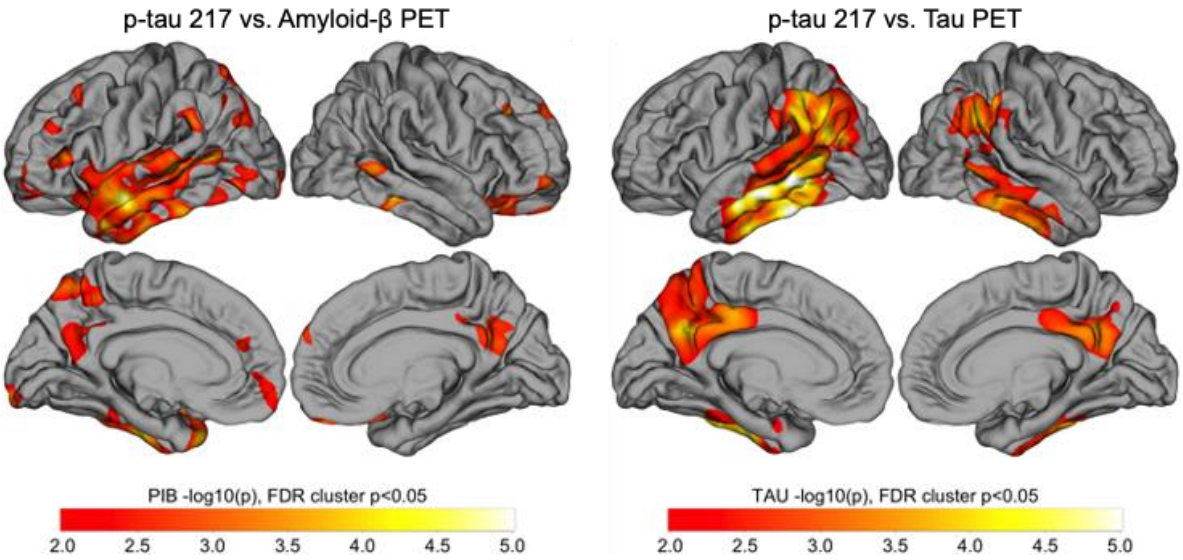

Figure 3. Whole-cortex analysis of Aβ- and tau-PET versus plasma p-tau217 in cognitively unimpaired carriers (n = 18). Pearson correlations were performed between p-tau217 concentrations and Aβ- (*left*) and tau- (*right*) PET. Results are displayed as -log10(p), significant at cluster p < .05 after false discovery rate (FDR) correction.

Supplementary Materials

Table S1

Statistical output from Pearson correlations with plasma p-tau217 for carriers and non-carriers

	Non-Carriers		Carriers	
	R	***p***	**R**	***p***
Age	-0.01	.974	0.64	.001
Cortical Aβ	0.16	.495	0.55	.005
Inferior Temporal Cortex Tau SUVR	0.08	.738	0.71	< .001
Entorhinal Cortex Tau SUVR	0.15	.517	0.61	.002
Precuneus Tau SUVR	0.39	.089	0.72	< .001
CERAD Word List Recall	-0.13	.574	-0.69	< .001