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Characterization of Alzheimer Disease Biomarker Discrepancies Using Cerebrospinal Fluid Phosphorylated Tau and AV1451 Positron Emission Tomography

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IMPORTANCE Fluid and imaging biomarkers of Alzheimer disease (AD) are often used interchangeably, but some biomarkers may reveal earlier stages of disease.

OBJECTIVE To characterize individuals with tau abnormality indicated by cerebrospinal fluid (CSF) assay or positron emission tomography (PET).

DESIGN, SETTING, AND PARTICIPANTS Between 2010 and 2019, 322 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent CSF and PET assessments of tau pathology. Data-driven, clinically relevant thresholds for CSF phosphorylated tau (P-tau) (≥26.64 pg/mL) and flortaucipir-PET meta–regions of interest (ROI) (standard uptake value ratio ≥1.37) indicated participants' tau status as CSF^-/PET^-, CSF^+/PET^-, CSF^-/PET^+, and CSF^+/PET^+. Of 1659 ADNI participants with a CSF or flortaucipir assessment, 588 had both measures (1071 were excluded). Among these, 266 were further excluded because they did not have flortaucipir and CSF testing within less than 25 months, leaving 322 for analysis. Of these, 213 were cognitively unimpaired (CU); 98 had mild cognitive impairment (MCI); and 11 had AD dementia.

MAIN OUTCOMES AND MEASURES We compared tau-positive vs tau-negative groups as indicated by either modality, demographic and clinical variables, amyloid β-PET burden, and flortaucipir-PET binding across Braak stage–related ROIs. We also compared 5-year rates of CSF P-tau accumulation and cognitive decline prior to flortaucipir-PET scanning.

RESULTS Among the 322 study participants, 180 were women (56%), and the mean (SD) age was 73.08 (7.37) years. Two hundred ten participants were CSF^-/PET^- (65%); 63 were CSF^+/PET^- (19.5%); 15 were CSF^-/PET^+ (4.6%); and 34 were CSF^+/PET^+ (10.5%). Most CSF^-/PET^+ participants had measures near CSF or PET tau thresholds. The CSF^+/PET^- participants showed faster 5-year accrual of P-tau and increased flortaucipir-PET binding in early Braak ROIs but similar memory decline compared with CSF^-/PET^- participants. Tau-positive individuals by either measure showed increased amyloid β-PET burden. All CSF^+/PET^+ individuals were amyloid-positive, and 26 had MCI or AD dementia (76%). Compared with the CSF^-/PET^- group, CSF^+/PET^+ individuals had experienced faster 5-year accrual of CSF P-tau and decline in memory and executive function, resulting in reduced cognitive abilities at the time of flortaucipir-PET assessment.

CONCLUSIONS AND RELEVANCE Suprathreshold CSF P-tau without flortaucipir-PET abnormality may indicate a stage of AD development characterized by early tau abnormality without measurable loss in cognitive performance. Persons with both tau CSF and PET abnormality appear to have reduced cognitive capacities resulting from faster antecedent cognitive decline. Elevation of CSF P-tau appears to precede flortaucipir-PET positivity in the progression of AD pathogenesis and related cognitive decline.

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Supplemental content

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Alzheimer disease (AD) includes a decades-long period of pathologic changes leading to dementia onset.[1,2] To improve and rationalize the early detection of disease, the AD community is considering a biology-based disease classification relying principally on evidence of characteristic AD amyloid-β (Aβ) and tau pathologies.[3] Such evidence can come from analysis of cerebrospinal fluid (CSF) or positron emission tomography (PET). Because these modalities are not typically available simultaneously, their results are often used interchangeably. However, CSF and PET indicators of Aβ pathology appear to provide overlapping, but not identical, information.[4,5] Thus, some have suggested that CSF Aβ abnormality may precede Aβ-PET positivity.[6] Discordance of these 2 biomarker measures may therefore indicate different stages of disease progression.

Fluorine 18-labeled [^{18}F] flortaucipir (AV1451) is a novel PET tracer that binds to the paired helical filaments of tau in neurofibrillary tangles (NFTs).[7] This tracer shows good correlation with CSF tau[8,9] and provides similar accuracy for AD diagnosis but may reveal different aspects of progressive tau pathology.[10,11] We therefore investigated whether discordant assessments of CSF and PET tau status denoted different stages of AD pathogenesis. Based on the comparison of fluid and imaging biomarkers of Aβ pathology, we hypothesized that abnormality in CSF tau alone would denote a stage of disease intermediate between concordant-negative and concordant-positive CSF/PET tau status.

Key Points

Question Do cerebrospinal fluid (CSF) and positron emission tomography (PET) measures provide different information about Alzheimer disease–related tau pathology?

Findings In this cohort study using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, one-third of participants had abnormal CSF tau or were tau positive on both CSF assay and PET, while tau-PET positivity alone was relatively rare. Individuals whose CSF was tau positive had a history of accelerated CSF tau accrual, but only persons with tau-PET abnormality showed a similar significant decline in cognition.

Meaning Cerebrospinal fluid tau abnormality may be detected earlier in the AD pathogenetic process than flortaucipir-PET positivity and may occur before measurable cognitive decline.

Methods

Participants

We downloaded Alzheimer's Disease Neuroimaging Initiative (ADNI) data from http://adni.loni.usc.edu in August 2019. The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael Weiner, MD. Its primary goal has been to test whether serial magnetic resonance imaging, PET, and various clinical, biologic, and neuropsychological markers can be combined to measure progression of mild cognitive impairment (MCI) and early AD dementia. Each ADNI study site received approval from its institutional ethical standards committee on human experimentation. Written informed consent was obtained from all research participants and from collateral informants when applicable. All research complied with ethical principles of the Declaration of Helsinki. Some 588 ADNI participants had at least 1 CSF assessment and 1 flortaucipir scan. Among these, 322 participants (213 cognitively unimpaired [CU], 98 with MCI, and 11 with AD dementia at time of flortaucipir-PET) had both assessments within a 25-month interval and are considered here.

PET Image Processing

Amyloid-β (florbetapir, or [^{18}F]AV45; florbetaben, or FBB) and tau (flortaucipir; [^{18}F]AV1451) data were downloaded from the ADNI website in their most fully preprocessed format (series description: ADNI-1 scans N3 and ADNI-GO/2 scans N3). These Aβ-PET and tau-PET data had been preprocessed using the ADNI pipeline. Briefly, each participant's magnetic resonance imaging T1-weighted magnetization-prepared rapid acquisition gradient echo image from the nearest available visit was segmented and parcellated with Freesurfer, version 5.3.0 (Martinos Center for Biomedical Imaging) to define regions of interest (ROIs) in native space. The PET images were then coregistered to the corresponding magnetization-prepared rapid acquisition gradient echo using SPM, version 5 (the FIL Methods Group). The intensity-normalized standard uptake value ratio (SUVR) value for each ROI was obtained by dividing tracer uptake in these regions by the value in a predefined reference region (whole cerebellum for florbetapir-PET and FBB-PET; inferior cerebellum gray matter for flortaucipir-PET). Composite SUVRs were obtained calculating volume-weighted means of groups of Freesurfer-defined regions (eg, global neocortical SUVR for florbetapir-PET or FBB-PET[12] and flortaucipir-PET Braak stage–specific ROIs).[13,14] Florbetapir-PET and FBB-PET results were considered positive if global SUVRs were at least 1.11 or at least 1.08, as recommended by ADNI.[12,15] For flortaucipir-PET, we considered tracer binding in a weighted composite (metaROI) of regions including bilateral entorhinal, amygdala, fusiform, inferior, and middle temporal cortices that was shown to be AD specific (eMethods in the Supplement).[16] Receiver operating curve analyses in an independent sample then identified the threshold for flortaucipir positivity as the SUVR that most efficiently (maximum percentage correct classification) differentiated 96 $A\beta^-$ CU individuals from 19 $A\beta^+$ ADNI participants with late-stage MCI (n = 8) or AD (n = 11). All these had Aβ-PET data but lacked CSF and flortaucipir-PET assessments within 25 months. To improve precision of this threshold estimate, we considered data from some participants having multiple scans, thereby yielding 104 data points for $A\beta^-$ CU individuals and 24 data points for $A\beta^+$ participants with MCI/AD. The resulting flortaucipir-PET meta-ROI SUVR cutoff of at least 1.37 yielded 71% sensitivity and 98% specificity with 93% efficiency (eFigure 2A in the Supplement). This and our main analyses considered data without partial volume correction.

Partial volume correction flortaucipir-PET data gave higher SUVR values (eFigure 1 in the Supplement) and a correspondingly higher positivity threshold (eFigure 2B in the Supplement). Nonetheless, the corrected data yielded a similar tau-PET categorization because only 8 people were categorized differently (eFigure 3 in the Supplement). Uncorrected SUVRs for these 8 were close to the original threshold. To assure that our results were not influenced unduly by these participants' results, we repeated our analyses after removing persons within 5% of the CSF or PET thresholds. The essentially unchanged results appear in eFigures 4 and 5 in the Supplement.

CSF Measurements

Lumbar punctures (LPs) were performed as described in the ADNI procedures manual (http://www.adni-info.org/). Cerebrospinal fluid samples were frozen within 1 hour after collection and shipped overnight on dry ice to the ADNI Biomarker Core laboratory. Aliquots of 500 µL were stored in polypropylene tubes at −80°C. Cerebrospinal fluid concentrations of Aβ1-42, ^{181}P-tau and total tau (t-tau) were measured using Elecsys immunoassays on a cobase 601 analyzer, version 05.02, as described.[17]

Because 2 participants lacked an Aβ-PET scan, their Aβ status was determined using a CSF Aβ1-42 cutoff of 1098 pg/mL, as described previously.[18] For CSF tau status, we used ^{181}P-tau, which is thought generally to reflect tau pathology (t-tau being considered a more general marker of neurodegeneration).[3] However, the 2 markers were highly correlated in this sample (R^2 = 0.96; eFigure 6 in the Supplement), and results were similar using t-tau to assess CSF tau positivity (data not shown). There is currently no established clinical threshold for Elecsys assessment of ^{181}P-tau. As with flortaucipir-PET, in an independent set of 330 ADNI participants (419 data points) having at least 1 LP and a concurrent florbetapir-PET scan, receiver operating curve analyses indicated a threshold of 26.64 pg/mL that best distinguished Aβ-negative CU individuals (158 persons; 224 data points) from Aβ$^+$ patients with AD (172 persons; 193 data points) with 76% sensitivity, 86% specificity, and 81% efficiency (eFigure 2C in the Supplement). Again, this independent sample lacked availability of flortaucipir and CSF tau assessments within a 25-month interval. Similarly to Aβ biomarkers, CSF was more sensitive for detection of AD, and PET was more specific.[19] While these observations likely reflect intrinsic differences between biomarker modalities, we obtained nearly identical results when forcing the PET threshold to achieve sensitivity comparable with the CSF threshold (eFigure 7 in the Supplement).

Cognitive Evaluation

All ADNI participants received detailed cognitive evaluations. We obtained composite scores reflecting memory and executive functions, as described previously,[20,21] for the LP visit and all available data in the preceding 5 years.

Statistical Analyses

Using described cutoffs for CSF P-tau and flortaucipir-PET, we classified the 322 ADNI participants as positive or negative on each modality. This resulted in 4 subgroups: CSF$^-$/PET$^-$ (concordant tau negative), CSF$^+$/PET$^-$ (discordant CSF tau-positive only), CSF$^-$/PET$^+$ (discordant tau-PET positive only), and CSF$^+$/PET$^+$ (concordant tau positive).

Using Fisher exact or Kruskal-Wallis tests, and applying post hoc Mann-Whitney *U* tests where appropriate, we compared group demographic variables (age, sex, education in years, and *APOE* ε4 carrier status) and cognitive performance (memory and executive function composite scores) at the LP visit. We also investigated CSF/PET tau groups' relation to florbetapir-PET or FBB-PET tracer binding, as well as flortaucipir uptake in Braak stage ROIs, using general linear models adjusted for participant age, sex, education (years), and delay between PET and CSF assessments.

Finally, in a retrospective analysis, we compared the 4 categories' rates of CSF P-tau accumulation and cognitive change in the 60 months preceding their flortaucipir-PET assessment. Participants having at least 2 measures (97 with CSF; 105 with cognition; available data at each time are listed in the eTable in the Supplement) were included in a linear mixed-effects analysis with random slope and intercept where the time by CSF/PET group interaction predicted change in the specified outcomes (CSF P-tau, memory, and executive function). To achieve consistency across participants, we considered the visit label (in months) as the time unit and anchored the PET visit as zero, thus attributing negative time values to retrospective data. These models were adjusted for participant age at PET, sex, *APOE* ε4 carrier status, education (years), cognitive performance at PET, and delay between PET and CSF assessments. Results using exact time instead of visit label were identical.

All analyses used Matlab, R2019a (MathWorks Inc). Two-sided *P* values of .05 or less were considered statistically significant.

Results

Demographic Characteristics

We considered 322 participants (mean [SD] age, 73.08 [7.37] years) of whom 180 were women (56%). Other demographics are summarized in the **Table**. Two hundred ten participants were classified as CSF$^-$/PET$^-$ (65%); 63 as CSF$^+$/PET$^-$ (19.5%); 15 as CSF$^-$/PET$^+$ (4.6%); and 34 as CSF$^+$/PET$^+$ (10.5%). Despite its small size, we included the interesting CSF$^-$/PET$^+$ group in our analyses. However, exclusion of persons within 5% of tau CSF and PET thresholds, or whose CSF and PET assessments occurred at different visits, reduced the size of the CSF$^-$/PET$^+$ group to only 8 and 9 individuals, respectively, further emphasizing the rarity of this group. All groups had similar age and sex ratios but differed by degree of education (Table). All tau-positive groups had a higher frequency of ε4 carriage than the CSF$^-$/PET$^-$ group. Among CSF$^+$ persons, the PET$^+$ group also had a higher frequency of ε4 carriage.

Biomarker and Cognitive Characteristics

Overall, there was good linear association between CSF P-tau and metaROI flortaucipir-PET uptake (R^2 = 0.26, P <.001;

Table. Sample Characteristics

Characteristic	Mean (SD)				P Value
	CSF⁻/PET⁻	CSF⁺/PET⁻	CSF⁻/PET⁺	CSF⁺/PET⁺	
No.	210	63	15	34	NA
Age, y	72.33 (7.06)	75.30 (7.58)	72.27 (7.34)	73.97 (8.30)	.04[a]
Female, No. (%)	118 (56)	35 (56)	6 (40)	21 (63)	.58
Diagnosis					
CU	151	49	6	8	<.001[b,c,d,e]
MCI	58	13	8	19	
AD	2	1	1	7	
Education, y	16.81 (2.33)	16.21 (2.39)	17.87 (1.69)	15.53 (2.60)	.004[c,d,f]
APOE ε4 carriers, No. (%)	58 (27)	28 (44)	10 (67)	23 (68)	<.001[a,b,c,e]
Memory composite	0.93 (0.62)	0.79 (0.64)	0.22 (0.89)	−0.17 (1.00)	<.001[b,c,d,e]
Executive function composite	1.08 (0.82)	0.95 (0.86)	0.51 (1.07)	−0.29 (1.02)	<.001[b,c,e,f]
CSF to PET, median (range), mo	0.71 (0.00 to 24.61)	0.68 (0.00 to 24.39)	0.39 (0.00 to 22.58)	1.23 (0.00 to 24.90)	.82

Abbreviations: AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography.

[a] CSF⁻/PET⁻ vs CSF⁺/PET⁻; $P < .05$.

[b] CSF⁻/PET⁻ vs CSF⁻/PET⁺; $P < .05$.

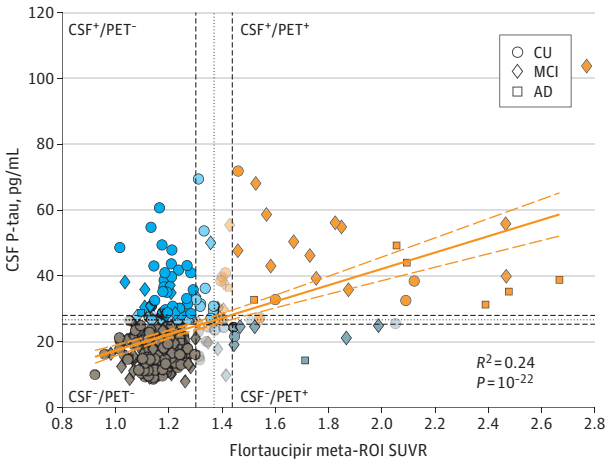
[c] CSF⁻/PET⁻ vs CSF⁺/PET⁺; $P < .05$.

[d] CSF⁺/PET⁻ vs CSF⁻/PET⁺; $P < .05$.

[e] CSF⁺/PET⁻ vs CSF⁺/PET⁺; $P < .05$.

[f] CSF⁻/PET⁺ vs CSF⁺/PET⁺; $P < .05$.

Figure 1. Classification of Alzheimer's Disease Neuroimaging Initiative (ADNI) Participants in Tau Cerebrospinal Fluid/Positron Emission Tomography (CSF/PET) Groups



We classified ADNI participants into tau CSF/PET categories based on their CSF phosphorylated tau (P-tau; positivity ≥26.64 pg/mL) and meta-regions of interest (meta-ROI) flortaucipir-PET binding (standard uptake value ratio [SUVR] threshold ≥1.37) measures. Color code represents the tau CSF/PET groups and shape indicates clinical diagnosis. Dotted lines delineate a 5% interval around tau CSF/PET thresholds. Faded dots indicate participants who would fall within this interval. CU indicates cognitively unimpaired; MCI, mild cognitive impairment; AD, Alzheimer disease.

Figure 1). In keeping with their increased *APOE* ε4 allele frequency (**Figure 2**A), individuals who were tau positive on either measure had a larger proportion of $^{A\beta+}$ individuals (Figure 2C) and, consequently, increased cortical Aβ-PET binding as compared with CSF⁻/PET⁻ participants (Figure 2D). As expected, flortaucipir-PET⁺ participants had increased tracer uptake across Braak stage I through VI ROIs. The CSF⁺/PET⁻ group also had increased flortaucipir-PET SUVR values in Braak stage ROIs I through IV when compared with the CSF⁻/PET⁻ group (eFigure 5A in the Supplement).

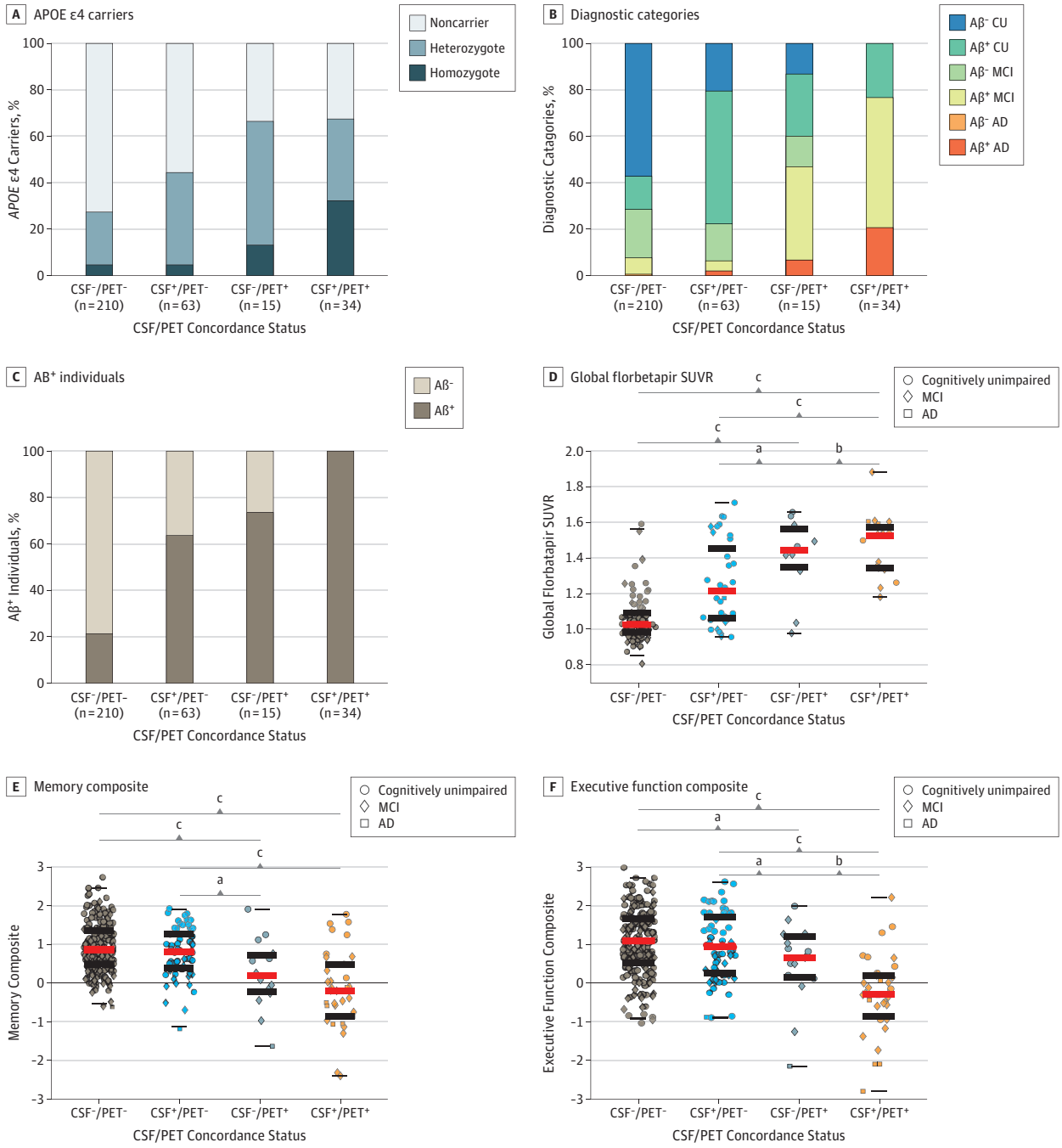
The frequency of cognitive impairment differed among groups (Figure 2B). Sixty CSF⁻/PET⁻ participants (29%) had cognitive impairment, while this was true of 14 CSF⁺/PET⁻ participants (22%), 9 CSF⁻/PET⁺ participants (60%), and 26 CSF⁺/PET⁺ participants (76%). As expected, therefore, CSF⁻/PET⁻ and CSF⁺/PET⁻ groups had comparable memory and executive function (Figure 2E and F), while the CSF⁻/PET⁺ and CSF⁺/PET⁺ groups performed worse than PET⁻ participants on memory and executive function.

Retrospective Analyses of Pathologic and Symptomatic Progression

To investigate further whether tau CSF/PET categories indicated distinct states of AD pathological progression, we inquired whether these groups had divergent antecedent biomarker and cognitive trajectories. Linear mixed-effects analyses suggested that the CSF⁺/PET⁻ and CSF⁺/PET⁺ groups had faster accrual of CSF P-tau than the CSF⁻/PET⁻ group (CSF⁺/PET⁻ time-by-group interaction β [SE], 0.06 [0.03] pg/mL/mo; $P = .02$; CSF⁺/PET⁺ time-by-group interaction β [SE], 0.11 [0.03] pg/mL/mo; $P < .001$; **Figure 3**A). A notable finding of this analysis was the difference in estimated model intercepts, (CSF⁺/PET⁻ β [SE], 17.65 [2.82]; $P < .001$; CSF⁺/PET⁺ β [SE], 29.45 [3.33]; $P < .001$; Figure 3B), suggesting that P-tau accumulation had likely begun earlier than the 5-year window considered here. Model intercepts and slope were indistinguishable among CSF⁻ groups.

Flortaucipir-PET⁺ groups had faster memory decline than the CSF⁻/PET⁻ group (Figure 3C and D). This finding was robust across the PET⁺ groups (CSF⁻/PET⁺ time-by-group interaction β [SE], −0.009 [0.004] standard units/mo; $P = .04$; CSF⁺/PET⁺ time-by-group interaction β [SE],−0.009 [0.003] standard units/mo; $P = .002$), while it appeared less certain for the CSF⁺/PET⁻ group (time-by-group interaction β [SE], −0.004 [0.003] standard units/mo; $P = .10$). The CSF⁺/PET⁺ group also

Figure 2. Demographic and Cross-Sectional Biomarker Characteristics of Tau Cerebrospinal Fluid/Positron Emission Tomography (CSF/PET) Groups



A, The proportion of *APOE* ε4 carriers was different among CSF/PET groups. In post hoc analyses, CSF⁺/PET⁻, CSF⁻/PET⁺, and CSF⁺/PET⁺ had a higher proportion of *APOE* ε4 carriers than the CSF⁻/PET⁻ group. B, The proportion of cognitively impaired participants was increased in PET⁺ groups when compared with PET⁻ groups, regardless of CSF status. C, There was a marked difference in the frequency of florbetapir and florbetaben-PET (amyloid β)⁺ individuals across groups. Post hoc analyses suggested that all tau⁺ groups on either modality had a higher proportion of florbetapir or florbetaben-PET-(amyloid β)⁺ participants compared with the CSF⁻/PET⁻ group. D, All 3 tau⁺ groups also had higher mean cortical florbetapir-PET uptake. The CSF⁻/PET⁺ and CSF⁺/PET⁺ groups had measurably lower executive function (E) and memory performance (F) compared with the CSF⁻/PET⁻ and CSF⁺/PET⁻ groups. Bars indicate group median (red line), 1st and 99th percentiles (small black line) and 25th and 75th percentiles (thick black lines).

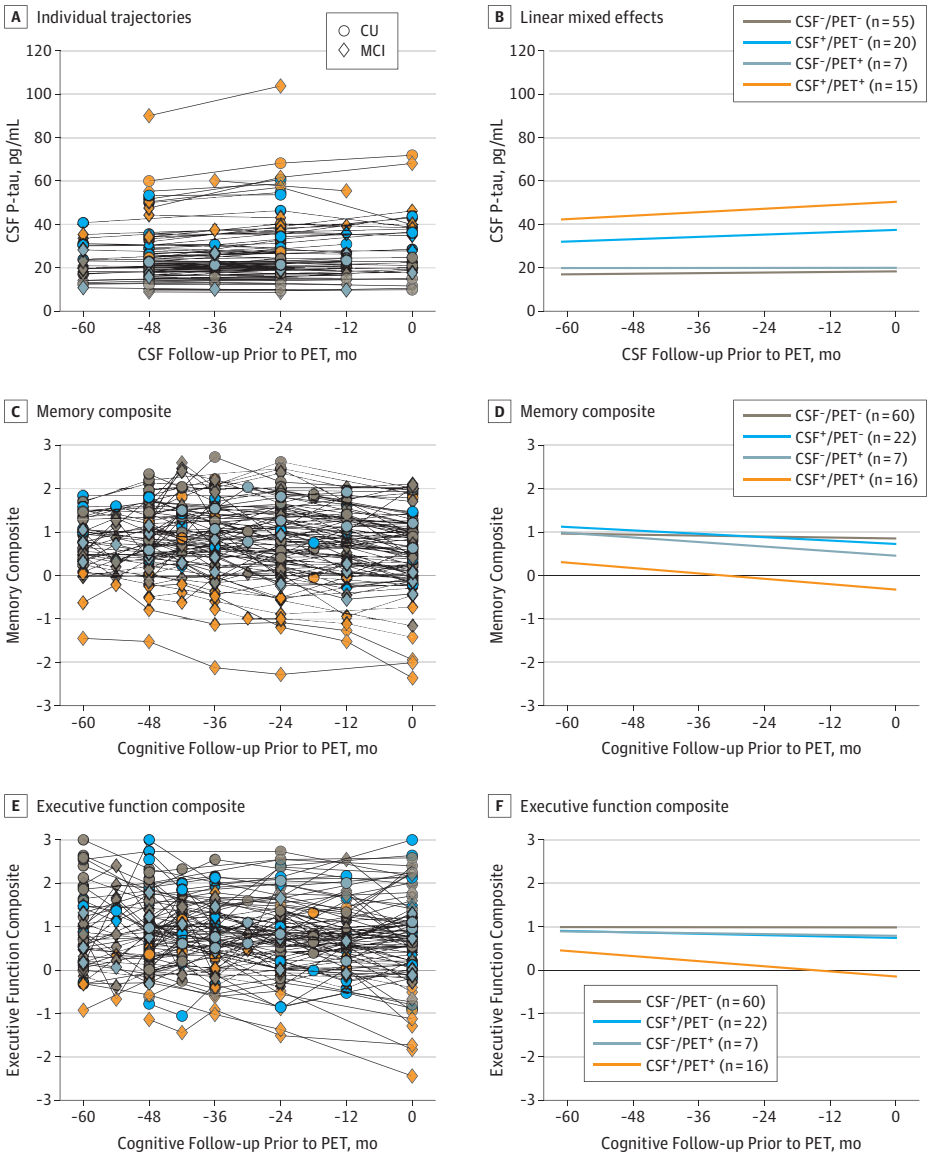
[a] $P < .05$

[b] $P < .01$

[c] $P < .005$

had a lower estimate of intercept (β [SE], −1.23 [0.22]; $P < .001$), suggesting that memory decline had also begun prior to the 5-year period considered. Similarly, as compared with the CSF⁻/PET⁻ group, the CSF⁺/PET⁺ group had accelerated ante-

Figure 3. Retrospective Trajectories of Cerebrospinal Fluid (CSF) Phosphorylated Tau (P-Tau), Memory and Executive Function



We investigated CSF P-tau and cognitive performance (memory and executive function) in the 5 years (60 months) preceding flortaucipir–positron emission tomography (PET) scanning (time 0) as a function of PET/CSF status. A, Individual trajectories and measures of CSF P-tau during the 5 years preceding the flortaucipir-PET scan. B, Results from linear mixed-effects analyses where 5-year change in CSF P-tau was estimated for each tau CSF/PET group. When compared with the CSF^-/PET^- groups, both CSF^+ groups had higher intercept values and faster rates of CSF P-tau accrual over the 5-year interval. C and D indicate the same information for the performance on the ADNI memory composite scale. All 3 tau^+ groups tended to have faster rates of memory decline over the 60 months antecedent to flortaucipir-PET scanning than the CSF^-/PET^- group. However, only the CSF^+/PET^+ group had a lower intercept when compared with the CSF^-/PET^- group, thereby suggesting that their memory decline had started earlier. D and F indicate the results of an identical analysis considering the Alzheimer's Disease Neuroimaging Initiative executive function composite. Concordant negative and discordant tau biomarker groups had similar intercept values for their performance on the executive function composite. When compared with the CSF^-/PET^- group, only the CSF^+/PET^+ group had faster decline in executive function over the 5-year period preceding flortaucipir-PET scanning.

cedent executive function decline (time-by-group interaction β [SE], −0.011 [0.004] standard units/mo; $P = .002$; Figure 3E and F) and a lower intercept (β [SE], −1.01 [0.24]; $P < .001$). A sensitivity analysis considering data only from participants who had CSF P-tau and flortaucipir assessments at the same visit recapitulated cross-sectional results, although sample sizes were too small to evaluate retrospective findings (eFigure 8 in the Supplement).

Discussion

Among 322 ADNI participants, we compared various characteristics of groups that were concordant or discordant for CSF (P-tau) and PET (flortaucipir-PET) assessments of tau positivity. As expected,[22] we observed high concordance (75%) between CSF and PET tau measures. Discordant CSF^+/PET^- participants were substantially more common than CSF^-/PET^+ persons (20% vs 5%), suggesting that CSF abnormality alone may represent the more typical intermediate state in AD pathogenesis. The CSF^-/PET^+ group principally included individuals close to CSF or PET tau positivity thresholds. This group might therefore occur as a result of variance in the 2 measures instead of reflecting real discordance between fluid and imaging markers. Interestingly, 29% of tau CSF^-/PET^- participants had cognitive impairment. However, only 15 of these were Aβ positive (25%), suggesting that their cognitive impairment resulted from causes other than AD. When compared with CSF^-/PET^- participants, CSF^+/PET^- and CSF^+/PET^+ groups had increased likelihood of Aβ

positivity, elevated flortaucipir-PET binding in Braak stage ROIs, and accelerated rates of P-tau accrual in the 5 years before flortaucipir-PET assessment. The CSF^+/PET^+ individuals also had impaired memory and executive function, presumably as a result of faster decline on these cognitive assessments during the 5 years preceding flortaucipir scanning. The CSF^-/PET^+ group had high average Aβ-PET and flortaucipir-PET binding, as well as rapid antecedent memory decline, but inference for this group was limited by its small sample size. The main results remained similar in analyses that excluded individuals close to either biomarker threshold for tau positivity, suggesting that results were not driven by these borderline instances. Only the elevation of flortaucipir retention in Braak ROIs for the CSF^+/PET^- groups was attenuated, suggesting that subthreshold flortaucipir binding may reflect early tau pathologic changes.[23] In general, these findings support the notion that CSF evidence of tau pathology indicates progressing AD pathology before flortaucipir-PET abnormality.

Given that AD pathology accrues for several decades prior to clinically apparent cognitive deficit, it should become increasingly practical to identify asymptomatic adults likely to develop subsequent dementia. Accordingly, the proposed biomarker-based classification of AD pathogenesis[3] is meant to improve the identification of asymptomatic individuals likely to show accrual of AD pathology[24] or cognitive decline.[25-27] However, application of this classification may encounter difficulties when researchers variably use imaging, CSF, or blood[28,29] markers to identify pathological change. Although it remains common practice, use of these measures interchangeably may obscure important information. For example, PET and CSF biomarkers of Aβ pathology show good association when considering individuals across the AD spectrum; yet these associations are lost when considering individual patient groups (eg, only patients with AD) or different stages of Aβ pathology (Aβ negative or positive).[30] Importantly, CSF Aβ abnormality may precede Aβ-PET positivity, thereby offering a potential indicator of earlier pathogenetic stage.[5,6]

While perhaps less dramatic than the association pattern for Aβ biomarkers, where PET and CSF modalities follow an L-shaped association, our results suggest that the CSF-then-PET sequence may apply also to tau biomarkers. CSF^+/PET^- persons may have ongoing changes in tau biochemistry that span several years prior to detectable cognitive decline. However, in our observations, this group showed only a modest increase of flortaucipir retention in Braak ROIs. This finding is consistent with the weak association between CSF ^{181}P-tau and brain NFT pathology,[31,32] for which flortaucipir has high affinity.[33,34] Cerebrospinal fluid ^{181}P-tau positivity without flortaucipir-PET anomaly may therefore indicate an intermediate pathological stage at which tau chemistry is modified but NFT pathology remains nascent and cognitive impairment is not yet apparent. However, we do note the possibility that similar investigations assaying different CSF P-tau epitopes could yield different results. For example, studies[35,36] using CSF ^{231}P-tau reported high sensitivity and specificity for detection of AD dementia vs control individuals[35] and differential diagnosis of AD.[35,36] The CSF levels of this latter epitope appear also to be more closely associated with NFT count post mortem.[37] Investigations of tau biomarker discrepancies using this assay might therefore yield less discordance.

Because tangle pathology is more strongly associated than Aβ plaque pathology with cognitive impairment,[38] and because anti-Aβ therapies have thus far failed to curb the progression of cognitive decline, tau-targeting therapies are appealing.[39] However, these may work best before NFTs are prevalent, and it may therefore be crucial to identify persons who may be at the cusp of exhibiting NFT pathology. Importantly, abnormal flortaucipir-PET binding may indicate an AD pathologic process that has already been ongoing for several years. Accordingly, CSF^+/PET^+ participants here had CSF P-tau levels that had been elevated for at least 5 years prior to their flortaucipir-PET assessment, although their antecedent P-tau change was comparable with the CSF^+/PET^- group. This last observation is consistent with slowing or even decreasing CSF P-tau change at or after onset of symptoms.[40,41] Indeed, CSF^+/PET^+ persons also had evident decline in cognitive function for at least 5 years preceding flortaucipir-PET scanning and may therefore have had concomitantly elevated flortaucipir-PET binding along with their cognitive decline.[42]

Strengths and Limitations

This study's principal strength is its reliance on large amounts of longitudinal data on CSF biomarkers of AD and cognitive evaluations, along with numerous scans using a newly available PET tracer for tau pathology. An additional strength was that results were robust to threshold modification, or the removal of individuals close to defined thresholds or having long delays between CSF and PET assessments. Among the study's weaknesses are a sample heavily weighted toward unimpaired and early clinical stages. Results might have been different had we studied a more impaired population, ie, retrospective rather than prospective longitudinal analyses of AD biomarker and cognitive trajectories. Nonetheless, these results are in keeping with knowledge of CSF biomarker trajectories and associations of flortaucipir-PET binding with cognitive change. To further investigate our hypothesis, prospective longitudinal analysis of CSF P-tau and flortaucipir-PET should investigate whether CSF^-/PET^- individuals at high risk for AD (eg, $A\beta^+$ individuals) are more likely to progress to tau CSF positivity than PET positivity in subsequent years. In parallel, these studies should test whether, and at what rate, $P\text{-}tau^+$ individuals become flortaucipir-positive and experience cognitive decline. Answering these questions may have strong implications for prevention trials.

Conclusions

Currently available CSF and PET tau measures are often concordant but may nonetheless suggest different stages of tau pathological progression. Prospective longitudinal investigations of this topic should clarify the sequence of biomarker abnormalities.

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Acquisition, analysis, or interpretation of data: Meyer, Gonneaud, Breitner, Villeneuve.
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