Normalization of CSF pTau measurement by $A\beta_{40}$ improves its performance as a biomarker of Alzheimer’s disease

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Abstract

Background: Alzheimer’s disease (AD)-related tauopathy can be measured with CSF phosphorylated tau (pTau) and tau PET. We aim to investigate the associations between these measurements and their relative ability to predict subsequent disease progression.

Methods: In 219 cognitively unimpaired and 122 impaired Alzheimer’s Disease Neuroimaging Initiative participants with concurrent amyloid-$\beta$ ($A\beta$) PET (18F-florbetapir or 18F-florbetaben), 18F-flortaucipir (FTP) PET, CSF measurements, structural MRI, and cognition, we examined inter-relationships between these biomarkers and their predictions of subsequent FTP and cognition changes.

Results: The use of a CSF pTau/$A\beta_{40}$ ratio eliminated positive associations we observed between CSF pTau alone and CSF $A\beta_{42}$ in the normal $A\beta$ range likely reflecting individual differences in CSF production rather than pathology. Use of the CSF pTau/$A\beta_{40}$ ratio also increased expected associations with $A\beta$ PET, FTP PET, hippocampal volume, and cognitive decline compared to pTau alone. In $A\beta+$ individuals, abnormal CSF pTau/$A\beta_{40}$ only individuals (26.7%) were 4 times more prevalent ($p < 0.001$) than abnormal FTP only individuals (6.8%). Furthermore, among individuals on the AD pathway, CSF pTau/$A\beta_{40}$ mediates the association between $A\beta$ PET and FTP PET accumulation, but FTP PET is more closely linked to subsequent cognitive decline than CSF pTau/$A\beta_{40}$.

Conclusions: Together, these findings suggest that CSF pTau/$A\beta_{40}$ may be a superior measure of tauopathy compared to CSF pTau alone, and CSF pTau/$A\beta_{40}$ enables detection of tau accumulation at an earlier stage than FTP among $A\beta+$ individuals.

Keywords: Tau, CSF pTau/$A\beta_{40}$, PET, Cognition, Alzheimer’s disease

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Background
Extracellular amyloid-β (Aβ) peptides in cortical Aβ plaques and intracellular phosphorylated tau protein as neurofibrillary tangles are key hallmarks of Alzheimer’s disease (AD) that can be measured in vivo with positron emission tomography (PET) imaging and biofluid markers including plasma and cerebrospinal fluid (CSF) assays. The relationship between CSF Aβ and Aβ PET in AD has been widely reported [1–8], but relationships between CSF tau and tau PET are uncertain [9–13]. Recent studies reported that individuals with abnormal CSF phosphorylated tau (pTau) were more prevalent than individuals with abnormal tau PET only [14], and that abnormal tau PET but not CSF pTau was related to cognitive decline [15], suggesting that CSF and PET may not be interchangeable indices of tau pathology.

There are also remaining technical questions involved in measurement of CSF biomarkers. Elevated (abnormal) CSF pTau has been observed in cases with exceptionally high levels of Aβ production but not CSF pTau was related to cognitive decline [15], suggesting that CSF and PET may not be interchangeable indices of tau pathology.

PET and MRI imaging
PET data was acquired in 5-min frames from 50 to 70 min (FBP), 90–110 min (FBB), and 75–105 min (FTP) post-injection (http://adni-info.org). PET and structural MRI scans were downloaded from the Laboratory of Neuroimaging (LONI) (ida.loni.usc.edu) and processed with Freesurfer V5.3.0. All fully pre-processed PET scans were co-registered to the structural MRI scan that was closest in time to the baseline PET. Regions of interest (ROIs) were defined on each structural MRI scan using Freesurfer (V5.3.0) and used to extract regional FBB, FTP, and FTP measurements from the co-registered PET images as described previously [30, 31].

Briefly, FBB or FTP standardized uptake value ratios (SUVRs) were calculated by dividing frontal, cingulate, parietal, and temporal regional uptake to that in the whole cerebellum to generate COMPOSITE SUVRs [30]. COMPOSITE SUVRs for FBP ≥ 1.11 or FBB ≥ 1.08 were defined as Aβ+ as described on the ADNI website. Aβ positivity was defined by Aβ PET in this study. FBP (UCBERKELEYAV45_05_12_20.csv) and FTP (UCBERKELEYFBB_05_12_20.csv) SUVRs were converted to Centiloids using the equations Centiloid = (196.9 × SUVRFBB) – 196.03 for FBP and Centiloid = (159.08 × SUVRFBB) – 151.65 for FBB (ADNI_Centiloid_Methods_Instruction_20181113.pdf in LONI website (ida.loni.usc.edu)).

For FTP (BERKELEYAV1451_05_12_20.csv), composite Temporal-metaROI (including entorhinal, parahippocampal, fusiform, amygdala, inferior temporal, and middle temporal) [32] and entorhinal cortex SUVRs were calculated using inferior cerebellar cortex intensity normalization [31]. To define FTP SUVR thresholds, we carried out ROC analyses with Temporal-metaROI and entorhinal SUVR values using the Youden index classifying 280 Aβ PET− ADNI CU participants and 183 Aβ PET+ ADNI MCI and AD patients as the endpoint (Supplemental Figs. 1–4). This resulted in a threshold of 1.25 for the Temporal-metaROI and 1.21 for entorhinal cortex. Among these 463 ADNI participants for the definition of tau PET cutoffs, 217 (47%) participants were included in the following analyses of this study. We also examined alternative thresholds for these regions defined by the mean + 2SD of 280 Aβ PET− ADNI CU participants and 183 Aβ PET+ ADNI MCI and AD patients as the endpoint (Supplemental Figs. 1–4). This resulted in a threshold of 1.25 for the Temporal-metaROI and 1.21 for entorhinal cortex. Among these 463 ADNI participants for the definition of tau PET cutoffs, 217 (47%) participants were included in the following analyses of this study. These results in more conservative thresholds of 1.34 for the Temporal-metaROI and 1.31 for entorhinal cortex. In total, 34% of 341 participants had longitudinal FTP data. FTP slope (ΔFTP, SUVR units per year) was calculated based on longitudinal FTP data for each individual using linear mixed effects (LME) model, including
the following independent variables: time, APOE-ε4 status, age and gender, and a random slope and intercept. Since white matter intensity normalization has shown less variability for longitudinal tau PET changes [33–35], we calculated FTP slopes using a white matter reference region.

Hippocampal volume (HCV) (mm³) was calculated across hemispheres from the structural MRI scan that was closest in time to the baseline PET scan and for subsequent MRI scans using Freesurfer, and adjusted by estimated intracranial volume (ICV) using the regression approach [36]: adjusted HCV (aHCV) = HCV − 0.0017 × (ICV − 1 498858), where 0.0017 and 1498858 represent the correlation coefficient between HCV and ICV, and the mean of ICV in Aβ− 323 ADNI CU participants. In total, 41% of 341 participants had longitudinal aHCV data. aHCV slope (ΔaHCV, mm³ units per year) was calculated based on longitudinal aHCV data for each individual using LME model, including the following independent variables: time, APOE-ε4 status, age, gender and education, and a random slope and intercept.

CSF Aβ40, Aβ42, and pTau

CSF Aβ40, Aβ42, and pτau were analyzed by the University of Pennsylvania ADNI Biomarker core laboratory using the fully automated Roche Elecsys and cobas® 601 immunoassay analyzer system [16, 37]. CSF data (UPENN_BIOMK10_07_29_19.csv) were downloaded from ADNI website. A threshold for abnormal CSF pTau was defined as ≥22 pg/mL based on an ROC analysis using the Youden index classifying 320 Aβ− ADNI CU participants and 429 Aβ+ ADNI MCI and AD patients as the endpoint (Supplemental Figs. 5–6). We also defined an alternative threshold of ≥31 for CSF pTau which was based on the mean + 2SD of CSF pTau in 320 Aβ− ADNI CU participants. We calculated the CSF pTau/Aβ40 ratio threshold as ≥0.0012 according to the same ROC classification 169 Aβ− PET− CU participants and 161 Aβ+ PET+ MCI and AD patients as the endpoint (Supplemental Figs. 7–8), and the alternative threshold was ≥0.0014 based on the mean + 2SD of the CSF pTau/Aβ40 ratio in 169 Aβ− PET− ADNI CU participants. Among these 749 ADNI participants for the definition of CSF pTau, 212 (28%) participants were included in the following analyses of this study. Among these 329 ADNI participants for the definition of CSF pTau/Aβ40, 201 (61%) participants were included in the following analyses of this study.

Cognition

The Delayed Recall portion of the Alzheimer’s Disease Assessment Scale (ADASSCORES.csv and ADAS_ADNIGO23.csv downloaded at April 28, 2020), the delayed recall score on the logical memory IIa subtest from the Wechsler Memory Scale, the digit symbol substitution test score from the Wechsler Adult Intelligence Scale—Revised (NEUROBAT.csv downloaded at April 28, 2020), and the MMSE total score (MMSE.csv downloaded at April 28, 2020) were transferred to standard z scores (using the mean values of ADNI CU participants). Preclinical Alzheimer Cognitive Composite (PACC) scores [38] were calculated by combining these 4 cognitive z scores to one composite score. In total, 59% of 341 participants had longitudinal PACC data. PACC slope (ΔPACC) was calculated for each participant based on longitudinal PACC scores using LME model, including the following independent variables: time, APOE-ε4 status, age, gender and education, and a random slope and intercept.

Statistical analysis

Normality of distributions was tested using the Shapiro-Wilk test and visual inspection of data. Data are presented as median (interquartile range (IQR)) or number (%). Baseline characteristics were compared between Aβ− and Aβ+ groups by using a two-tailed Mann-Whitney test or Fisher’s exact test.

In order to evaluate the feasibility of using CSF pτau/ Aβ40 as an alternative to CSF pτau, we first used generalized linear models (GLM) to examine the relationships of CSF Aβ40 with Aβ PET and tau PET to confirm that CSF Aβ40 is not related to AD biomarkers, and subsequently investigated the cross-sectional associations between CSF Aβ42, pτau and pτau/Aβ40, and controlling for APOE-ε4 status, diagnosis, sex, and age. A false discovery rate of 0.05 using the Benjamini-Hochberg approach was employed for 35 regions. The slopes of FTP SUVR, aHCV, and PACC post baseline CSF collection were calculated using LME models over time from the first measurement point post baseline CSF collection (time = 0) to the last measurement point for each participant. The time variable is anchored to the baseline CSF measurement. In order to study whether elevated CSF pτau/ Aβ40 is more related to the progression of AD than high CSF pτau, we also used GLM models to investigate the associations of CSF pτau and pτau/Aβ40 with Aβ PET, tau PET, aHCV, ΔaHCV, PACC, and ΔPACC, controlling for APOE-ε4 status, diagnosis, sex, age, and education. Since there was a time difference between baseline CSF collection point and the first measurements of FTP SUVR, aHCV, and PACC post baseline CSF collection, we included these time differences in the GLM models. Because we found use of the CSF pτau/Aβ40 ratio abolished the positive correlation between CSF pτau and Aβ42 among Aβ PET− range (see Fig. 1c, d in “Results”) and improved the associations with Aβ PET, tau PET, aHCV,
ΔaHCV, PACC, and ΔPACC (see Fig. 2 in “Results”), we used this ratio in subsequent analyses.

We then explored the biological plausibility of the CSF pTau/Aβ40 by examining associations between CSF pTau/Aβ40 and FTP SUVRs in 35 Freesurfer-defined ROIs, controlling for Aβ PET (in Centiloids), APOE-ε4 status, diagnosis, sex, and age. Spearman’s rho was calculated between CSF pTau/Aβ40 and FTP SUVR. Subsequently, we examined the associations between Aβ PET, CSF pTau/Aβ40, CSF pTau, and tau PET (entorhinal or Temporal-metaROI) in Aβ− and Aβ+ participants, controlling for APOE-ε4 status, diagnosis, sex, and age.

In order to investigate the predictive effect of baseline Aβ PET, CSF pTau/Aβ40, and FTP on subsequent ΔFTP and ΔPACC, we used these variables at baseline to predict subsequent ΔFTP and ΔPACC in participants with longitudinal tau PET and PACC data respectively. In order to explore temporal relationships between Aβ and tau, we also examined the sequential associations between baseline Aβ PET, CSF pTau/Aβ40 ratio, FTP, and ΔFTP in Aβ+ participants using latent variable modeling (R; Lavaan package) [39].

For GLM models with non-Gaussian distribution outcomes (Aβ and tau PET), we used a “log” link function in the Gaussian family to study the associations between predictor and outcome. Spearman’s rank correlation coefficient (rho) was calculated between predictor and outcome. We selected $p < 0.05$ as the significance level. All statistical analyses were performed in the statistical program $R$ (v3.6.2, The R Foundation for Statistical Computing).

**Results**

**Demographics**

Measurements were acquired between September 21, 2015 and April 9, 2020. Demographics can be found in Table 1. In total, 341 participants had contemporaneous CSF Aβ40, Aβ42 and pTau, Aβ PET, tau PET, structural MRI, and PACC cognitive score. At baseline, Aβ+ participants were significantly older and had greater CSF pTau, CSF pTau/Aβ40 and Temporal-metaROI FTP SUVR, lower aHCV, lower cognitive test scores, and a higher percentage of APOE-ε4 carriers than Aβ− participants. Longitudinally, 116, 139, and 202 participants had...
> 2 FTP PET scans (median follow-up 1.2 (range 0.7–3.3) years), structural MRI scans (median follow-up 1.4 (range 0.8–3.8) years), and PACC cognitive scores (median follow-up 1.2 (range 0.7–4.0) years) respectively.

Use of CSF Aβ_{40} to adjust CSF pTau
CSF Aβ_{40} was not associated with Aβ PET or tau PET regardless of Aβ PET status (Fig. 1a, b). Before normalizing to CSF Aβ_{40}, CSF pTau was positively (standardized β (β_{std}) = 0.59[95% confidence interval (CI), 0.48, 0.71]) associated with CSF Aβ_{42} in Aβ PET− participants, whereas no association was found in Aβ+ participants (Fig. 1c). We also verified that there was a similar positive association between CSF pTau and CSF Aβ_{42} analyzed with mass spectrometry rather than the Roche Elecsys immunoassay in a partially overlapping (9.8%) sample of 384 Aβ− participants (Supplemental Fig. 9). After normalizing CSF pTau using CSF Aβ_{40}, CSF pTau/Aβ_{40} was negatively (Fig. 1d) associated with CSF Aβ_{42} in both Aβ− (β_{std} = −0.27 [95% CI, −0.41, −0.13]) and Aβ+ (β_{std} = −0.32 [95% CI, −0.48, −0.15]) participants.

Fig. 2 Associations between CSF pTau and pTau/Aβ_{40}, Aβ PET, tau PET, neurodegeneration and cognition. Associations of baseline CSF pTau and pTau/Aβ_{40} with baseline Aβ PET (a, b), baseline Temporal-metaROI FTP SUVR (c, d), baseline (e, f), and slope (g, h) of adjusted hippocampal volume (aHCV) (mm³), baseline (i, j) and slope (k, l) of PACC cognitive score. Different colors reflect the concordance and discordance between CSF pTau and CSF pTau/Aβ_{40}. For example, pTau−/pTau/Aβ_{40}− indicates the individual was negative according to both CSF pTau and CSF pTau/Aβ_{40}, while pTau+/pTau/Aβ_{40}− indicates the individual was positive according to CSF pTau but negative according to CSF pTau/Aβ_{40}.
Notably, the association with Aβ PET increased from rho value 0.51 when using CSF pTau alone to 0.67 using the CSF pTau/Aβ40 (Fig. 2a, b). Likewise, the association with tau PET increased from rho value 0.43 when using CSF pTau alone to 0.46 using the CSF pTau/Aβ40 (Fig. 2c, d). We also compared CSF pTau and CSF pTau/Aβ40 in terms of their associations with other measures of neurodegeneration biomarkers and cognition in order to further investigate the validity of CSF pTau/Aβ40. CSF pTau/Aβ40 but not CSF pTau was negatively associated with baseline aHCV (Fig. 2e, f), and the association with aHCV slope increased from rho value −0.18 when using CSF pTau alone to −0.38 using the CSF pTau/Aβ40 (Fig. 2g, h). The association with baseline PACC and PACC slope increased from rho values −0.33 and −0.24 when using CSF pTau alone to −0.45 and −0.39 using the CSF pTau/Aβ40 respectively (Fig. 2i, l).

Based on these findings, CSF pTau/Aβ40 was used to represent tauopathy in CSF instead of CSF pTau for all subsequent analyses.

We also found that CSF pTau and CSF pTau/Aβ40 were both more strongly associated with Aβ PET than they were with tau PET (Fig. 2a–d).

Regions with significant associations between CSF pTau/Aβ40 and tau PET

CSF pTau/Aβ40 was significantly associated with tau PET SUVRs in all the 35 ROIs, and the strongest

| Table 1 Characteristics of participants in this study |
|-----------------|-----------------|-----------------|-----------------|
| Aβ PET status   | Aβ− | Aβ+ | p value |
|-----------------|-----------------|-----------------|-----------------|
| Sample size     | 341 participants with CSF Aβ40, Aβ42 and pTau, Aβ PET, and tau PET | | |
| CU/MCI/AD       | 195 (57%)       | 146 (43%)       | |
| Age (years)     | 70.4 (9.4)      | 74.7 (10.4)     | < 0.001 |
| Education (years) | 18 (2) | 16 (3) | 0.07 |
| Female (%)      | 115 (59%)       | 78 (53%)        | 0.44 |
| APOE-ε4 (%)     | 37 (19%)        | 83 (57%)        | < 0.001 |
| Aβ PET (Centiloids) | 4.9 (11.0)     | 71.2 (59.0)     | < 0.001 |
| CSF Aβ42        | 1421 (817)      | 653 (377)       | < 0.001 |
| CSF Aβ42        | 18,440 (7680)   | 17,770 (6150)   | 0.56 |
| CSF pTau        | 17.8 (8.2)      | 27.2 (19.9)     | < 0.001 |
| CSF pTau/Aβ40   | 0.0010 (0.0002) | 0.0016 (0.0009) | < 0.001 |
| FTP SUVR (Temporal-metaROI) | 1.16 (0.08) | 1.28 (0.27) | < 0.001 |
| aHCV (mm³)      | 7530 (1469)     | 6990 (1750)     | < 0.001 |
| PACC            | 0.25 (5.06)     | −2.33 (11.64)   | < 0.001 |

| Sample size     | 116 participants with ≥ 2 tau PET scans | 75 (65%) |
| CU/MCI/AD       | 41 (35%) | 39/25/11 |
| FTP visits (median (IQR, range), no.) | 2.0 (1.0, 2–4) | 2.0 (1.0, 2–4) |
| FTP follow-up (Median (IQR, range), years) | 1.8 (1.1, 0.8–3.3) | 1.2 (1.0, 0.7–3.1) |

| Sample size     | 139 participants with ≥ 2 aHCV data | 75 (54%) |
| CU/MCI/AD       | 64 (46%) | 39/24/12 |
| MRI visits (median (IQR, range), no.) | 2.0 (0, 2–4) | 2.0 (0.5, 2–4) |
| MRI follow-up (median (IQR, range), years) | 2.0 (1.0, 0.9–3.8) | 1.2 (0.9, 0.8–3.2) |

| Sample size     | 202 participants with ≥ 2 PACC measurements | 103 (51%) |
| CU/MCI/AD       | 99 (49%) | 49/36/18 |
| PACC visits (median (IQR, range), no.) | 2 (0, 2–4) | 2 (1, 2–5) |
| PACC follow-up (median (IQR, range), years) | 2.0 (1.0, 0.9–3.0) | 1.1 (1.0, 0.7–4.0) |

Abbreviations: Aβ amyloid-β, AD Alzheimer’s disease, aHCV adjusted hippocampal volume, CU cognitively unimpaired, FTP 18F-flortaucipir, IQR interquartile range, MCI mild cognitive impairment, PACC Preclinical Alzheimer Cognitive Composite, pTau phosphorylated tau, SUVR standardized uptake value ratio
association regions were within the Temporal-metaROI region (Fig. 3). We repeated these analyses in Aβ−, Aβ+, CU, and non-demented (CU and MCI) participants. The results were similar for Aβ+ participants (supplemental Fig. 10A), whereas no association was found for Aβ− participants. Similar features were observed for CU and non-demented (CU and MCI) participants (supplemental Fig. 10B-C). Because the strongest associations between CSF pTau/Aβ40 and tau PET were within the Temporal-metaROI (Fig. 3), which has been commonly used to detect tau deposition in brain [40–46], temporal tau PET (Temporal-metaROI FTP SUVR) was selected to represent tau deposition for further analyses unless otherwise noted.

Cross-sectional associations between Aβ PET, CSF pTau/ Aβ40, and tau PET

We found Aβ PET was significantly associated with CSF and PET tau measurements, which were driven by Aβ+ individuals. Baseline Aβ PET was positively associated with CSF pTau (Fig. 4a, $β_{std} = 0.32$ [95% CI, 0.15, 0.48]), CSF pTau/Aβ40 (Fig. 4b, $β_{std} = 0.43$ [95% CI, 0.28, 0.58]), and tau PET in Temporal-metaROI (Fig. 4c, $β_{std} = 0.34$ [95% CI, 0.21, 0.48]) and entorhinal (Supplemental Fig. 11A, $β_{std} = 0.36$ [95% CI, 0.23, 0.48]) in Aβ+ participants. Notably, the association with Aβ PET increased from rho value 0.38 when using CSF pTau alone to 0.60 using the CSF pTau/Aβ40 (Fig. 4a). In Aβ− participants, Aβ PET was weakly but significantly associated with tau PET in entorhinal (Supplemental Fig. 11A, $β_{std} = 0.17$ [95% CI, 0.02, 0.33]).

In order to investigate the prevalence of abnormal CSF pTau, CSF pTau/Aβ40, and tau PET (entorhinal or Temporal-metaROI), Aβ− and Aβ+ participants were classified as tau normal (T−)/abnormal (T+) using CSF pTau or CSF pTau/Aβ40 or tau PET thresholds, dividing the whole cohort into A−/T−, A−/T+, A+/T−, and A+/T+ groups. Few Aβ− participants had abnormal CSF pTau/Aβ40 (7.6%) and temporal tau PET (5.3%), whereas Aβ+ participants showed a 3.0–4.5 times higher percentage of abnormal CSF pTau/Aβ40 (32.6%) and temporal tau PET (24.0%) than Aβ− participants (Fig. 4b, c). Among Aβ− participants, abnormal CSF pTau had 1.66 times (12.6% vs. 7.6%, odds ratio = 1.66) higher prevalence (Fig. 4e, 13.8% vs. 5.1%, odds ratio =
2.7 [95%CI, 1.3–6.3], \( p = 0.008 \) than abnormal CSF pTau/A\( \beta \) only in A\( \beta \)– participants, whereas abnormal CSF pTau/A\( \beta \) only had marginally higher prevalence (Fig. 4f, 12.3% vs. 5.5%, odds ratio = 2.3 [95%CI, 0.9–6.0], \( p = 0.08 \)) than abnormal CSF pTau only in A\( \beta \)+ participants. CSF pTau/A\( \beta \) (Fig. 4g, \( \beta_{\text{std}} = 0.59 \) [95% CI, 0.51, 0.68]) were positively associated with temporal tau PET across all participants. A\( \beta \)+ participants were responsible for this relationship because no association was found in A\( \beta \)– participants (Fig. 4h, i). We found that in A\( \beta \)– participants, the proportion of participants with abnormal CSF pTau/A\( \beta \) only was comparable to those with an abnormal temporal
tau PET only (10.8% vs. 6.7%) (Fig. 4h). In contrast, in $\alpha$β+ participants, those with abnormal CSF pTau/Aβ40 only were fourfold more prevalent than the abnormal temporal tau PET only (Fig. 4i, 26.7% vs. 6.8%, odds ratio = 3.9 [95% CI, 1.9–8.8], $p < 0.001$). The results were similar for entorhinal tau PET (Supplemental Fig. 11B-D).

The conservative cutoffs of CSF pTau, CSF pTau/Aβ40, entorhinal tau PET, and temporal tau PET were higher and defined fewer “T+” individuals, while the results of concordance of different biomarkers were substantially the same as the initial cutoffs (Supplemental Figs. 12–13).

**Associations between $\alpha$β PET, CSF pTau/Aβ40, tau PET and longitudinal tau PET change**

Baseline $\alpha$β PET (Fig. 5a, $\beta_{\text{std}} = 0.42$ [95% CI, 0.22, 0.63]), CSF pTau/Aβ40 (Fig. 5b, $\beta_{\text{std}} = 0.61$ [95% CI, 0.43, 0.79]), and Temporal-metaROI tau PET (Fig. 5c, $\beta_{\text{std}} = 0.63$ [95% CI, 0.45, 0.81]) were all associated with subsequent tau PET increase ($\Delta$FTP) in $\alpha$β+ participants (Fig. 5a–c). In contrast, no predictive effect was found in $\alpha$β− participants.

The latent variable model demonstrated that the direct association between $\alpha$β and $\Delta$FTP increase in $\alpha$β+ participants was not significant after including the CSF pTau/Aβ40 and FTP (Fig. 5d), reducing the $\beta$ value from 0.47 to 0.04 (91% change). CSF pTau/Aβ40-involved pathways (pathway1: from $\alpha$β PET to CSF pTau/Aβ40 to $\Delta$FTP; pathway2: from $\alpha$β PET to CSF pTau/Aβ40 to FTP to $\Delta$FTP) explained 70% of the association (total effect) between $\alpha$β PET and $\Delta$FTP increase in $\alpha$β+ participants.

**Prediction of longitudinal cognitive decline**

Baseline $\alpha$β PET (Fig. 6a, $\beta_{\text{std}} = -0.41$ [95% CI, $-0.59$, $-0.23$]), CSF pTau/Aβ40 (Fig. 6b, $\beta_{\text{std}} = -0.53$ [95% CI, $-0.69$, $-0.36$]), and Temporal-metaROI tau PET (Fig. 6c, $\beta_{\text{std}} = -0.73$ [95% CI, $-0.86$, $-0.60$]) were all associated...
with subsequent cognitive decline in Aβ+ participants (Fig. 6), whereas only tau PET ($\beta_{std} = -0.68\,[95\%\ CI, -0.87, -0.48], \ p < 0.001$) remained predictive when all variables were added into one multivariate model. The results were similar for entorhinal tau PET. In contrast, only CSF pTau/Aβ40 ($\beta_{std} = -0.22\,[95\%\ CI, -0.42, -0.03], \ p = 0.03$) was associated with subsequent cognitive decline in Aβ- participants.

**Discussion**

This study had several primary findings: (1) use of a CSF pTau/Aβ40 ratio reduced noise in pTau likely introduced by individual variability in CSF production rates, and increased associations with Aβ PET, tau PET, hippocampal volume, and cognition compared with CSF pTau alone. (2) Tau PET associations with CSF pTau/Aβ40 were highest in medial and lateral temporal regions. (3) Associations between Aβ PET, CSF pTau/Aβ40 and tau PET (cross-sec-
tionally and longitudinally) were substantially driven by Aβ PET-positive individuals. (4) Among these Aβ+ individuals, most participants (66%) were concordant on CSF pTau/Aβ40 and Temporal-metaROI tau PET, but among discordant individuals, those with abnormal CSF pTau/Aβ40 and normal tau PET were 4 times more prevalent (26.7%) than those with abnormal tau PET and normal CSF pTau/Aβ40 (6.8%). (5) Among these Aβ+ individuals, baseline Aβ PET, CSF pTau/Aβ40 and tau PET were all associated with subsequent tau PET increase, while CSF
pTau/Aβ40 significantly mediates the association between Aβ PET and tau PET (cross-sectionally and longitudinally). (6) Only tau PET was predictive of longitudinal cognitive decline when baseline Aβ PET, CSF pTau/Aβ40, and tau PET were put in one multivariate model.

Our motivation to adjust CSF pTau measurements was based on our observation that Aβ PET-negative individuals had abnormal (“positive”) CSF pTau that correlated positively with high (“normal”) CSF Aβ42 (Fig. 1c), suggesting that these elevated measurements reflect high CSF total production rate but not abnormal tau. Similar patterns of elevated pTau and CSF Aβ42 in the negative range that are presumably artifactual have been observed in other recent studies from ADNI, BIOFINDER, and Washington University [7, 16], and with CSF data analyzed with mass spectrometry (Supplementary Fig. 9) and immunoassays. CSF pTau/Aβ40 appears to be a compelling strategy for improving sensitivity to CSF tau pathology, since this approach reversed the biologically implausible association between CSF pTau and Aβ42 and improved associations with downstream markers of AD progression compared with CSF pTau alone. Because CSF Aβ40 was not associated with PET measures of either Aβ or tau (Fig. 1a, b) and is not elevated in AD [21–29], its use as a normalization variable is unlikely to bias estimates of CSF pTau. This strategy is in line with recent work supporting use of CSF Aβ42/Aβ40 instead of CSF Aβ42 alone [6, 7, 17–19], and use of CSF pTau/tTau instead of CSF pTau [47]. However, our results did not exclude other possibilities for the enhanced associations between CSF pTau/Aβ40 and downstream markers of AD progression. For example, a few studies [48–51] have reported that CSF Aβ40 may decrease in cognitively impaired individuals, which may thereby increase the CSF pTau/Aβ40 ratios of cognitively impaired individuals. In addition, one animal study [52] observed that CSF Aβ40 may increase in the earliest phase of Aβ accumulation in mouse models, which may delay the increase of CSF pTau/Aβ40 in the preclinical stage of AD. We found only trend-level decreases in CSF Aβ40 in Aβ− unimpaired and Aβ+ impaired groups relative to Aβ+ unimpaired individuals (data not shown), but it is possible that early and late changes in CSF Aβ40 may contribute to the tau-related effects we observed.

Associations between CSF pTau/Aβ40 and tau PET were stronger in ROIs in the temporal lobe than other areas such as frontal and occipital lobes that accumulate tau in later stages of disease [53, 54], consistent with our observation and recent studies [14, 15, 55] that CSF tauopathy is an early marker of tau pathology. The strongest associations were within the medial and lateral temporal regions that overlapped with a tau composite region (Temporal-metaROI) reported previously as well as a “Braak III/IV” like ROI [40, 41, 45, 56]. Notably, the relationship between CSF pTau/Aβ40 and tau PET was primarily driven by Aβ PET positivity and less influenced by clinical diagnosis (Supplementary Fig. 10), which could also reflect a greater range of tau pathology in Aβ+ individuals and a stronger relationship between Aβ and tau than between tau and clinical symptoms [57, 58]. Consistent with the present study, Chhatwal et al. [10] reported a significant association between CSF pTau and tau PET in limbic regions of the temporal lobe in CU elderly adults. However, two studies [9, 12] did not find significant association between CSF pTau and tau PET in CU individuals, perhaps due to methodological factors such as sample size and the use of CSF pTau alone rather than the CSF pTau/Aβ40 ratio.

Elevated Aβ PET was weakly associated with greater tau (CSF pTau/Aβ40 or tau PET) in the Aβ− individuals, which was in line with previous reports [59–62]. However, also consistent with previous studies [42, 63, 64], we found that tau (CSF pTau/Aβ40 or tau PET) was rarely (5.3–7.9%) abnormal in the Aβ− range (Fig. 4). Furthermore, baseline Aβ PET, CSF pTau/Aβ40, and tau PET were predictive of subsequent tau PET increase in the Aβ+ group only, which is in agreement with recent tau PET studies [40, 65]. Together, these findings suggest that tau is rarely increasing or abnormal when Aβ is absent.

In line with our findings, one recent study [15] also reported that CSF pTau mediated the association between Aβ PET and tau PET, and higher CSF pTau was associated with faster tau PET increase rates in cognitively impaired individuals. Unlike this study, we found baseline tau PET was also related to the tau PET rate. The discrepancy may be explained by the larger sample size and the use of white matter reference for longitudinal tau PET in the present study. In the mediation analyses, two significant CSF pTau/Aβ40-linked pathways were identified, which explained 70% of the association between Aβ PET and longitudinal brain tau accumulation among Aβ+ individuals.

Finally, consistent with three recent reports [14, 15, 66], we found that tau PET was more predictive of subsequent cognitive decline than CSF tau among Aβ+ individuals, suggesting brain tau may reflect a later stage closer to cognitive decline than CSF tau on the Alzheimer’s continuum. Interestingly, previous comparisons of CSF and PET measurements of Aβ were analogous in showing that cognitive decline is more related to Aβ PET than CSF Aβ [1, 3, 67, 68]. We also noticed that higher CSF pTau/Aβ40 was significantly related to faster longitudinal cognitive decline in amyloid-negative individuals. No previous studies reported the association between CSF pTau and cognitive decline in amyloid-negative individuals, which should be cautious to interpret this result and may need to be validated in other samples.
This study has several limitations. The CSF pTau/Aβ40 threshold was derived from the existing sample of ADNI participants and only pTau181 was available in the ADNI sample at this time, so it would be helpful to validate the findings in other samples and with other phosphorylation sites (i.e., pTau17 [47, 69]) and tau PET ligands. Furthermore, only 9% (31/341) of the participants in this study were AD patients and the longitudinal observation was of relatively short duration, so it would be helpful to confirm those findings using additional participants and extended longitudinal data. Finally, one possible explanation for the differences we observed between tau PET and CSF pTau measurements is that CSF pTau may reflect Aβ in addition to tau pathology. Our observation that both CSF pTau and CSF pTau/Aβ40 had stronger associations with Aβ PET than they did with tau PET (Fig. 2a–d) is consistent with this possibility, but further pathology studies are needed to verify this interpretation.

Conclusions
In summary, we found that the use of a CSF pTau/Aβ40 ratio improves the sensitivity to detect CSF tau by adjusting for individual differences in CSF production. Furthermore, although PET and CSF measures of tau are broadly concordant in the majority (76%) of individuals when measured dichotomously, our findings support recent work [14] indicating that CSF and PET measures of tau may not be interchangeable in the A/T/N research framework [70]. Among amyloid-positive individuals, higher tauopathy measured with CSF and PET is related to faster tau accumulation, while tau PET was more predictive of subsequent cognitive decline than CSF tau. Taken together, these findings suggest that the interchangeability of PET and CSF measures of tau likely depends on the goals of the study, the phase of AD being studied, and the clinical characteristics of the population.

Supplementary information
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Additional file 1: Figure S1. The ROC analysis using the Youden index classifying 280 Aβ- ADNI cognitively unimpaired (CU) participants and 183 Aβ + ADNI MCI and AD patients as the endpoint to define the cutoff ≥ 2.25 for Temporal-metaROI FTP SUVR. AUC: 0.876 (95%CI, 0.84, 0.912). Among these 463 ADNI participants, 217 (47%) participants were included in the analyses of the manuscript. Figure S2. Histograms of Temporal-metaROI FTP SUVRs of (A) all 775 ADNI participants, (B) 280 Aβ-ADNI CU participants and (C) 183 Aβ + ADNI MCI and AD patients with tau PET scan. Red dotted line is the cutoff of Temporal-metaROI FTP SUVR 1.25. Figure S3. The ROC analysis using the Youden index classifying 280 Aβ- ADNI CU participants and 183 Aβ + ADNI MCI and AD patients as the endpoint to define the cutoff ≥ 2.11 for entorhinal FTP SUVR. AUC: 0.891 (95%CI, 0.856, 0.926). Figure S4. Histograms of entorhinal FTP SUVRs of (A) all 775 ADNI participants, (B) 280 Aβ- ADNI CU participants and (C) 183 Aβ + ADNI MCI and AD patients with tau PET scan. Red dotted line is the cutoff of entorhinal FTP SUVR 1.21. Figure S5. The ROC analysis using the Youden index classifying 320 Aβ- ADNI CU participants and 429 Aβ = ADNI MCI and AD patients as the endpoint to define the cutoff ≥ 2.22 for CSF p-Tau. AUC: 0.865 (95%CI, 0.84, 0.89). Among these 749 ADNI participants, 212 (28%) participants were included in the analyses of the manuscript. Figure S6. Histograms of CSF p-Tau of (A) all 1534 ADNI participants, (B) 320 Aβ- ADNI CU participants and (C) 429 Aβ + ADNI MCI and AD patients with CSF p-Tau measurement. Red dotted line is the cutoff of CSF p-Tau 22. Figure S7. The ROC analysis using the Youden index classifying 169 Aβ- ADNI CU participants and 160 Aβ + ADNI MCI and AD patients as the endpoint to define the cutoff ≥ 0.0012 for the CSF p-Tau/Aβ40 ratio. AUC: 0.976 (95%CI, 0.96, 0.99). Among these 329 ADNI participants, 201 (61%) participants were included in the analyses of the manuscript. Figure S8. Histograms of CSF p-Tau/Aβ40 for (A) all 447 ADNI participants, (B) 169 Aβ- ADNI CU participants and (C) 160 Aβ + ADNI MCI and AD patients with CSF p-Tau/Aβ40. Red dotted line is the 0.0012 cutoff for the CSF p-Tau/Aβ40 ratio. Figure S9. Cross-sectional associations between CSF MASS Aβ42 and CSF p-Tau. The vertical gray dashed line reflects the abnormal threshold of CSF p-Tau. Abbreviations: p-Tau = phosphorylated tau; Aβ = amyloid-β; SUVR = standardized uptake value ratio; Aβ = amyloid-β; FTP = 18F-flortaucipir; MCI = mild cognitive impairment; AD = Alzheimer’s disease. Figure S10. Regions with significant association between CSF p-Tau and FTP tau in (A) Aβ+, (B) CU and (C) non-demented participants. Abbreviations: Spearman ρ = Spearman’s correlation coefficient; p-Tau = phosphorylated tau; Aβ = amyloid-β; FTP = 18F-flortaucipir; SUVR = standardized uptake value ratio; CU = cognitively unimpaired; MCI = mild cognitive impairment; AD = Alzheimer’s disease. Figure S11. Cross-sectional associations between Aβ PET, CSF p-Tau/Aβ40 and entorhinal tau PET. (A), Associations between baseline entorhinal tau PET and Aβ PET. Associations between baseline CSF p-Tau/Aβ40 and entorhinal tau PET in the whole cohort (B), Aβ- (C) and Aβ+ (D) participants. The vertical and horizontal gray dashed lines reflect the abnormal thresholds of corresponding biomarkers in x-axis and y-axis respectively. Abbreviations: Aβ = amyloid-β; A = Aβ PET; – = negative; + = positive; AD = Alzheimer’s disease; CU = cognitively unimpaired; FTP = 18F-flortaucipir; MCI = mild cognitive impairment. Figure S12. Cross-sectional associations between Aβ PET, CSF p-Tau/Aβ40 and tau PET using alternative cutoffs. Associations between baseline Aβ PET and (A) CSF p-Tau, (B) CSF p-Tau/Aβ40 and (C) temporal tau PET. Associations between baseline CSF p-Tau and CSF p-Tau/Aβ40 in the whole cohort (D), Aβ- (E) and Aβ + (F) participants. Associations between baseline CSF p-Tau/Aβ40 and Temporal-metaROI tau PET in the whole cohort (G), Aβ- (H) and Aβ+ (I) participants. The vertical and horizontal gray dashed lines reflect the abnormal thresholds of corresponding biomarkers in x-axis and y-axis respectively. Abbreviations: Aβ = amyloid-β; A = Aβ PET; – = negative; + = positive; AD = Alzheimer’s disease; CU = cognitively unimpaired; FTP = 18F-flortaucipir; MCI = mild cognitive impairment; SUVR = standardized uptake value ratio. AUC: 0.891 (95%CI, 0.856, 0.926). Figure S13. Cross-sectional associations between Aβ PET, CSF p-Tau/Aβ40 and entorhinal tau PET using alternative cutoffs. (A), Associations between baseline entorhinal tau PET and Aβ PET. Associations between baseline CSF p-Tau/Aβ40 and entorhinal tau PET in the whole cohort (B), Aβ- (C) and Aβ+ (D) participants. The vertical and horizontal gray dashed lines reflect the abnormal thresholds of corresponding biomarkers in x-axis and y-axis respectively. Abbreviations: Aβ = amyloid-β; A = Aβ PET; – = negative; + = positive; AD = Alzheimer’s disease; CU = cognitively unimpaired; FTP = 18F-flortaucipir; MCI = mild cognitive impairment.

Abbreviations
Aβ: Amyloid-β; ADNI: Alzheimer’s Disease Neuroimaging Initiative; β∥: Standardized β coefficient; CSF p-Tau: CSF phosphorylated tau; CU: Cognitively unimpaired; CI: Confidence interval; FTP: 18F-flortaucipir; FBP: 18F-flortebetan; GLM: Generalized linear model; MCI: Mild cognitive impairment; PACC: Preclinical Alzheimer Cognitive Composite; ROI: Regions of interest; SNAP: Non-Alzheimer’s pathology; SUVR: Standardized uptake value ratio

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Page 12 of 15
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Authors’ contributions
T.G. contributed to the study design, drafting and editing of the manuscript, data and statistical analysis, and interpretation of results; D.K. contributed to acquiring data and editing the manuscript; R.L. contributed to interpretation of results and editing the manuscript; L.M.S. and J.Q.T contributed to acquiring data, interpretation of results, obtaining funding, and editing the manuscript; W.J.J. and S.M.L. contributed to acquiring data, interpretation of results, obtaining funding, editing the manuscript, and study supervision. The author(s) read and approved the final manuscript.

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Availability of data and materials
The dataset supporting the conclusions of this article is available in the ADNI repository (adni.loni.usc.edu). Derived data is available from the corresponding author on request by any qualified investigator subject to a data use agreement.

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Formed written consent was obtained from all participants at each site of ADNI.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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