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Florbetapir positron emission tomography and cerebrospinal fluid biomarkers

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Abstract

Background: We evaluated the relationship between florbetapir-F18 positron emission tomography (FBP PET) and cerebrospinal fluid (CSF) biomarkers.

Methods: Alzheimer's Disease Neuroimaging Initiative-Grand Opportunity and Alzheimer's Disease Neuroimaging Initiative 2 (GO/2) healthy control (HC), mild cognitive impairment (MCI), and Alzheimer's disease (AD) dementia subjects with clinical measures and CSF collected ±90 days of FBP PET data were analyzed using correlation and logistic regression.

Results: In HC and MCI subjects, FBP PET anterior and posterior cingulate and composite standard uptake value ratios correlated with CSF amyloid beta ($A\beta_{1-42}$) and tau/$A\beta_{1-42}$ ratios. Using logistic regression, $A\beta_{1-42}$, total tau (t-tau), phosphorylated tau_{181P} (p-tau), and FBP PET composite each differentiated HC versus AD. $A\beta_{1-42}$ and t-tau distinguished MCI versus AD, without additional contribution by FBP PET. Total tau and p-tau added discriminative power to FBP PET when classifying HC versus AD.

Conclusion: Based on cross-sectional diagnostic groups, both amyloid and tau measures distinguish healthy from demented subjects. Longitudinal analyses are needed.

Keywords: Alzheimer's disease; Florbetapir positron emission tomography; Cerebrospinal fluid; Mild cognitive impairment; Alzheimer's Disease Neuroimaging Initiative; Biomarkers

1. Introduction

Hallmark neuropathological lesions of Alzheimer's disease (AD) at autopsy are amyloid beta (Aβ) protein deposition in plaques and hyperphosphorylated tau deposition in neurofibrillary tangles [1]. However, data from the National Institute on Aging (NIA) Alzheimer's Disease Centers collected from 2005 to 2010 found ranges for sensitivity of 70.9% to 87.3% and specificity of 44.3% to 70.8% when clinical diagnoses of possible and probable AD dementia are compared with post-mortem histopathology diagnosis [2]. Florbetapir-F18 positron emission tomography (FBP PET) for estimating Aβ neuritic plaque density was Food and Drug Administration (FDA)-approved in April 2012 and has high sensitivity (96%; 95% CI [confidence interval]

[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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80%–100%) and specificity (100%; 95% CI 78%–100%) versus autopsy within 1 year [3]. Another PET radiotracer used to quantify amyloid deposits in the brain in research settings is Pittsburgh compound B (PiB) [4,5]. Cerebrospinal fluid (CSF) levels of $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau_{181P} (p-tau) [6] are additional research tools with ongoing efforts to standardize across laboratories and patients [7,8].

A model of the temporal order in which clinically measurable AD biomarkers become abnormal throughout the progression of AD has been proposed by Jack and colleagues [9]. According to this model, abnormal CSF $A\beta_{1-42}$ and amyloid PET findings are detected earliest, followed by CSF tau and other biomarker types. Deposition of Aβ into plaques appears very early in the disease process during the asymptomatic stages before AD dementia. In contrast, elevated tau levels are downstream biomarkers that become strikingly more abnormal closer to the development of clinical symptoms [9]. Evidence continues to accumulate in support of this model [10–12]. Fagan and colleagues reported a similar CSF biomarker phenotype in patients with very mild AD symptoms (Clinical Dementia Rating [CDR] = 0.5) versus patients with more advanced AD (CDR $>$ 1) [13].

There is no consensus for the ante-mortem staging of AD clinical phases using biomarker thresholds and where the progression of neuropathological changes is hypothesized to be on a continuum beginning with a long asymptomatic period and culminating in dementia [14,15]. Furthermore, symptom severity is influenced by multiple factors, such as age [16], premorbid functioning [17], education [18], cognitive reserve [14], apolipoprotein E epsilon 4 (*APOE* ε4) allele carrier status [19], and certain concurrent medical conditions [20]. Thus, there may be a discrepancy between the presence and degree of AD neuropathology with the expression of AD symptoms on an individual basis. These challenges underscore the need for additional tools, such as AD clinical biomarkers, to aid the accurate diagnosis and staging of AD across the continuum of clinical progression [21].

The CSF $A\beta_{1-42}$ and tau analytes and amyloid PET neuroimaging as adjunctive biomarkers for the diagnosis of AD are not commonly used in clinical practice but have the potential to significantly affect the accuracy of a clinical diagnosis. There is a small amount of emerging literature about their relationship to each other across the spectrum of disease progression. Studies of the amyloid brain deposits assessed with PiB PET and CSF levels of $A\beta_{1-42}$ found an inverse relationship between them, no relationship between PiB and CSF t-tau or p-tau, and discordance with clinical diagnosis where some healthy controls showed evidence of amyloid positive status by both PiB and CSF $A\beta_{1-42}$ [4,5]. Binary classification using PiB PET and CSF-$A\beta_{1-42}$ overlapped in 96.4% [4].

We explored cross-sectional relationships between FBP PET and CSF biomarkers among groups of healthy control (HC), mild cognitive impairment (MCI), and AD dementia subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) using approaches not previously reported. We measured correlations between regional and composite FBP PET values and CSF $A\beta_{1-42}$, t-tau, and p-tau, and their ratios in diagnostic groups. We used logistic regression to compare composite FBP PET values with CSF $A\beta_{1-42}$, t-tau, and p-tau in distinguishing between diagnostic groups including evaluating for additive contributions by the other biomarker type.

2. Methods

2.1. Subjects and study design

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the NIA, the National Institute of Biomedical Imaging and Bioengineering, the FDA, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, and lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California—San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects, but ADNI has been followed by ADNI-Grand Opportunity (ADNI-GO) and ADNI 2. To date these three protocols have recruited more than 1500 adults, ages 55 to 90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI 1 ADNI 2, and ADNI-GO. Subjects originally recruited for ADNI 1 and ADNI-GO had the option to be followed in ADNI 2. For up-to-date information, see www.adni-info.org.

Data were downloaded in August 2012 from ADNI-GO/2 which included FBP PET scans. Participants were recruited from outpatient memory clinics. Clinical diagnoses were assigned to participants by the site investigators and reassessed at each visit. Normal age-matched control subjects showed no signs of depression, MCI, or dementia (www.adni-info.org). Participants with MCI were required to present education-adjusted ranges on the Logical Memory II subscale from the Wechsler Memory Scale-Revised: $\geq$16 years of education—9 to 11 for early MCI, $\leq$8 for late MCI; 8 to 15 years of education—5 to 9 for early

MCI, ≤4 for late MCI; and 0 to 7 years of education—3 to 6 for early MCI, ≤2 for late MCI. Additionally, participants with MCI had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a CDR of 0.5 with a Memory Box score ≥0.5, and preserved activities of daily living. Participants with AD dementia met the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria for probable AD. At subsequent visits, diagnoses were categorized as HC, MCI, or AD. For this cross-sectional analysis, we selected all HC, MCI, and AD dementia subjects who had clinical measures, diagnoses, and CSF analyte levels within ±90 days of their FBP PET scans.

2.2. Clinical measures

The following clinical measures were included to describe the sample: Estimated Verbal Intelligence Quotient (EVIQ), Functional Activities Questionnaire, Geriatric Depression Scale, Neuropsychiatric Inventory-Questionnaire, 11- and 13-item versions of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog11; ADAS-Cog13), and MMSE.

2.3. Biomarker variables

2.3.1. Florbetapir-F18 positron emission tomography

FBP PET data for all subjects were analyzed using a semiautomatic method, which includes spatial normalization to a standard template in the Talairach space [3]. Standard uptake value ratios (SUVRs) using whole cerebellum as the reference region were calculated for six FBP PET regions of interest (ROIs): posterior cingulate, precuneus, parietal, temporal, anterior cingulate, frontal; and the composite, which is their mean SUVR. The six target ROIs were defined in a previous study [22], in which PET uptake was increased in AD subjects compared with control subjects. Raw FBP PET data were initially preprocessed at the Laboratory of Neuroimaging at the University of California, Berkeley (http://resource.loni.ucla.edu/research/data-interpretation/).

2.3.2. Cerebrospinal fluid measures

Samples were analyzed using the Luminex® xMAP® platform (Austin, TX) and Innogenetics/Fujirebio AlzBio3 immunoassay kits (Gent, Belgium) by the ADNI Core Laboratory at the University of Pennsylvania Medical Center. The following variables were determined: $A\beta_{1-42}$, t-tau, p-tau, t-tau/$A\beta_{1-42}$ ratio, and p-tau/$A\beta_{1-42}$ ratio.

2.4. Genotyping

A blood sample for genomic deoxyribonucleic acid extraction was obtained at enrollment for all study participants. The *APOE* genotyping on these samples was performed by Illumina® (San Diego, CA).

2.5. Statistical analyses

Pearson correlation coefficients were calculated among five CSF and seven FBP PET variables by diagnostic group. Demographic and other clinical characteristics were compared among three diagnostic groups with Chi-square/Fisher's exact test for categorical characteristics and analysis of variance for continuous variables. A significance cut-off of $P < .0014$ based on Bonferroni correction was applied (i.e., taking into account 35 correlations for each diagnostic group).

Logistic regression modeling assessed relationships between clinical diagnosis with CSF variables (not ratios) and the FBP PET composite SUVR. The likelihood ratio test was used to examine whether adding CSF biomarkers to the model, which regresses clinical diagnosis on FBP PET composite SUVR, significantly improved model fit, and vice versa. Analyses were adjusted for the following subject demographics: *APOE* ε4 carrier status (binary), age at FBP PET scan, gender, and EVIQ. Data are expressed with bolded *P*-value notation for analyses meeting the statistical significance threshold after Holm-Bonferroni correction [23] for multiple comparisons (i.e., taking into account 30 analyses). All regression analyses were done separately for three pairs of diagnoses: HC versus MCI, MCI versus AD, and HC versus AD. For all analyses, statistical significance was defined as $P \leq .05$, except where corrections were applied.

3. Results

3.1. Subject characteristics

A total of 577 subjects underwent FBP PET scans and had clinical diagnoses available within ±90 days of the scan. Of these, 344 subjects had all data points available for FBP PET, CSF, clinical diagnosis, age, and EVIQ, and sex and *APOE* ε4-carrier status, and were the basis of this analysis. These 344 subjects consisted of 97 HC, 226 MCI, and 21 AD dementia subjects; mean ages were 74.5 (±5.6) years in HC, 71.4 (±7.5) years in MCI, and 74.0 (±10.0) years in AD dementia subjects (Table 1). Neuropsychiatric assessment scale scores differed significantly ($P \leq .05$) among groups, with AD dementia subjects most severely affected (Table 1).

3.2. Correlation analyses of biomarker variables by diagnostic group

Pearson's correlation coefficients were assessed between FBP PET SUVR and CSF biomarkers. The highest statistically significant ($P < .05$, Bonferroni corrected) correlations were between FBP PET anterior cingulate, posterior cingulate, and composite SUVRs with CSF $A\beta_{1-42}$, t-tau/$A\beta_{1-42}$

Table 1
Subject demographics and neuropsychiatric assessment

	HC (n = 97)	MCI (n = 226)	AD dementia (n = 21)	*P*-value*
Mean age, years (SD)	74.5 (5.6)	71.4 (7.5)	74.0 (10.0)	.002
Male sex, n (%)	52 (53.6)	126 (55.8)	13 (61.9)	.781
Race, n (%)				.968
American Indian or Alaskan Native	0	1 (0.4)	0	
Asian	1 (1.0)	3 (1.3)	0	
Native Hawaiian or other Pacific Islander	0	2 (0.9)	0	
Black or African American	3 (3.1)	6 (2.7)	0	
White	92 (94.8)	207 (91.6)	21 (100.0)	
Multiracial	1 (1.0)	5 (2.2)	0	
Unknown	0	2 (0.9)	0	
APOE ε4-carrier, n (%)				<.001
No	76 (78.4)	128 (56.6)	7 (33.3)	
Yes	21 (21.6)	98 (43.4)	14 (66.7)	
Mean education, years (SD)	16.4 (2.6)	16.1 (2.6)	15.8 (2.8)	.382
AmNART error rate, mean (SD)	10.2 (8.4)	11.8 (8.4)	16.3 (10.6)§	.011
FAQ, mean (SD)	0.2 (0.7)	2.4 (3.7)‡	12.9 (7.0)‡,#	<.001
EVIQ, mean (SD)	118.8 (8.0)	117.2 (8.0)	113.1 (10.4)§,¶	.012
GDS, mean (SD, n)	0.7 (1.1, 94)	1.8 (1.5, 205)‡	2.0 (1.2, 18)‡	<.001
NPI, mean (SD, n)	0.4 (1.1, 95)	2.0 (2.9, 226)‡	2.7 (3.0, 21)‡	<.001
ADAS-Cog11, mean (SD)	6.2 (3.1)	8.9 (4.3)‡	19.6 (6.2)‡,#	<.001
ADAS-Cog13, mean (SD)	9.7 (4.5)	14.2 (6.6)‡	30.3 (8.0)‡,#	<.001
MMSE, mean (SD, n)	29.0 (1.2, 94)	28.2 (1.7, 207)‡	22.8 (1.7, 18)‡,#	<.001

Abbreviations: HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; *APOE* ε4, apolipoprotein E epsilon 4; SD, standard deviation; AmNART, American National Adult Reading Test; FAQ, Functional Activities Questionnaire; EVIQ, Estimated Verbal Intelligence Quotient; GDS, Geriatric Depression Scale; ADAS-Cog11, Alzheimer's Disease Assessment Scale, 11-item cognitive subscale; ADAS-Cog13, Alzheimer's Disease Assessment Scale, 13-item cognitive subscale; MMSE, Mini-Mental State Examination; n, number of subjects.

**P*-values from analysis of variance model for continuous variables; from Chi-square/Fisher's exact test for categorical variables.

‡*P*-value <.001 versus HC (*P*-values versus HC are only indicated in the MCI and AD dementia columns to avoid repetition).

§*P*-value <.01 versus HC.

¶*P*-value ≤.05 versus MCI.

#*P*-value <.001 versus MCI.

ratio, and p-tau/Aβ_{1-42} ratio for HC and MCI groups (Table 2).

Although significant correlations between CSF tau measures and FBP PET variables were seen, the values of the correlation coefficients were relatively lower unless CSF tau was in a ratio with Aβ_{1-42}. Correlations between both t-tau and p-tau and several FBP PET variables did reach statistical significance in the MCI group. In the AD dementia group, no significant correlations were observed (Table 2).

3.3. Regression analyses of biomarker variables

After Holm-Bonferroni correction, logistic regression modeling of biomarkers found no variables that statistically significantly differentiated HC from MCI (Table 3). Amyloid biomarkers alone (FBP PET and CSF Aβ_{1-42}) significantly distinguished between diagnostic groups when comparing HC and AD dementia groups (FBP PET, P =.0002; CSF Aβ_{1-42}, P =.0007). CSF t-tau significantly differentiated AD dementia from both HC (P <.0001) and MCI groups (P =.0003), and CSF p-tau distinguished between HC and AD dementia groups (P =.0001).

Table 3 also shows the effect of adding CSF or FBP PET variables to the other biomarker type to assess any additional contribution to differentiating diagnostic groups (where the reported *P*-values represent the impact of just the additional information). No significant gain in differentiation was observed when testing FBP PET variables in the presence of CSF variables for any group comparison. However, adding CSF t-tau or CSF p-tau to FBP PET significantly improved the differentiation between HC and AD dementia groups.

4. Discussion

This cross-sectional analysis explored relationships between two types of AD biomarkers, amyloid PET imaging (FBP PET) and CSF analytes (Aβ_{1-42}, t-tau, and p-tau), for their ability to differentiate clinical diagnostic group status among HC, MCI, and AD dementia subjects in ADNI. Both amyloid-related biomarkers were highly correlated with each other. Overall, the amyloid-related biomarkers were not appreciably different with respect to categorical clinical classification in that adding one to the other in logistic regressions did not improve classification.

Specifically, in logistic regression analyses, neither CSF Aβ_{1-42} nor FBP PET distinguished HC and MCI, probably because amyloid pathology in those who could later progress

Table 2
Pearson correlation coefficients between FBP PET SUVR and CSF biomarker levels by diagnostic group

CSF biomarkers	Posterior cingulate	Precuneus	Parietal	Temporal	Anterior cingulate	Frontal	Composite
HC group (n = 97)							
$A\beta_{1-42}$	−0.661*	−0.374*	−0.364*	−0.325*	−0.629*	0.338*	−0.681*
t-tau	0.346*	0.054	0.073	0.042	0.388*	0.065	0.392*
p-tau	0.219	0.068	0.083	0.059	0.288	0.096	0.286
t-tau/$A\beta_{1-42}$ ratio	0.600*	0.181	0.185	0.146	0.603*	0.162	0.643*
p-tau/$A\beta_{1-42}$ ratio	0.562*	0.260	0.266	0.228	0.613*	0.253	0.635*
MCI group (n = 226)							
$A\beta_{1-42}$	−0.651*	−0.326*	−0.286*	−0.267*	−0.662*	−0.287*	−0.697*
t-tau	0.557*	0.190	0.139	0.154	0.560*	0.178	0.573*
p-tau	0.559*	0.268*	0.200	0.214*	0.533*	0.245*	0.558*
t-tau/$A\beta_{1-42}$ ratio	0.624*	0.222*	0.171	0.173	0.620*	0.198	0.644*
p-tau/$A\beta_{1-42}$ ratio	0.661*	0.301*	0.241*	0.241*	0.638*	0.267*	0.678*
AD dementia group (n = 21)							
$A\beta_{1-42}$	−0.375	−0.215	−0.252	−0.208	−0.580	−0.193	−0.563
t-tau	−0.058	0.404	0.404	0.428	0.180	0.417	0.082
p-tau	0.173	0.391	0.433	0.437	0.256	0.438	0.235
t-tau/$A\beta_{1-42}$ ratio	0.002	0.371	0.400	0.397	0.322	0.383	0.224
p-tau/$A\beta_{1-42}$ ratio	0.170	0.268	0.331	0.309	0.317	0.306	0.297

Abbreviations: FBP PET, florbetapir-F18 positron emission tomography; SUVR, standard uptake value ratio; CSF, cerebrospinal fluid; HC, healthy controls; n, number of subjects; $A\beta_{1-42}$, beta-amyloid protein; p-tau, phosphorylated tau_{181P}; t-tau, total tau; MCI, mild cognitive impairment; AD, Alzheimer's disease.
*P-value ≤.0014 based on Bonferroni correction.

to clinical AD had already manifested. However, CSF $A\beta_{1-42}$ and FBP PET each distinguished HC from AD groups, as did CSF t-tau and p-tau. Additionally, CSF t-tau also significantly differentiated AD dementia from MCI, and CSF p-tau distinguished between HC and AD dementia groups.

These findings with CSF tau are consistent with CSF tau abnormalities manifesting later and progressively in the disease, as compared with amyloid plaque, which exhibits substantial deposition by the time patients present with MCI [9].

CSF $A\beta_{1-42}$ but not FBP PET significantly distinguished MCI from AD dementia groups; however, FBP PET was close to the threshold applied by the Holm-Bonferroni correction for the multiple comparisons method, and it is possible that a better-powered study might have found a different result. Once a person has positive binary status the rate of amyloid SUVR increase is slower during MCI and dementia stages than in the decades before MCI [15].

We found a number of statistically significant correlations between the biomarker types, especially those that involved Aβ. Although significant correlations between CSF tau measures and FBP PET variables were seen, the values of the correlation coefficients were relatively lower unless CSF tau were in a ratio with CSF $A\beta_{1-42}$.

Table 3
Logistic regression analyses of clinical diagnostic group on CSF and FBP PET variables, adding one biomarker to the other to determine an additive contribution in distinguishing among groups

	HC vs MCI		MCI vs AD		HC vs. AD	
	Chi-square (df)	*P*-value	Chi-square (df)	*P*-value	Chi-square (df)	*P*-value
Test FBP PET without CSF	5.7502 (1)	.0165	8.7197 (1)	.0031	14.3044 (1)	**.0002**
Test of CSF $A\beta_{1-42}$ when added to FBP PET	0.5176 (1)	.4718	4.6972 (1)	.0302	1.9339 (1)	.1643
Test of CSF t-tau when added to FBP PET	1.6375 (1)	.2007	6.9011 (1)	.0086	10.7866 (1)	**.0010**
Test of CSF p-tau when added to FBP PET	0.3143 (1)	.5751	2.0160 (1)	.1556	9.5094 (1)	**.0020**
Test $A\beta_{1-42}$ without FBP PET	0.6942 (1)	.4047	9.9783 (1)	**.0016**	11.5618 (1)	**.0007**
Test of FBP PET when added to CSF $A\beta_{1-42}$	5.5238 (1)	.0188	1.7866 (1)	.1813	3.5791 (1)	.0585
Test CSF t-tau without FBP PET	4.5379 (1)	.0332	13.2332 (1)	**.0003**	15.2843 (1)	**<.0001**
Test of FBP PET when added to CSF t-tau	2.6964 (1)	.1006	2.8014 (1)	.0942	5.4003 (1)	.0201
Test CSF p-tau without FBP PET	2.2812 (1)	.1310	6.1506 (1)	.0131	14.5239 (1)	**.0001**
Test of FBP PET when added to CSF p-tau	3.8047 (1)	.0511	5.1704 (1)	.0230	7.4634 (1)	.0063

Abbreviations: CSF, cerebrospinal fluid; FBP PET, florbetapir-F18 positron emission tomography; HC, healthy controls; MCI, mild cognitive impairment; df, degrees of freedom; AD, Alzheimer's disease; $A\beta_{1-42}$, beta-amyloid protein; p-tau, phosphorylated tau_{181P}; t-tau, total tau.

FBP PET includes all six regions of interest, and CSF includes all five, unless otherwise specified. *P*-values that meet statistical significance with Holm-Bonferroni corrected cut-off are in bold.

Within the HC and MCI groups, we found some strong and significant correlations for FBP PET with CSF $A\beta_{1-42}$, with the anterior and posterior cingulate ROIs and composite SUVRs being the most notable. This is consistent with the known neuroanatomical progression pattern of AD where cingulate gyri are affected early with Aβ plaque. In the AD dementia group, the highest correlations were between CSF $A\beta_{1-42}$ and FBP PET, but no correlations reached statistical significance. However, it needs to be considered that the sample size for the AD dementia group was much smaller than the other groups.

Interestingly, CSF t-tau provided differentiation in the comparisons of HC versus AD dementia and MCI versus AD dementia, but not HC versus MCI. This suggests that amyloid-related biomarkers are informative as adjunctive tests for establishing an AD diagnosis because the associated pathology starts long before clinical symptoms appear, whereas tau may be more helpful for staging because it accumulates in the later stages of the disease, as has been described previously. Although CSF $A\beta_{1-42}$ changes are observed 5 to 10 years before the conversion of MCI to AD dementia, CSF t-tau and p-tau seem to be markers of later stage pathology [24]. Thomann and colleagues associated changes in CSF t-tau and p-tau with neurodegenerative changes in MCI subjects who converted to early AD dementia [25]. Alternatively, some studies have suggested that tau abnormalities at the cellular level may begin in the asymptomatic period before or simultaneously with amyloid [26], but our current clinical biomarker methodologies may not be targeted or sensitive enough to detect those [27].

Doré and colleagues recently described longitudinal (18- and 36-months) relationships among Aβ deposition, cortical thickness, and memory [28]. They reported a faster rate of gray matter atrophy in the temporal cortex and hippocampi and greater episodic memory impairment in clinically unimpaired individuals who were amyloid positive on PiB PET than those who were amyloid negative [28]. A longitudinal study published by the Australian Imaging Biomarkers and Lifestyle research group estimated that it takes 19.2 years (95% CI 16.8–22.5) for subjects to progress from the threshold of PiB PET positivity to amyloid levels observed in AD dementia [15]. After the emergence of symptoms of AD, the rate of Aβ deposition slowed and then plateaued at the dementia stage [15]. Additionally, a study of 401 ADNI subjects found that reduction in the CSF $A\beta_{1-42}$ level becomes dynamic early, whereas changes in CSF t-tau levels and adjusted hippocampal volumes occur later and may be biomarkers of downstream pathophysiologic processes [29]. However, a study by Driscoll and colleagues in nondemented individuals did not observe a correlation between the level of amyloid load and longitudinal brain volume changes [30].

The generalizability of our results to the broader population is uncertain and potentially limited by the study sample. We used data from ADNI-GO and ADNI 2 cohorts, which represents a selected convenience sample including subjects with amnestic MCI, and also higher education and cognitive reserve. Compared with the ADNI cohort, the population-based sample in the Mayo Clinic Study of Aging (MCSA) [31] was older and less educated, and had lower MMSE scores and a less frequent family history of AD. The rate of hippocampal volume decline was larger in ADNI subjects compared with MCSA, suggesting more advanced brain pathology in ADNI subjects [31]. Additionally, analyzing early and late MCI subjects as one group might have affected our findings. Furthermore, because ADNI used a central laboratory to test CSF, the lack of standardization of CSF AD biomarker measurements across clinical sites and assays may limit the applicability of our results to clinical practice. Finally, the analyses presented here are based on cross-sectional and not longitudinal data. Prospective, longitudinal studies are needed to confirm or refute our findings. The strengths of our study are the relatively large HC and MCI sample sizes and the combination of CSF and FBP PET measures where most prior work was reported using PiB PET.

In conclusion, we found some unique characteristics, but also considerable overlap between CSF and FBP PET measures when assessing their ability to distinguish among pairs of HC, MCI, and AD dementia groups. We report both composite and ROI correlations for FBP PET with CSF. Our findings of differences in the differentiation of AD stages by amyloid versus tau biomarkers might aid in the development of further diagnostic and staging tools for AD.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the currently available literature on florbetapir positron emission tomography (FBP PET) and cerebrospinal fluid (CSF) biomarkers in Alzheimer's disease (AD) and combined their findings with their clinical experience in this patient population.
2. Interpretation: The authors found some unique characteristics but also considerable overlap between CSF and FBP PET measures when assessing their ability to distinguish among pairs of healthy control, mild cognitive impairment, and AD groups using a variety of analytic methods. These findings of differences in the differentiation of Alzheimer's disease stages by amyloid versus tau biomarkers might aid in the development of further diagnostic and staging tools for AD.
3. Future directions: Prospective, longitudinal studies are needed to confirm the results of the presented retrospective cross-sectional analyses.

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