Plasma Levels of Phosphorylated Tau 181 Are Associated With Cerebral Metabolic Dysfunction in Cognitively Impaired Individuals

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Abstract

Background

Alzheimer’s disease (AD) biomarkers are primarily evaluated through MRI, PET, and CSF methods in order to diagnose and monitor disease. Recently, advances in the assessment of blood-based biomarkers have shown promise for simple, inexpensive, accessible, and minimally invasive tools with diagnostic and prognostic value for AD. Most recently, plasma phosphorylated tau181 (p-tau181) has shown excellent performance. The relationship between plasma p-tau181 and cerebral metabolic dysfunction assessed by $[^{18}\text{F}]$FDG PET in AD is still unknown.

Methods

This study was performed on a total of 892 individuals (297 cognitively unimpaired; 595 cognitively impaired) from the ADNI cohort. Plasma p-tau181 was assessed using single molecular array (Simoa) technology and metabolic dysfunction was indexed by $[^{18}\text{F}]$FDG PET. Cross-sectional associations between plasma and CSF p-tau181 and $[^{18}\text{F}]$FDG were assessed using voxelwise linear regression models, with individuals stratified by diagnostic group and by $\text{A}\beta$ status. Associations between baseline plasma p-tau181 and longitudinal rate of brain metabolic decline were also assessed in a subset (n=389) of individuals using correlations and voxelwise regression models.

Results

Plasma p-tau181 was elevated in $\text{A}\beta+$ and cognitively impaired individuals as well as in $\text{APOE}\varepsilon 4$ carriers, and was significantly associated with age, worse cognitive performance, and CSF p-tau181. Cross-sectional analyses showed strong associations between plasma p-tau181 and $[^{18}\text{F}]$FDG PET in $\text{A}\beta+$ and cognitively impaired individuals. Voxelwise longitudinal analyses showed that baseline plasma p-tau181 concentrations were significantly associated with annual rates of metabolic decline only in cognitively impaired individuals, bilaterally in the medial and lateral temporal lobes.

Conclusions

The associations between plasma p-tau181 and reduced brain metabolism, primarily in cognitively impaired and in $\text{A}\beta+$ individuals, supports the use of plasma p-tau181 as a simple, low-cost, minimally invasive, and accessible tool to both assess current and predict future metabolic dysfunction associated with AD, comparatively to PET, MRI, and CSF methods.

Background

The pathognomonic signs of Alzheimer’s disease (AD) are the accumulation of amyloid-β (Aβ) and the aggregation of hyperphosphorylated tau into intraneuronal tangles[1]. AD is also importantly characterized by brain glucose metabolism dysfunction and cerebral atrophy[2]. As these pathological
changes precede the appearance of clinical symptoms by many years[3], these pathologies may play an important role in both research and clinical trials for the screening, diagnosis, and progression monitoring of AD[4].

Currently, these biomarkers, i.e. Aβ, tau, glucose metabolism, and brain atrophy, are primarily assessed through positron emission tomography (PET), magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) measures[3,5]. However the excessive cost, relative invasiveness, and time-consuming nature[6] of these methods obstruct their use in clinical practice. As such, given the need for more accessible AD biomarkers, blood-based biomarkers, such as measures of phosphorylated tau, Aβ42/40 ratio, and neurofilament light protein, constitute a viable promise and warrant thorough investigation with regards to their specificity to AD[7].

Phosphorylated tau is the principal component of neurofibrillary tangles and dystrophic neurites in AD. Tau protein phosphorylated at threonine-181 (p-tau181) has been examined in CSF[8], and it has been demonstrated that p-tau181 is highly specific for AD-related tau aggregation[2]. Importantly, recent technological advancements have led to ultrasensitive assays of p-tau181 in blood samples (i.e. plasma and serum) using ultrasensitive immunoassays[9–13] and mass spectrometry methods[14]. Plasma p-tau181 levels have been shown to be strongly associated with brain tau pathology, significantly elevated in AD, and differentiate AD from other neurodegenerative diseases [9–13]. However, to date the associations between plasma p-tau181 and AD-related brain metabolic dysfunction, a well-recognized pathophysiological process underlying AD, remains unknown.

In order to address this knowledge gap, the current study was designed to measure plasma p-tau181 levels and brain glucose metabolism as assessed by [18F]FDG PET in participants of the Alzheimer’s Disease Neuroimaging Initiative (ADNI). The goal of the study is to examine (1) how the plasma biomarker compares to the CSF biomarker in terms of its association to [18F]FDG PET cross-sectionally, and (2) how baseline levels of plasma p-tau181 relate to longitudinal trajectories of brain metabolic decline. We hypothesize that plasma p-tau181 performs similarly to CSF p-tau181 with regards to its relationship to brain metabolic dysfunction and that baseline plasma p-tau181 is able to predict reduction of brain metabolism over time.

**Methods**

**Study participants**

The current study was based on data from the ADNI database. ADNI is a multicentre study launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. ADNI’s primary goal is to test whether the combination of neuroimaging and biochemical biomarkers and clinical and neuropsychological assessments can be used for early detection and monitoring of AD dementia[15]. The ADNI study was approved by local Institutional Review Boards of all of the participating institutions, and informed written consent was provided by enrolled participants at each site. Full information regarding
the ADNI inclusion/exclusion criteria is described elsewhere[16]. ADNI is a prospective cohort study that continues to recruit participants; this study was based on participants with available plasma p-tau181 data (data downloaded in June 2020).

The study population was classified into two diagnostic groups: cognitively unimpaired (CU) and cognitively impaired (CI) individuals. The CU classification was based on a CDR of 0; participants who had no cognitive dysfunction but reported subjective cognitive decline were analyzed together with CU, as per the National Institute of Aging-Alzheimer's Association's biological AD research framework[2]. The CI group consisted of individuals that were clinically defined as having MCI or AD dementia. MCI and AD dementia classification followed the criteria described elsewhere.[15,17] CSF p-tau181 and [18F]FDG PET data were matched with plasma p-tau181 data collected on the same ADNI study visit. Cross-sectional analysis was based on CSF and plasma measures of p-tau181 and PET measures of glucose metabolism ([18F]FDG) in a subset of n=823 participants (CU, n=262; CI, n=561 [MCI, n=426; AD, n=135]). Longitudinal analysis was based on a subset of participants with a baseline and longitudinal (up to 24 months) plasma p-tau181 and [18F]FDG PET assessment, which consisted of n=389 participants (CU, n=138; CI, n=251 [MCI, n=213; AD, n=38]). A description of the cross-sectional and longitudinal sample selections can be found in Additional file 1. The first available plasma p-tau181 measurement was used as the baseline time point for longitudinal analyses, as well as for age and diagnostic classification for cross-sectional and longitudinal analyses.

**Plasma p-tau181 measurement**

Blood samples were collected, shipped, and stored as described by the ADNI Biomarker Core Laboratory[18]. Plasma p-tau181 was analyzed with the Single Molecule Array (Simoa) technique, using a clinically validated in-house assay described previously[9]. Plasma p-tau181 was measured on Simoa HD-X instruments (Quanterix, Billerica, MA, USA) in April 2020 at the Clinical Neurochemistry Laboratory, University of Gothenburg, Mölndal, Sweden. Plasma p-tau181 data was collected over 47 analytical runs. Assay precision was assessed by measuring two different quality control samples at the start and end of each run, resulting in within-run and between-run coefficients of variation of 3.3%-11.6% and 6.4%-12.7%, respectively. Out of 3762 ADNI samples, four were removed due to inadequate volumes. The remaining 3758 all measured above the assay's lower limit of detection (0.25 pg/ml), with only six below the lower limit of quantification (1.0 pg/ml). Plasma p-tau181 measurements were downloaded from the ADNI database (accessed 2020-06-20).

**CSF p-tau181 measurement**

CSF samples were collected by lumbar puncture, shipped, and stored as described by the ADNI Biomarker Core Laboratory[18]. CSF concentrations of p-tau181 were quantified using fully automated Elecsys immunoassays (Roche Diagnostics) at the ADNI Biomarker Laboratory at the University of Pennsylvania. The lower and upper technical limits for CSF p-tau181 were 8 and 120 pg/mL. Procedures have been described in detail previously[19,20].
MRI acquisition and processing

Pre-processed 3T MRI T1-weighted magnetization-prepared rapid acquisition gradient echo images were downloaded from the ADNI database; full information regarding ADNI acquisition and pre-processing protocols of MRI data can be found elsewhere [21,22]. Images underwent linear and non-linear registration to the ADNI template space, and all images were visually inspected to ensure proper alignment to the ADNI template.

PET acquisition and processing

Pre-processed $^{[18]}$F-FDG and $^{[18]}$F-Florbetapir PET images were downloaded from the ADNI database; full information regarding ADNI acquisition and pre-processing protocols of PET data can be found elsewhere[23]. Images underwent spatial normalization to the ADNI standardized space using the automatic registration of PET images to their corresponding T1-weighted image space as well as the linear and non-linear transformations from the T1-weighted image space to the ADNI template space. PET images were spatially smoothed to achieve a final resolution of 8 mm full width at half maximum (FWHM) and were visually inspected to ensure proper alignment to the ADNI template.

$^{[18]}$F-FDG and $^{[18]}$F-Florbetapir standardized uptake value ratio (SUVR) maps were generated using the pons and the full cerebellum as the reference region, respectively. For each participant, a global $^{[18]}$F-FDG SUVR value was estimated by averaging the SUVR from the angular gyrus, posterior cingulate, and inferior temporal cortices[24]. A global $^{[18]}$F-Florbetapir SUVR value was similarly estimated using the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices[24]. Amyloid-β (Aβ) positivity was determined for each participant by a global $^{[18]}$F-Florbetapir SUVR exceeding 1.11[25].

Statistical analyses

All nonimaging statistical analyses were performed using R v4.0.0. Voxelwise imaging statistical analyses were executed using the VoxelStats toolbox [26] in MATLAB version 9.4. Subjects were considered outliers if their baseline plasma p-tau181 value was three standard deviations above the population mean, and their data were excluded. Comparing demographic and clinical characteristics between diagnostic groups was done using $\chi^2$ test with continuity correction for categorical variables, Mann-Whitney $U$ test for non-normal continuous variables, and one-way ANOVA for normal continuous variables. Correlations between plasma p-tau181 levels and demographic and clinical characteristics used Pearson's correlation coefficient (r). All $p$ values were two-tailed and $p$ values <0.05 were considered significant.

Cross-sectional data were evaluated with correlations between CSF and plasma p-tau181 concentrations using Pearson's correlation coefficient, with subjects stratified by diagnostic group and Aβ status. Voxelwise linear regression models tested the cross-sectional associations between $^{[18]}$F-FDG PET uptake
and both CSF and plasma p-tau181 concentrations, adjusting for age and sex, in diagnostic groups (with and without Aβ status stratification).

Longitudinal analyses investigated the associations between baseline plasma p-tau181 levels and longitudinal metabolic decline. Annual rates of change were calculated both for global $[^{18}\text{F}]$FDG SUVR and voxelwise for $[^{18}\text{F}]$FDG images by subtracting the baseline value from the follow-up value and normalizing by time difference between time points, in years. Correlations and voxelwise linear regression models then tested the associations between annual rate of change in metabolic decline (using $[^{18}\text{F}]$FDG SUVR and images, respectively) and baseline concentration of plasma p-tau181 and, adjusting for age and sex. Log-transformation of CSF and plasma p-tau181 measurements in pg/mL was used in all voxelwise analyses in order to reduce the skew of the distribution. Random field theory with a cluster threshold of $p < 0.001$ was used to correct voxelwise analyses for multiple comparisons[27].

| Characteristic                              | Cross-sectional dataset ($n = 823$)                                                                 | Longitudinal dataset ($n = 389$)       |
|---------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------|
| Diagnostic group                            | **CU**                                                                                         |(Cl)                                   |
| $n$                                         | 262                                                                                           | 138                                   |
| Age (median [IQR])                          | 73.00 [68.52, 78.56]                                                                         | 75.04 [69.93, 80.38]                  |
| Males ($n$, %)$^\dagger$                    | 120 (45.8)                                                                                    | 75 (54.3)                             |
| Education (median [IQR])$^\dagger$          | 16.00 [15.00, 18.00]                                                                         | 16.00 [16.00, 18.00]                  |
| $APOE \epsilon 4$ carriers ($n$, %)$^\dagger$| 75 (28.6)                                                                                     | 35 (25.4)                             |
| MMSE (median [IQR])$^\dagger$               | 29.00 [29.00, 30.00]                                                                         | 28.00 [28.25, 29.00]                  |
| CDRSB (median [IQR])$^\dagger$              | 0.00 [0.00, 0.00]                                                                             | 0.00 [0.00, 0.00]                     |
| Plasma p-tau181 (median [IQR])$^\S$         | 13.54 [9.32, 18.15]                                                                          | 13.93 [9.72, 19.08]                   |
| CSF p-tau181 (median [IQR])$^\S$            | 19.67 [15.49, 26.61]                                                                          | -                                     |
| Aβ+ ($n$, %)$^\dagger$                      | 52 (19.8)                                                                                     | 28 (20.3)                             |
| $[^{18}\text{F}]$Florbetapir SUVR (median [IQR])$^\dagger$ | 0.96 [0.89, 1.07]                                                                             | 0.96 [0.90, 1.06]                     |
| $[^{18}\text{F}]$FDG SUVR (mean (SD))$^\dagger$ | 1.80 (0.20)                                                                                   | 1.78 (0.19)                           |
**Table 1**: Demographic and clinical characteristics of the samples

- Measured in pg/mL

† Statistically significant difference between groups (p < 0.05)

CU = cognitively unimpaired; CI = cognitively impaired; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; Aβ = amyloid-β; SUVR = standardized uptake value ratio; SD = standard deviation; IQR = interquartile range.

Table 1: The demographic and clinical characteristics for participants in the cross-sectional and longitudinal datasets are presented, stratified by cognitive status. Normal variables were summarized using mean and standard deviation, while non-normal variables were summarized using median and interquartile range. Statistical differences between the cognitively unimpaired and impaired groups were tested for both datasets, using $\chi^2$ test with continuity correction for categorical variables, Mann-Whitney U test for non-normal continuous variables, and one-way ANOVA for normal continuous variables.

**Results**

**Demographic characteristics**

A total of 823 participants was included in the cross-sectional dataset, while 389 participants were included in the longitudinal dataset, resulting in 892 unique participants and a total of 1281 individual measures of plasma p-tau181. From the unique participants, 297 were classified into the CU group and 595 into the CI group. Demographic and clinical characteristics are summarized for both datasets stratified by diagnostic group in Table 1.

Of the 892 unique individuals, 476 (53.4%) were male and median age at baseline plasma collection was 73.0 years (IQR, 67.9-78.1). CI individuals were significantly younger ($p<0.001$) than CU participants only in the longitudinal dataset, whereas significantly more CI individuals were male ($p=0.005$) only in the cross-sectional dataset. CU individuals had more years of education ($p_{\text{cross}}=0.016, p_{\text{long}}=0.027$) than CI individuals in both datasets. As expected, in both datasets, CI individuals had significantly worse performance in cognitive tests (MMSE and CDR; $p_{\text{cross}}<0.001, p_{\text{long}}<0.001$ for both tests), higher amyloid load indexed by $[^{18}\text{F}]$Florbetapir SUVR ($p_{\text{cross}}<0.001, p_{\text{long}}<0.001$), lower brain metabolism indexed by $[^{18}\text{F}]$FDG SUVR ($p_{\text{cross}}<0.001, p_{\text{long}}=0.011$), and significantly more CI individuals were APOE ε4 carriers ($p_{\text{cross}}<0.001, p_{\text{long}}<0.001$) and Aβ-positive ($p_{\text{cross}}<0.001, p_{\text{long}}<0.001$).

CI individuals had significantly elevated ($p<0.001$) levels of CSF p-tau181 compared with CU individuals in the cross-sectional dataset. Plasma p-tau181 concentrations were significantly higher ($p<0.001$) in CI individuals in both cross-sectional and longitudinal datasets. Considering the 892 unique participants at baseline, plasma p-tau181 levels were significantly higher in males ($p=0.007$), irrespective of diagnosis. Plasma p-tau181 was also highly significantly elevated in APOE ε4 carriers ($p<0.0001$) and in Aβ+
individuals ($p<0.0001$). Furthermore, plasma p-tau181 was positively associated with age ($r=0.17$, $p=3.7e-07$), CDR sum of boxes score ($r=0.28$, $p<2.2e-16$), and $[^{18}\text{F}]$Florbetapir SUVR ($r=0.36$, $p<2.2e-16$), and negatively associated with education ($r=-0.09$, $p=0.006$) and MMSE score ($r=-0.26$, $p=6.6e-15$). When stratifying CU and CI individuals of the cross-sectional dataset by Aβ status, we observed significant differences in CSF and plasma p-tau181 levels between CU Aβ- and CU Aβ+ groups, CI Aβ- and CI Aβ+ groups, and CU Aβ+ and CI Aβ+ groups ($p<0.001$), but not CU Aβ- and CI Aβ- groups (Fig.1A-B). Similarly, in the longitudinal dataset, we observed significant differences in baseline plasma p-tau181 levels between CU Aβ- and CU Aβ+ groups ($p<0.01$) and CI Aβ- and CI Aβ+ groups ($p<0.001$; Fig.2A).

**Plasma p-tau181 associates cross-sectionally with CSF p-tau181 and brain metabolism**

In the cross-sectional dataset, increased concentrations of plasma p-tau181 were correlated with greater CSF p-tau181 levels in CU Aβ+ ($r=0.231$, $p=9.8e-05$), CI Aβ- ($r=0.367$, $p=0.007$), and CI Aβ+ ($r=0.213$, $p=0.0003$), but not in CU Aβ- individuals ($r=0.116$, $p=0.094$; Fig.1C). At the voxel level, linear regression models found no significant associations in CU individuals between $[^{18}\text{F}]$FDG uptake and CSF p-tau181 whereas for plasma p-tau181, negative associations were observed in very small clusters in the anterior cingulate and left temporal and parietal lobes (results not pictured, peak t-value of -4.82). Within CI individuals, negative associations between CSF p-tau181 and $[^{18}\text{F}]$FDG retention were observed bilaterally in the inferior temporal, posterior cingulate, precuneus, and orbitofrontal cortices (Fig.1D; peak t-value of -9.67). Negative associations were found in the same brain regions between $[^{18}\text{F}]$FDG uptake and plasma p-tau181 levels among CI participants (peak t-value of -8.82). Associations between both CSF and plasma p-tau181 and $[^{18}\text{F}]$FDG uptake in CI participants stratified by Aβ status are shown in Additional file 2. Associations between both CSF and plasma p-tau181 were more pronounced in Aβ+ individuals.

**Baseline plasma p-tau181 is associated with longitudinal decrease in brain metabolism**

In the longitudinal dataset, mean $[^{18}\text{F}]$FDG PET follow-up time was 23.8 ($±1.67$) months. We calculated annual rate of change in brain metabolism for global $[^{18}\text{F}]$FDG SUVR, as well as annual rate of change in every brain voxel. Average rate of change in global $[^{18}\text{F}]$FDG SUVR was -0.024 ($±0.062$; negative symbol representing reduction in $[^{18}\text{F}]$FDG uptake) per year, and rate of brain metabolic decline was significantly higher ($p=0.011$) in CI individuals (-0.029$±0.061$) than in CU individuals (-0.013$±0.062$). Average $[^{18}\text{F}]$FDG voxelwise annual rate of change is shown in Additional file 3 and is highest (i.e. more negative values representing more pronounced metabolic decline) in the posterior cingulate, precuneus, temporal, and medial and lateral prefrontal cortices.

Correlations between baseline concentration of plasma p-tau181 and annual rate of change in $[^{18}\text{F}]$FDG SUVR was significant and negative within CI individuals ($r=-0.163$, $p=0.0096$), but not statistically significant in CU individuals (Fig.2B). When stratifying individuals by both diagnostic group and Aβ status, correlations were not statistically significant in any group (Additional file 4). Voxelwise associations between baseline plasma p-tau181 and rate of change in $[^{18}\text{F}]$FDG SUVR did not survive correction for multiple comparisons in CU individuals. In CI individuals, baseline plasma p-tau181
predicted rate of change of $[^{18}\text{F}]\text{FDG SUVR}$ in the bilateral medial and lateral temporal lobes (Fig.2C, peak t-value of -5.01).

**Discussion**

In this study, performed in 892 participants from the ADNI cohort, we provide evidence for associations between plasma measures of p-tau181 and brain metabolism as assessed by $[^{18}\text{F}]\text{FDG PET}$. To our knowledge, this is the first investigation of the cross-sectional and longitudinal associations between plasma p-tau181 and cerebral hypometabolism. Our main findings were that cross-sectionally, plasma p-tau181 is associated with the metabolic signatures of AD. Moreover, in cognitively impaired individuals, levels of plasma p-tau181 at baseline were associated with rates of metabolic decline in the medial and lateral temporal lobes. Taken together, our study suggests that plasma p-tau181 may provide a cost-effective and minimally invasive method to assess existing disease pathophysiology highly associated with metabolic dysfunction.

We found that plasma p-tau181 was higher in males and in $\text{APOE} \varepsilon 4$ carriers, which to our knowledge is a finding that has not been yet described. We also observed plasma p-tau181 to be significantly associated with older age, fewer years of education, elevated global cortical composite measure of Aβ-PET, and worse performance on cognitive scores, which, with the exception of education, concur with earlier studies on plasma p-tau181[9–12,28]. As previously described, in our cross-sectional analyses, plasma p-tau181 was correlated with CSF p-tau181.[9–11] Moreover, in agreement with previous research, plasma levels of p-tau181 in our sample were significantly elevated in cognitively impaired individuals, as well as in Aβ+ individuals independent of their cognitive status.[9–12]

Our cross-sectional data indicated that p-tau181 was associated with neuronal injury in AD. Plasma p-tau181 levels and metabolic dysfunction were associated in the inferior temporal, posterior cingulate, precuneus, and orbitofrontal cortices in CI individuals. Interestingly, one can speculate that the small clusters in the anterior corpus callosum present in CU individuals may indicate a link between white matter energetic abnormalities in early states of the disease.[29] Importantly, in both groups, higher plasma p-tau181 levels were linked with Aβ status. Furthermore, baseline plasma and CSF p-tau181 had highly similar associations with $[^{18}\text{F}]\text{FDG PET}$, with higher correlations in individuals on the Alzheimer continuum as well as in similar brain regions. This indicates that glucose metabolism associates with abnormal tau phosphorylation at threonine-181 measured in either blood or CSF.

The link between plasma p-tau181 and neuronal dysfunction is further corroborated in our longitudinal analyses. We found that baseline concentrations of plasma p-tau181 were significantly associated with annual rate of metabolic decline assessed by decrease in global $[^{18}\text{F}]\text{FDG SUVR}$, only within CI individuals. Similarly, voxelwise analysis conducted in the CI group revealed that plasma p-tau181 was associated with annual rate of change in $[^{18}\text{F}]\text{FDG}$ uptake in the medial and lateral lobes. Together, these results support the concept that elevated plasma p-tau181 implies the presence of amyloidosis and neurodegeneration.
In our results, the topography of hypometabolism was consistent with brain regions that are known to be affected in AD. Specifically, metabolic dysfunction in the posterior cingulate gyrus, precuneus, and medial and lateral temporal lobes are commonly observed in amnestic MCI and AD dementia[30-32]. Moreover, the posterior cingulate gyrus, precuneus, and medial and lateral temporal lobes are brain regions that are affected by significant tau aggregation in AD[33,34]. Metabolic dysfunction in these regions is further associated with cognitive decline as well as increased risk of progression to dementia[35]. Because tau aggregation as measured by PET[36] and by CSF[37] is tightly associated with brain metabolism, the results of our study suggest that plasma p-tau181 can serve as a less invasive and more accessible measure of AD-related cerebral metabolic dysfunction.

Neurodegeneration biomarkers in isolation are neither sensitive nor specific to AD[2]. In both cross-sectional and longitudinal analyses, we found little associations between plasma p-tau181 and [18F]FDG PET in CU individuals. This finding is consistent with the observation that metabolic dysfunction is tightly related to cognitive decline[38] and thus significant metabolic decline is more commonly observed in individuals with cognitive impairment. Furthermore, we conducted stratified analyses of relationships between plasma p-tau181 and [18F]FDG PET in Aβ+ and Aβ- individuals. In individuals on the AD continuum (Aβ+), we observed significantly more pronounced cross-sectional associations between plasma p-tau181 and [18F]FDG PET in regions vulnerable to hypometabolism in AD. However, in individuals who were not on the AD continuum (Aβ-), we did not observe associations between plasma measures of p-tau181 and brain metabolic dysfunction. This was observed for both CU and CI Aβ- individuals. These results are consistent with accepted disease models in which (detectable) Aβ aggregation occurs upstream of (detectable) tau aggregation[3,39]. Taken together, these results suggest that the specificity of plasma p-tau181 for AD-type pathology [9,10,40] provides important information about the etiology of neurodegeneration and corresponding cognitive decline.

Associations between plasma measures of p-tau181 and [18F]FDG PET have important clinical implications. [18F]FDG PET is a commonly employed test in the differential diagnosis of individuals with cognitive impairment[41]. Brain metabolism, as indexed with [18F]FDG PET, correlates with cognitive function[38] and reduced brain metabolism constitutes an important risk for clinical progression to dementia[42]. [18F]FDG PET abnormalities are also observed before MRI atrophy[43], suggesting that [18F]FDG PET is a sensitive marker of neurodegeneration. Therefore, plasma measures of p-tau181 have potential as a simple tool for the diagnosis and monitoring of AD, as well as for the screening of individuals for disease-modifying clinical trials.

The validity of our results is potentially influenced by methodological limitations. First, we only included ADNI participants with a 24-month follow-up [18F]FDG PET relative to plasma p-tau181 assessment as imaging data was not consistent at later time points (i.e. 36, 48 months). As a consequence, we may have observed stronger and more compelling associations between plasma p-tau181 and [18F]FDG PET, as accepted biomarker models of AD demonstrate that tau accumulation occurs upstream of metabolic dysfunction and neurodegeneration[3]. Moreover, the ADNI cohort, from which all subjects in this study
were selected, does not encompass individuals with neurodegenerative or tau-related diseases other than AD. Therefore, it is not known how plasma p-tau181 may perform in predicting current and future metabolic dysfunction in other neurodegenerative diseases. Further studies should conduct similar analyses in other more varied observational cohorts, as well as track brain metabolism through \([^{18}\text{F}]\text{FDG}\) PET over a longer time frame.

**Conclusion**

Our study provides evidence for associations between plasma measures of p-tau181 and brain metabolic dysfunction as measured by \([^{18}\text{F}]\text{FDG}\) PET. Subgroup analyses revealed more widespread associations in CI individuals as compared to CU individuals. Moreover, extensive associations were observed in Aβ+ individuals, whereas no associations between plasma p-tau181 and \([^{18}\text{F}]\text{FDG}\) PET were observed in AB-individuals. Finally, baseline levels of plasma p-tau181 were associated with rates of metabolic decline in CI individuals. Together, our results suggest that plasma p-tau181 provides interrelated information to \([^{18}\text{F}]\text{FDG}\) PET in the differential diagnosis of individuals with cognitive impairment, and may be useful to predict metabolic dysfunction associated with AD.

**Abbreviations**

Aβ = Amyloid-β; AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; ANOVA = Analysis of Variance; APOE = Apolipoprotein E; CDR = Clinical Dementia Rating; CI = Cognitively Impaired; CSF = Cerebrospinal Fluid; CU = Cognitively Unimpaired; FDG = Fluodeoxyglucose; FWHM = Full Width at Half Maximum; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; p-tau181 = phosphorylated tau at threonine 181; SUVR = Standardized Uptake Value Ratio.

**Declarations**

**Ethics approval and consent to participate**

The ADNI study was approved by local Institutional Review Boards of all of the participating institutions. Informed written consent was provided by enrolled participants at each site.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The dataset supporting the conclusions of this article is available on the ADNI site, at http://http://adni.loni.usc.edu/data-samples/access-data/.
**Competing interests**

SG has received honoraria for serving on the scientific advisory boards of Alzheon, Axovant, Lilly, Lundbeck, Novartis, Schwabe, and TauRx and on the Data Safety Monitoring Board of a study sponsored by Eisai and studies run by the Alzheimer's Disease Cooperative Study and by the Alzheimer's Therapeutic Research Institute. KB has served as a consultant or on advisory boards for Axon Neuroscience, Biogen, CogRx, Lilly, MagQu, Novartis and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. HZ has served on scientific advisory boards for Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. The other authors declare no competing interests.

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**Authors' contributions**

FZL, ALB, JT, TAP, CT, HZ, KB, and PR-N conceptualized the research; NJA, TKK, KB, and HZ performed plasma p-tau181 measurements, data quality control and data compilation; FZL, ALB, JT, TAP, CT, SM,
and MS contributed to data analysis; FZL, ALB, JT, TAP, CT, and PR-N wrote the original manuscript draft. All authors reviewed, edited and approved the final manuscript for submission.

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Figures
Figure 1

Cross-sectional associations between plasma and CSF p-tau181 and between p-tau181 and [18F]FDG SUVR Description: (A) CSF p-tau181 levels in pg/mL were compared in individuals in the cross-sectional dataset, stratified by both their cognitive status (cognitively unimpaired (CU) or impaired (CI)) and Aβ status (+ or -), using Mann-Whitney U test. Significant differences in CSF p-tau181 were found between the CU- and CU+ groups (p<0.001), the CU+ and CI+ groups (p<0.001), and the CI- and CI+ groups.
(p<0.001). (B) Similarly, plasma p-tau181 levels in pg/mL were compared cross-sectionally in individuals stratified by both cognitive and Aβ status. Significant differences in plasma p-tau181 were found between the CU- and CU+ groups (p<0.001), the CU+ and CI+ groups (p<0.001), and the CI- and CI+ groups (p<0.001). (C) Pearson's correlation coefficient (r) was computed for associations between CSF and plasma p-tau181 levels, both in pg/mL, in individuals in the cross-sectional dataset stratified by cognitive and Aβ status. These measures were significantly positively correlated in the CU+ (r=0.231, p=9.8e-05), CI- (r=0.367, p=0.007), and CI+ groups (r=0.213, p=0.0003), but not in the CU- group (r=0.116, p=0.094). (D) Voxelwise linear regressions were performed to assess associations between log-transformed CSF p-tau181 and plasma p-tau181 in CI individuals, adjusting for age and sex. Negative associations between CSF p-tau181 and [18F]FDG SUVR were observed bilaterally in the inferior temporal, posterior cingulate, precuneus, and orbitofrontal cortices (peak t-value of -9.67). Negative associations were found in the same brain regions between [18F]FDG uptake and plasma p-tau181 levels among CI participants (peak t-value of -8.82). Voxelwise results were corrected for multiple comparisons.
Figure 2

Associations between baseline levels of plasma p-tau181 and longitudinal change in [18F]FDG SUVR

Description: (A) Baseline plasma p-tau181 levels in pg/mL were compared in individuals in the longitudinal dataset, stratified by both their cognitive status (cognitively unimpaired (CU) or impaired (CI)) and Aβ status (+ or -), using Mann-Whitney U test. Significant differences in baseline plasma p-tau181 levels were found between the CU- and CU+ groups (p<0.001), and the CI- and CI+ groups (p<0.001). (B) Pearson's correlation coefficient (r) was computed for associations between baseline plasma p-tau181 and [18F]FDG SUVR rates of change per year. (C) Annual change in [18F]FDG ~ baseline plasma p-tau181 in CI individuals.
levels and annual rate of change in global [18F]FDG SUVR in individuals in the longitudinal dataset stratified by cognitive status. Baseline plasma p-tau181 and change in global [18F]FDG SUVR were not significantly correlated in CU individuals ($r=0.062, p=0.472$), but were significantly negatively correlated in CI individuals ($r=-0.163, p=0.0096$). (C) Voxelwise linear regression models were used to investigate associations between baseline log-transformed plasma p-tau181 and annual rate of change in [18F]FDG SUVR in CI individuals in the longitudinal dataset, adjusting for age and sex. Significant associations were found in the medial and lateral temporal lobes (peak t-values of -5.01). Voxelwise results were corrected for multiple comparisons.

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